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INSTRUMENTS FOR IMAGE GUIDED PROCEDURES — IIGP

Review Summaries for minimal invasive and image guided technologies and clinical procedures

Michael Friebe *Editor*

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Bundesministerium für Bildung und Forschung

INSTRUMENTS FOR IMAGE GUIDED PROCEDURES — Note from the Editor

The MASTER OF SCIENCE IN MEDICAL SYSTEMS ENGINEERING (http://www.lmt.ovgu.de/MasterMSE.html) at the Otto-von-Guericke-University in Magdeburg, Germany (www.ovgu.de) is an english language program. The current enrolment is very international (> 20 nations) with more than 50% coming from non-German language countries.

While it is very exciting to have such an international student body it also shows huge differences in what the students are capable of and what their undergraduate degree prepared them for. Some of them have never been exposed to scientific evaluation, to analyse and to present scientific data. Besides teaching the technical essentials and attending laboratory sessions (total 3 SWS, 5 ECTS) the students had therefore several additional assignments to complete to address some of these issues.

Part of the lecture INSTRUMENTS FOR IMAGE GUIDED PROCEDURES (IIGP) for example was an individual final project that should also teach the students on how to prepare themselves for future scientific work, by evaluating current technologies and procedures for a relatively narrowly formulated topic in the field of IMAGE GUIDED PROCEDURES.

This project consisted of a “review” paper with approx. 3.000 - 4.000 words and a maximum of 25 references, as well as a poster that summarises the findings. The main focus for their analysis was on describing the technologies and their limitations with an outlook on future developments … with an exclusive focus on minimal-invasive and image guided procedures.

The review documents and the posters came from 21 students (5 nations) that had capabilities that are very typical for a master lecture class and resemble a standard gauss distribution. Some are above average (6), average (10), and also some below average (5). You will easily recognise the good works and the ones where the students could have invested more time and effort in preparing the assignment. The included works have not been edited except for spellchecking.

We are nevertheless very happy about the results. The summaries and poster presentations provide a great value for Master students in this field of study and also for academic staff, and other researchers by giving them a short introduction and overview, as well as some of the references for further more depth information. This is the reason why we decided to publish this work.

In the coming semesters the assignments below average will be replaced and also many new topics from the exciting field of IMAGE GUIDED PROCEDURES will be added.

Magdeburg, Germany, January 2016

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IIGP Lecture - Overview and Introduction - Review papers of technologies and clinical procedures

Summary of the final projects (Biomedical Engineering Graduate Students) of the Instruments for Image Guided Procedures Lecture (IIGP)

Keywords: image guided procedures, minimal invasive therapies,

Introduction and Motivation

Image guided minimal invasive surgeries (IGS) and therapies are growing in importance. Many clinical procedures - and particularly the patient - benefit from new therapy methods that are using small incisions to reach target areas in the human body and subsequently perform the corrective procedure. There are many issues that still need to be resolved or improved and that are addressed in the ongoing research at our chair and in many other institutions worldwide.

Just to name a few: availability of intra-operative imaging, navigation and tracking of tools, quality assurance of the procedure, steerability of tools and devices, molecular information and pathology information at the surgery site, and many more.

To be able to work as innovator in that segment the students need to understand the limitations of the current procedures (image guided and conventional) to be able to recognise unmet clinical needs and subsequently develop solutions.

A special lecture series was developed that teaches technology and clinical basics (see figure 1), followed by actual innovation generation in a real clinical setup and subsequent translation of the results into projects / products and services [1].

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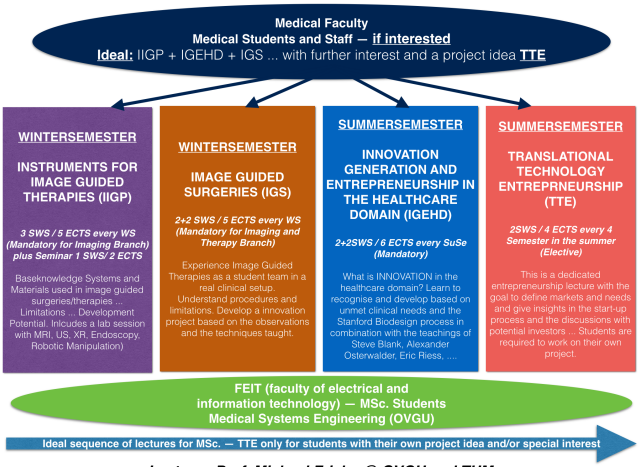

Fig. 1: Lecture series for graduate students that leads from clinical understanding and technologies used (IIGP) to working on and understanding the clinical limitations of Image Guided Procedures (IGS), and subsequently recognising innovation potential and unmet clinical needs (IGEHD) to be translated into products and services (TTE)

For the first lecture of that series titled INSTRUMENTS FOR IMAGE GUIDED PROCEDURES (IIGP) the graduate students were individually assigned a topic related to technologies or procedures that are image guided or have a minimal invasive therapy component.

The students had to prepare a review document on that topic with a special emphasis on the tools and systems used for the procedure and the current limitations of these technologies or procedures. The enclosed booklet is the summary of the student reviews that we believe are very helpful for engineers and scientist that are already working or that are interested in working in the field of Image Guided Surgeries, where incremental innovation is normally not a technology push (technology delivered) but rather a pull (by learning and working with the clinical users) from understanding how these surgeries are performed.

What is very often lacking during the university education is the actual interaction with clinicians, active participation in medical procedures, comprehension of healthcare economics, and a structured engineering approach to innovation creation in that field.

Also interesting is that medical technology innovation delivered to the clinicians (technology push) at the moment is very often not developed together with the clinicians, but comes predominantly from the engineering or business side .

Developments however that are based on medical needs by observing the clinical use and environment [1, 3, 4], and that are done in close cooperation with the actual users (technology pull) may not be as disruptive, but are easier to recognise and implement, provide a relatively quick feedback, and can be used as teaching tool for interdisciplinary innovation generation.

Lecture Format and Goals

All in all 7 lectures of 4 academic hours each, discussing and presenting the imaging essentials [2, 5], tracking and navigation, minimal invasive and image guided surgery tools for different clinical applications, robots and manipulation units and biocompatibility and interventional materials (see Fig. 2).

The objectives of the lecture are listed in figure 3 and focus mainly on the limitations of the technologies and procedures as currently used and practised. Once the limitations and problems are known it is possible to think about potential improvements.

The lecture was complimented by 4 lab sessions of 4 academic hours each (in teams of 5-6) on MRI (small bore 0.55T Pure Devices and full body 3T Magnetom Skyra, Siemens), Ultrasound (Venue 50 and Logiq e7, both GE), endoscopic imaging (Olympus), and robotic systems (iSYS + Medineering).

For the final semester project the students had to individually finish a review document (approx. 8-10 pages with 20-40 references) and a poster on the same topic that was presented in a dedicated poster session at the end of the lecture.

These poster were presented in three minute talks by the students to an invited audience of students, university staff, and other interested people. An examination (60 minutes) of the lecture content was also part on this last day (Fig. 4).

The documentation as well as the posters had to be prepared like normal journal papers / scientific posters and the results of the review documents are now listed in this booklet, that we will continuously update and expand with additional topics.

- **LECTURE I:** GENERAL INTRODUCTION (Diagnostic Imaging Systems, Minimal Invasive Surgeries, Tools and Systems, ...) — **MF - 6 academic hours**
- **LECTURE II:** IMAGING and IMAGING PROBLEMS for IGS (Compatibility, Size, Handling, Cost, ...) — **MF - 6 academic hours**
- **LECTURE III:** IMAGING Contrast Issues, Artefacts + Avoidance Strategies (CT, MRI, US, XR, END) — **JK - 3 academic hours /** TRACKING and NAVIGATION / FUSION for IGS — Systems and Limitations (EM, NIR, Fiduciary, Inside-Out, Workstation, Registration, ...) — **JK / SA - 3 academic hours**
- **LECTURE IV:** NEURORADIOLOGY / VASCULAR therapy tools — e.g. stents, implants, coils, flow diverter, catheters, guidewires, ... — **AB + AI - 3 academic hours /** MIS TOOLS — optical systems, trokar, SILS, cauterisation, CO2, ... — **AB + AI - 3 academic hours**
- **LECTURE V:** INTRAOPERATIVE RADIATION THERAPY — HDR / LDR / Photons / Beta-Emitter — **MF - 3 academic hours /** INTERVENTIONAL THERAPY TOOLS using RFA, laser, cryotherapy, hyperthermia, ... — **AO - 3 academic hours**
- **LECTURE VI:** ROBOTS and MANIPULATION for IGP — **RO - 3 academic hours /** BIOCOMPATIBILITY and MATERIALS — **MF - 3 academic hours**
- **LECTURE VII:** DEVELOPMENT NEEDS and FUTURE DEVELOPMENTS plus Review of Lecture Content — **MF - 6 academic hours**
- **LECTURE VIII - XI:** LABORATORY SESSIONS - ULTRASOUND, MRI, ENDOSCOPY, NAVIGATION, ROBOTIC — **AB, JK, AO, RO, SA, AI - total of 24 academic hours**
- **LECTURE XII:** EXAMINATION AND INDIVIDUAL POSTER PRESENTATION — **ALL - 6 academic hours**

12 LECTURES WITH A TOTAL OF 72 ACADEMIC HOURS
+ 80 ACADEMIC HOURS FOR POSTER AND REVIEW PAPER
= 152 ACADEMIC HOURS

Fig. 2: IIGP lecture plan (MF: Michael Friebe, AO: Alexander van Oepen, AI; Alfredo Illanes, JK: Johannes Krug, SA: Shiras Abdurahman, RO: Robert Odenbach)

The lecture was graded as a sum of attendance/ participation, examination/test, poster, review paper (1/4 each). The students invested between 60 and 100 hours in the paper and poster presentation.

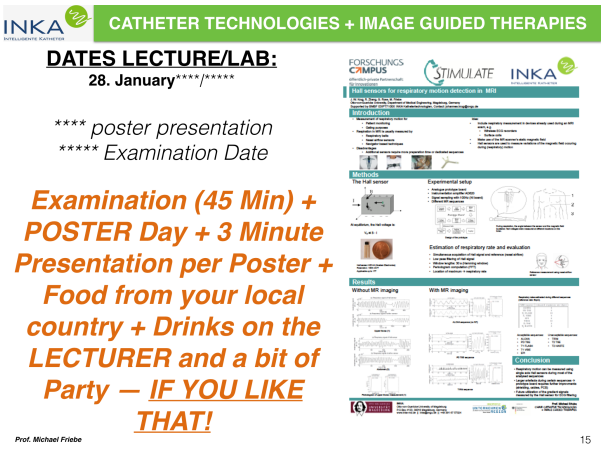

Fig. 3: IIGP lecture objectives

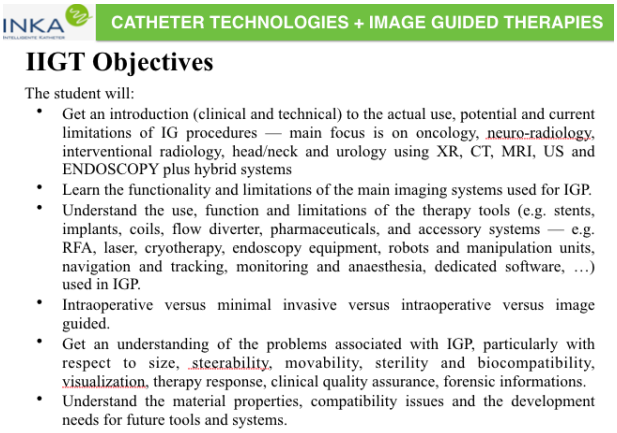

Fig. 4: Poster format template

Conclusion and Next Steps

The quality of the review papers (21 in total) was generally high, with 9 exceptional papers. The students that prepared these papers were asked to continue for a subsequent journal paper publication. All of the students agreed to this voluntary work.

The summary of the paper and posters (this document) will be updated at least yearly with additional new topics and with replacements of papers that were below average quality.

Innovation in IMAGE GUIDED PROCEDURES requires excellent knowledge of the technologies used, but it also needs to prepare the future engineers for the reality of their work environment. They will work with clinical users (MEDICAL), but also need to understand that economic questions need to be asked and answered. This concept (EME) in combination with the Standford Biodesign principle [3] of searching for "unmet clinical needs" (IDENTIFY), creating initial solutions (INVENT), and after iteration with the clinical staff IMPLEMENT needs to be presented and understood by the students. This EME I3 concept (Fig. 5) is the core principle of creating innovation in the IMAGE GUIDED PROCEDURE workspace [1, 3-4].

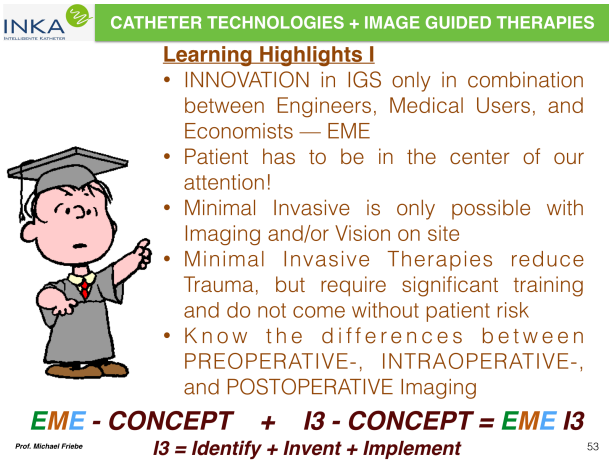

Fig. 5: EME + I3 - CONCEPT = EME I3 = the concept of the lecture series and the core principle of creating innovation for Image Guided Surgeries

Acknowledgement

I thank the entire staff of the Catheter Technologies chair, namely the Senior Researcher Axel Boese, Johannes Krug, and Alfredo Illanes; the PhD students Alexander van Oepen, Shiras Abdurahman, Robert Odenbach; the chair secretary Nadine Tress; and of course all the MSc. students that participated.

Disclosure

Nothing to disclose.

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NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY (NOTES)- The future in minimal invasive surgery

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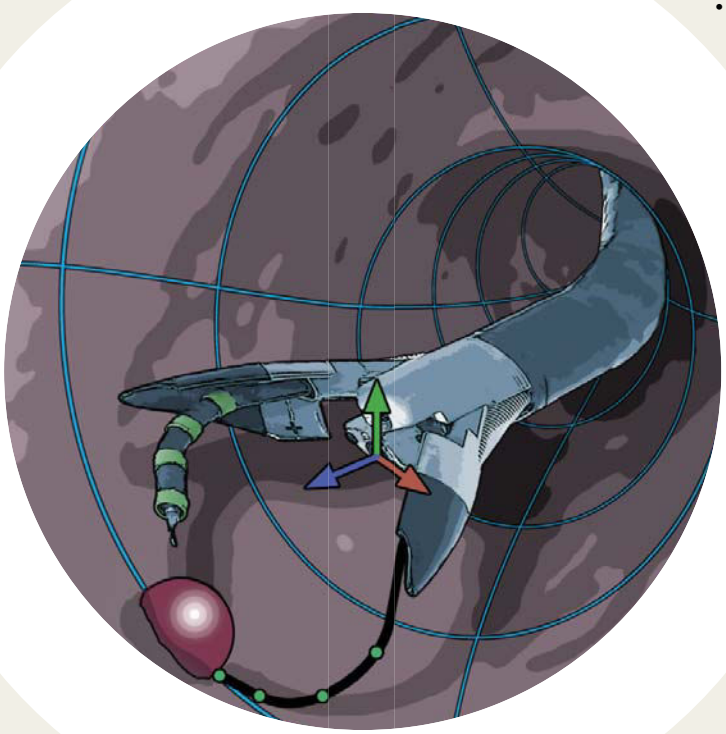
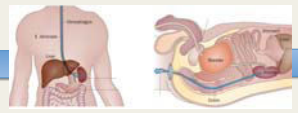
INTRODUCCTION

Minimally Invasive surgery has radically changed surgical procedures. Natural Orifice Transluminal Endoscopic Surgery (NOTES) seems to be the evolution of MIS. By using natural orifice in patients, there is the possibility to access into the peritoneal cavity in order to perform several surgical procedures. Contrary to traditional laparoscopy, NOTES brings new options for diagnosis and resection without abdominal scars, faster recovery, less pain and a quicker return to daily life. The main goal is to reach the peritoneal cavity by using endoscopic tools inside natural passages such as the vagina, rectum or stomach. An incision is made and an endoscope is inserted and located in the peritoneal cavity. Then, the required task is performed and finally a suture is made in order to close the previous injury. Despite multiple current problems, complete true NOTES transvaginal cholecystectomies have been safely performed without any negative result.

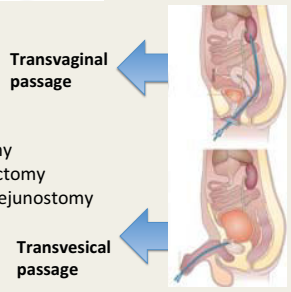


ACCESS PATHS AND SCOPE

NOTES operations in humans have been reported into cholecystectomy and appendectomy in a margin of 84% and 7% respectively. The scope of NOTES goes further away however. Some of them are mentioned as follows [9].



- Colectomy
- Hepatectomy
- Splenectomy
- Nephrectomy
- Gastric sleeve
- Pancreatectomy
- Cholecystectomy
- Gastrojejunostomy



OUTLOOK

Image 2. Control platform for endoscope [3].

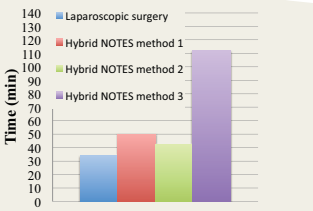
Image 3. Endosamurai endoscope tools [3].

CHALLENGES

- Instruments are designed for obtaining biopsies, visualization or hemostasis problems.
- Retraction, suturing or resection functions are necessary.
- Augmented reality images help the surgeon to understand the patient's organs.

Potential barriers to clinical application [8]:

- Control of intra-peritoneal hemorrhage
- Development of a multitasking platform
- Prevention of infection
- Development of suturing device
- Compression syndromes
- Training other providers
- Spatial orientation



Graph 1. Comparison hybrid Notes with Laparoscopy [6].

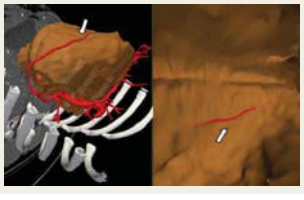


Image 4. Augmented reality in a porcine model [1].

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NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY (NOTES) - THE FUTURE IN MINIMALLY INVASIVE SURGERY

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ARTICLE INFO

Keywords:

Minimal Invasive Surgery
Natural orifices

Abbreviations:

MIS Minimal Invasive Surgery

ABSTRACT

Minimally Invasive surgery has radically changed surgical procedures. Natural Orifice Transluminal Endoscopic Surgery (NOTES) seems to be the evolution of MIS. The main goal in the next study is to present the different types of NOTES methodologies, the possible surgeries that would be performed and the main challenges. Additionally, a comparison among traditional surgery, laparoscopy and NOTES is made followed by the current solutions that have been tested. Finally, innovative tools and the changes that must be developed in order to make NOTES a viable procedure in future are discussed.

1. INTRODUCCTION

Surgery has changed with technology in the last decades. From traditional surgery to minimally invasive techniques, surgeons have created new procedures to enhance patients´ health. Laparoscopy has notoriously improved recovery rate after surgery and reduced trauma in patients. Natural Orifice Transluminal Endoscopic Surgery (NOTES) has also brought promising outcomes. They include no-scar surgery, faster recovery, less pain and a quicker return to daily life [1]. The main goal is to reach the peritoneal cavity by using endoscopic tools inside natural passages such as the vagina, rectum or stomach. An example is transvaginal access, in which a colpotomy (incision in the vagina´s wall) is made with an endoscope inserted and located in the peritoneal cavity. Then, the required task is performed and finally a suture is made in order to close the previous injury [2]. NOTES did not appear suddenly though; the first step was made in 1901 when Dimitri Oskarovich Ott tried to reach the peritoneal cavity through the vagina. Afterwards, Basil Hirshowitz and Larry Curtiss started developing processes in the endosonoscopes and the microendoscopes [3]. The application of fiberoptic endoscopy in 1960 allowed surgeons to create proper assessments by looking at the gastrointestinal pathway [4]. First, the diagnosis was focused on gastric diseases such as gastritis, varices, ulcesr, etc. Meanwhile, after therapeutic procedures were included, new gastrointestinal hemorrhages treatments were successfully implemented [4]. Currently, as a consequence of NOTES' appearance, several animal operations have been achieved to evolve in the proceeding. Among them are Pelvic organs surgery, Appendectomy, Splenectomy, Peritoneoscopy, etc. [5]. All of these implementations have shown that NOTES is a reliable procedure with a high potential for growth. Hybrids NOTES with Laparoscopy have been

already well performed in human patients by fulfilling appropriate requirements. Such hybrids are used due to the possible unaware problems that may occur in surgery, the spatial visualization and the limited difficulties to operate with pure endoscopic instruments. Until the date, Hybrid NOTES procedures have mostly used transvaginal access to introduce endoscopes and one or two abdominal access to locate laparoscopic instruments [6]. Although the majority of the cases have implemented hybrids NOTES rather than true NOTES, it can be seen the advantages when reducing multiple abdominal incisions necessary in laparoscopy. Amine et al. [6] described hybrid tasks where only transvaginal and umbilicus port were used to accomplish the surgery. Despite contradictory discussions and the lack of some innovative tools, complete true NOTES transvaginal cholecystectomies have been safely performed without any negative result [2-6].

The emergence of NOTES has brought not only potential ideas and innovations, but also doubts regarding its viability in the future. Hence, the aim of this paper is to describe procedures in NOTES, the improvements it requires and its challenges in comparison to traditional surgery and laparoscopy. Moreover, it will illustrate the current solutions to the main problems and helpful tools for the future. Likewise, the viability of NOTES and the most pertinent outlooks that could be achieved will be analyzed.

2. NOTES PROCEDURES AND GOALS

2.1 Access paths

In order to avoid infections, hernias, pain and scars, NOTES procedure uses natural pathways to reach the peritoneal cavity. After the endoscope is located, the abdominal zone is inflated with carbon dioxide to create a proper working space. Transvaginal, transgastric, transvesical and transrectal access are the main passages that have been studied and analyzed [1].

2.1.1 Transvesical passage

In transvesical NOTES, the main goal is to obtain access into the peritoneal cavity by placing instruments through the urinary bladder. In order to perform future surgeries in humans, transvesical NOTES procedures have been made first in animal survival and human cadaveric models [7]. Transvesical pure NOTES procedures have been developed in multiple porcine models safely, quickly and without complications [8]. The surgeon inserts an ureteroscope through the urogenital sinus and the urethra. Then an incision in the topside in the urinary bladder is created through cystotomy. Finally, the ureteroscope is situated into the peritoneal cavity to complete the desired surgery [8]. Resectioning of the kidney through nephrectomy has demonstrated advantages in NOTES in multiple animal models. Therefore, scientific groups as American Society of Gastrointestinal Endoscopy (ASGE), the Society of American Gastrointestinal and Endoscopic Surgeons (SASGE) and the European Society of Gastrointestinal Endoscopy have defined NOTES as a promissory field in urology [7].

2.1.2 Transgastric passage

By using the transgastric path, the surgeon uses the stomach instead of the urinary bladder to obtain access into the peritoneal cavity. After gastrostomy takes place, an endoscope is moved inside the abdominal working space. By using the required tools, the team performs the intended surgery and the puncture is then closed with clips [1]. Transgastric NOTES provides positive outcomes regarding optimal peritoneal cavity visualization and extraction of biopsy specimens. Consequently, there is a reduction in the number of unnecessary medical examinations and patients' deaths due to late diagnosis [9]. Yang Bai et al. [9] reported in NOTES a better accuracy in assessments of patients with fluids in the peritoneal cavity. This results in early treatments of diseases as tuberculosis or metastatic tumors. It was also confirmed procedures in NOTES without problems like gastric leakage, peritonitis or esophageal perforation announced in previous studies. Finally, 78 successful NOTES procedures were illustrated in which the 92.3% were clearly diagnosed [9], with notorious advantages over traditional laparoscopy.

2.1.3 Transrectal passage

Contrary to the previous path described, transrectal NOTES is focused on a rectal access followed by

an incision in the rectal wall and the insertion of the endoscope. There have been several procedures made in porcine models that confirm transrectal NOTES is completely safe [7]. Wassim et al. [7] described transrectal hybrid NOTES nephrectomy (resection of kidney) procedures performed in porcine models. The transrectal access was used to insert the respective grastroscope and an additional abdominal access to help the use of retractors and dissectors. Firstly, it was made an umbilicus incision followed by the location of a 12 mm trocar. Secondly, a gastroscope is introduced after the incision is made in the rectal wall. The kidney is resected and extracted over the rectal incision. Finally, the laceration in the wall is closed through rectotomy. The research demonstrates proper nepherectomies made in a pig with optimal results. Additionally, there has been a particular interest in the field of oncology since NOTES has developed a good solution in rectal resections. By using transanal mini-laparoscopy assisted NOTES, there is less pain and morbidity [10]. Indeed, NOTES brings positive alternatives in minimal invasive surgery in the oncology future.

2.1.4 Transvaginal passage

In transvaginal NOTES, the access into the peritoneal cavity is achieved by an incision in the wall of the vagina (colpotomy). Then, the cavity is insufflated with CO_2 so as to obtain working space and the proper endoscopic tools are introduced.
Transvaginal NOTES has been the most inquired area in this innovative procedure, since previous intra abdominal specimen extractions through colpotomy have been accomplished for years [3]. Therefore, there is a work path made that helps the performance of the new method. As transvaginal NOTES procedure is the most developed area nowadays, it will be explained in detail in the posterior chapter.

2.2 Scope in surgery

Due to the fact that NOTES is still in the experimental phase, trials have been addressed on the evaluation of the consequences after passing across lumens. The possible infections caused by bacteria in the access paths are the principal concern. As a result, research groups and surgeons work first in animal models in order to confirm safe conditions. In Table 1, Wagh [11] states the transluminal procedures published till the date. The tasks included the number of subjects used in each study, some of them with survival and others with non-survival models. Thus far, NOTES operations in humans have been reported into cholecystectomy and appendectomy in a margin of 84% and 7% respectively [12]. The scope of

Table 1. Summary of transluminal endoscopic procedures published in full [11]

Procedure	Number of subjects	Type of model
Peritoneoscopy	12	Nonsurvival
Liver biopsy	5	Survival
Tubal ligation	6	Survival
Gastrojejunostomy	2	Survival
Gallbladder surgery	11	Nonsurvival
Gastrotomy closure	8	Survival
Exploration	9	Nonsurvival
Organ resection	6	Survival
Oophorectomy and tubectomy	6	Survival
Partial hysterectomy	5	Survival
Splenectomy	6	Nonsurvival
Transcolonic cholecystectomy	5	Survival

Table 2. Feasible Procedures in NOTES [12]

Procedure	Description
Cholecystectomy	Resection of gallbladder
Hepatectomy	Resection of liver
Splenectomy	Resection of spleen
Nephrectomy	Resection Kidney
Gastrojejunostomy	Connection between the stomach and the jejunum
Gastric sleeve	Reduction of partial stomach section
Tubal ligation	Sterilization procedure
Distal pancreatectomy	Resection of partial pancreas´ section
Colectomy	Resection of partial intestine´ section

NOTES goes further away however. Several possible approaches can be achieved with NOTES by keeping safe conditions and positive results. Some of them incorporate hepatectomy, nephrectomy, splenectomy, etc. [12], and they are listed and described in Table 2.

2.3 Transvaginal cholecystectomy

As it was mentioned previously, transvaginal cholescystectomy (resectioning of the gallbladder) is probably the most accepted and tested approach in NOTES. One of the main reasons is related to the access into the peritoneal cavity. The endoscope is introduced through an incision made in the wall of the vagina denominated Colpotomy. This procedure is used in multiple gynecologic protocols as a step in surgeries. Some of these surgeries are hysterectomy, dysmenorrhea, extraction of myomas, pelvic cysts or masses, etc. The extraction of internal specimens inside the abdominal cavity with this method has been performed for years [2]. Consequently, this brings an advantage over the other procedures that are in an experimental phase. To initiate the resectioning of the gallbladder (Cholecystectomy), the patient is laid in a position that facilitates the use of the endoscopic tools. Afterwards, a colpotomy is made in the vaginal wall point p.1, as can be seen in figure 1[1], and then a trocar is used to locate the endoscopic tools. Later, the peritoneal cavity is insufflated to create a suitable working space. An endoscope is inserted to localize the gallbladder p.2 point 9.2 Figure 1. Endoscopic tools are inserted and, by using heat, the cystic duct and artery are uncovered by the fat that usually surrounds them. Clips are used to close the duct and the artery in both sides; usually three clips grab each duct. In the meantime, the endoscopic shear is prepared to cut the ducts and the gallbladder extraction is made as it can be seen in figure 2 [2]. Gumbs et al. [2] presented a complete true NOTES transvaginal cholescystectomy in humans. First, three hybrid NOTES procedures were accomplished to guarantee the safe performance of the true NOTES. In each procedure, the use of laparoscopic tools was reduced in order to achieve the true NOTES without transabdominal incisions. All the hybrid procedures required a veress needle to do the insufflation of the peritoneal cavity (pneumoperitoneum) and the gallbladder was extracted from the vagina. In the first task, a laparoscope was inserted via umbilicus to have visualization of the endoscope through the vagina. Two more trocars were inserted transabdominally to retract the gallbladder and place the clips on the cystic artery and duct. In the second and the third hybrid, the team avoided two laparoscopic accesses and used just one transabdominal incision through umbilicus to record the entrance of the endoscope transvaginally and to locate the clips. As the first three practices were perfectly managed, the team realized that the use of the umbilicus tool was not required anymore. Hence, a true NOTES procedure was carried in the fourth setup out. All four operations were finished successfully and after four weeks no complications were reported. In spite of the challenges in NOTES transvaginal cholecystectomy, this research proved safeness and feasibility. There are still requirements that must be improved before this method is accepted without any rejection. In a study made in German speaking countries, 70 % of the gynecology departments described transvaginal NOTES as an ethical procedure and the rest defined it as experimental method [2]. Moreover, it is also necessary to analyze the women´s perception regarding the procedure, since if the methodology solves all the barriers, they will have the final decision in the execution of the process. Carrie et al. [18], illustrated data about women´s impression in

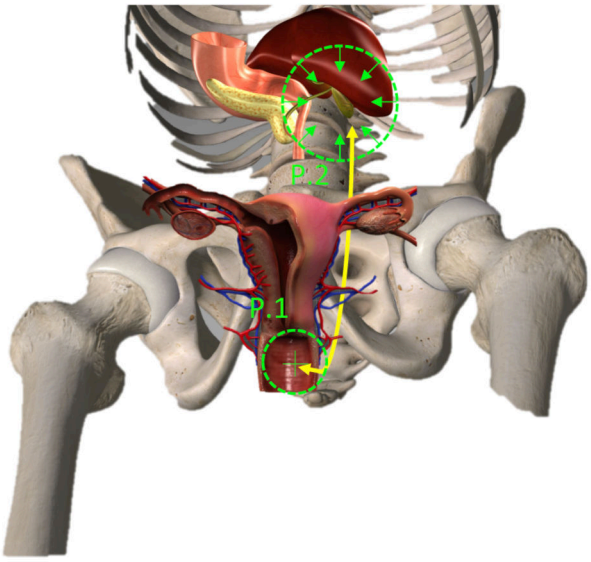


Figure 1. Transvaginal Cholecystectomy places[1].

[1] 3D4Medical and Human Female Reproductive System,

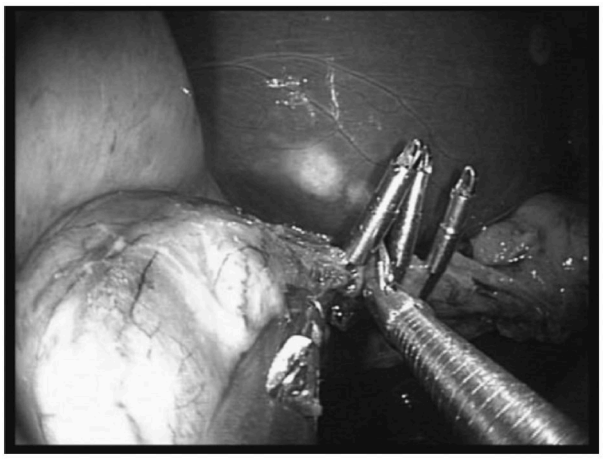


Figure 2. Cutting of the cystic duct in a cholecystectomy [2].

NOTES transvaginal procedures. The analysis included 100 women between 18 and 79 years old. They declared that if the transvaginal NOTES and the laparoscopy were equivalent, 68% of them would prefer the NOTES approach. The main reasons for the surgery that were listed in the analysis were cosmetic features, probable hernias and reduction of pain. The investigation also showed several concerns related to infections, such as an impact of sexual life and fertility. It is possible to confirm that NOTES transvaginal is accepted and preferred by women.

3. NOTES BARRIERS

3.1 Main challenges

Even supposing that the complete medical guild accepts NOTES as proper surgery methodology, there are still several problems it faces and improvements that need to be made. The American Society of Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Surgeons (SAGES) have defined 12 parameters as the most potential challenges in the future [13]. These barriers were deeply discussed by surgeons and endoscopists, and they are listed in the table 3. Moreover, Keller [12] infers three crucial obstacles regarding access problems, ergonomics and training. He stated in transgastric passage the surgeon could injure blood vessels or organs when perfoming the entry incision. Meanwhile, the long male urethra represents a complicated work challenge. After colpotomy in transvaginal NOTES, there are risks of injuries in the rectum, ureters, colon and bladder. In addition, there are not any proper tools to insufflate the peritoneal cavity (pneumoperitoneum) and there is no appropriate manipulation of the gallbladder [2]. In addition, there is not proper evidence that clarifies if pneumoperitoneoum will behave in the same manner than in Laparoscopy [3]. In transrectal approach, the biggest problem would be closure leak that would have catastrophic results. Furthermore, Keller [12] mentions ergonomics problems that hamper manipulation, visualization and independent performance of tasks. As regards training, training platforms must be created to simulate the exact procedures including visualization and manipulation sequences to guarantee success in human models.

As far as potential barriers are concerned, ASGE and SAGES describe how each challenge affects the use of NOTES [13] and it will be described as follows. In the access the peritoneal cavity there are not unique standards in the manner of creating and locating the access point. There is a bigger problem in the gastric closure since it cannot be even a 1 % leak. NOTES must be 100 % comparable with MIS in terms of success; therefore, the closure must be perfectly done. As the endoscopic tools are introduced through natural ducts, there is always the risk of moving bacteria inside the peritoneal cavity. Nevertheless, the

Table 3. Potential barriers to clinical practice [13]

Access to the peritoneal cavity
Gastric (intestinal) closure
Prevention of infection
Development of suturing device
Development of anastomotic (nonsuturing device)
Spatial orientation
Development of a multitasking platform to accomplish procedures
Control of intraperitoneal hemorrhages
Management of iatrogenic intraperitoneal complications
Physiological untoward events
Compression syndromes
Training other providers

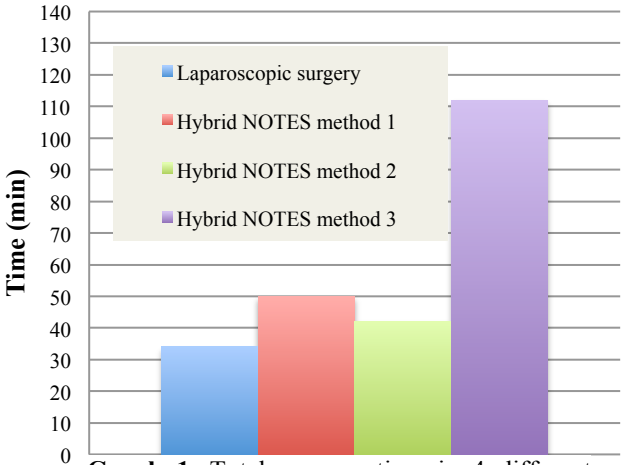
stomach and the devices are sterilized and the patient is provided with prophylactic antibiotics to avoid infections. There should be more research about bacteriological impact though. Companies also need to develop capable suturing devices since the technic cannot depend on the surgeon´s skills, the suture must be proper independently the experience. That is why, the use of new innovative methods as laser welding, biologic glues or anastomic devices should be included. Related to the spatial orientation, the fact that the camera is located in the same direction of the endoscopic tools would be a problem in advance procedures. To confront the situation, visualization systems, stabilization, inversion of the image and multiple cameras in the endoscopic tools are proposed. Besides, manual control of the endoscope when working with tissue as grasping or cutting tasks might be a problem. Consequently, the inclusion of multitasking platforms will improve the performance of the endoscope. Another large complication involves the unexpected injuries during NOTES. It was agreed that before new suturing devices are created, surgeons and gastroenterologists must assist and be prepared for any situation during the procedure. Also, new complications will appear in NOTES and they must be reported to create a detailed registration that can be helpful in future operations.

3.2 Traditional surgery, laparoscopy and NOTES

The evolution from traditional surgery to MIS has notoriously enhanced surgery procedures not only because of the reduction of undesired scares, but also because of the decrease in post-surgery infections and excessive trauma. Additionally, the fast recovery has brought satisfaction and benefits in medical systems, companies and finally in patients. This can be translated into less time in the hospitals and faster introduction in the daily life. Laparoscopy, for instance, is commonly used to examine organs like appendix, gallbladder, liver, etc., and also to make resectioning processes such as cholecystectomy, nephrectomy, splenectomy, etc. easier. With the rise of NOTES, there are several doubts with respect to the real advantages compared to traditional surgery and MIS. The main differences between such procedures are proposed by Kobiela et al. [3], and listed in the table 4. The principal variables analyzed were the facility to perform the procedures, inflammation, pain levels, infections, and physical consequences. It can be seen that as far as NOTES is included in surgery, procedures become less invasive with the same positive results. As it was mentioned before, there are not any standard procedures when performing hybrid NOTES, however. This fact impedes the possibility of finding proper differences between laparoscopy, hybrid and true NOTES from a surgical methodological point of view. In view of this problem, studies have been made in order to understand the disadvantages and possible advances. Chellali et al. [6] studied the complexity level form laparoscopic method to hybrid NOTES. In the study, information is collected from multiple procedures made in laparoscopy and hybrid NOTES cholecystectomy. Subsequently, the information is categorized into laparoscopy and three different hybrid NOTES procedures. The information is then organized and divided in chronological sequence steps by using hierarchical task analysis. In laparoscopy four abdominal ports were used, an umbilicus access to locate the laparoscope and three ports to perform the cholecystectomy. The steps in the surgery are:

1. Location of gallbladder.
2. Dissection of tissue surrounding the cystic duct and cystic artery.
3. Enforcement of clip closure.
4. Cutting by using laparoscopic scissors.
5. Extraction of the gallbladder through one of the abdominal ports.

Respecting the hybrids NOTES, the differences showed that in the first method, a rigid endoscope



Graph 1. Total average time in 4 different cholecystectomies. [6]

Table 4. Comparison of some aspects connected with the kind of surgical method [3].

Feature	Classic open surgery	Laparoscopic surgery	NOTES
Ease of access to operative field	Large skin incision assures a good access	Difficult but possible in experienced hands	Cumbersome, no specialists in this area
Inflammatory factors level	Significant growth (from tissue trauma)	Minimal growth (minor trauma)	Minimal growth (minimal trauma)
Pain level	High, depended on the trauma expanse	Moderate, passes in short term	Low, minimal trauma to the tissues
Frequency of the infection	Relatively often, wound infection, peritonitis	Less frequent because of the smaller skin incisions	Lack of skin incisions—rare cases of internal infection
Time of recovery	Weeks (depended on the range of surgery)	Several days	A few days
Cosmetic effects	Unsatisfactory; ugly, large scar	4–5 small scars, less visible; good effect	No scars perfect effect
Psychological aspects	Patient not satisfied of his look	Patient quite satisfied of his look	Patient very satisfied of his look

was used and the resection was made with laparoscopic tools. In the second hybrid, a flexible endoscope was included and the removal of the gallbladder was also performed with laparoscopic tools. In the third task, however, a flexible endoscope was also used, but the resection was accomplished by using endoscopic tools. In the three hybrids the specimen was extracted transvaginally. The study displayed positive and negative results. From laparoscopy to hybrid 1, hybrid 2 and hybrid 3, there is a trauma decrease since abdominal incisions are reduced. From the technical method perspective there is an increase in time due to the addition of sub-steps when moving from hybrid 1 to hybrid 3. In the graph 1 [6] shows the difference in the total average time for the four procedures. In the research two reasons for the increase of time were determined. The first is the lack of experience in the performance of the procedure and the second is the lack of proper instruments for resection. Consequently, one of the biggest challenges in NOTES will be to create endoscopic tools that fulfill the required degrees of freedom to perform surgeries comfortably and successfully [3].

4. Outlooks and developments

So as to find out applicable solutions to the current problems in NOTES, different groups around the world are constantly working in the development of technics and devices. As follows it will be presented some of these methodologies and innovative tools.

4.1 Augmented reality guidance

As it was in illustrated in table 3, spatial orientation is one of the biggest problems in NOTES. Contrary to laparoscopy procedures, the endoscope tip does not provide a comfortable view inside the patient. As a result, it exists the possibility to generate internal vessel injuries that can produce hemorrhages. In response to this problem, several methodologies have been proposed including augmented reality guidance [14-15-16]. The inclusion of the Image Registration provides potential solutions in NOTES. Vosburgh [14], shows how the use of image registration speeds up and facilitates the performance of laparoscopic and endoscopic devices. By using tracking sensors and a software slicer, computer tomography images and ultrasound data are integrated into augmented reality images that help the surgeon view and understand the patient's organs. This reduces the possibility of injuring arteries when performing the access incisions during NOTES procedures [14]. Further studies in Germany are in development in order to enhance surgeries by using augmented reality guidance [15-16]. By using intraoperative imaging, functional imaging and advanced visualization methodologies, surgeons can see internal structures of the body prior to surgery [16].

This information could be convenient in NOTES since it gives a complete map of the internal organs that helps the surgeon to puncture transgastric, transrectal, transvesical and transvaginal passages without making undesired dissections. The problem regarding the loss of view would also be compensated.

4.2 Developments and tools

One of the biggest challenges that engineers are facing is the inappropriate endoscopic tools used in it. These instruments are designed for obtaining biopsies, visualization or hemostasis problems. Nonetheless, they are not designed for retraction, suturing or resection functions required in NOTES [11]. For this reason, special devices must be created to fulfill these demands. A flexible endoscope compatible with MRI was tested in a phantom and showed potential [19]. By using gradient fields of the MRI and a micro tracking sensor, it showed successful compatibility when activating its 6 degrees of freedom through the path. These types of endoscopes would be used in the future to improve the lack of spatial orientation and help the surgeon to maneuver the device. Hattor et al. [19], described the manipulation of a robotic endoscope located in Thailand by using a surgery tele-control system in Japan. The surgeon in Thailand was responsible for the location of the endoscope and the surgeon form Japan controlled all the robots movements. A cadaveric model was used and by using two forceps, the endoscope was able to grasp, make incision and place clips. These types of developments would give the future possibility in NOTES to perform accurate procedures in medical centers without control robotic technology. It means, that the problem of unsuitable tools would be partially solved. Procedures would include participation of multiple medical centers separated by significant distance.

The limitations of the endoscopic equipment will define the future of NOTES procedures. By using the traditional endoscopic tools, surgeons have an extra limitation that does not occur in laparoscopy [12]. In consequence, companies are working to design and manufacture tools that match necessities as the EndoSAMURAI robot. In the surgery department of the University of British Columbia, the performance of the EndoSAMURAI robot with

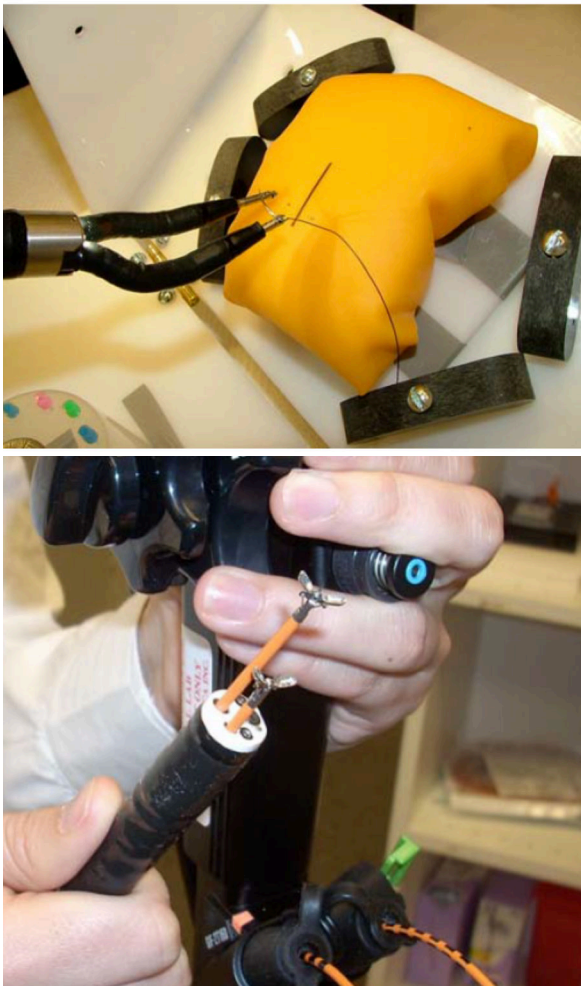


Figure 3. EndoSAMURAI (superior) and dual channel endoscope (inferior) [17].

a standard dual channel endoscope was compered [17]. The dual channel endoscope consists in a two forceps device design for gastrointestinal tasks. The EndoSAMURAI from the company Olympus however, is a device design for NOTES and it is able to control two arms similarly to laparoscopic tools. Both instruments can be shown in the figure 3 [17]. This research illustrated the capabilities of EndoSAMURAI over the dual endoscope by performing a binomial coordination task and a surgical suture. In the first task, the EndoSAMURAI took 304 ± 125 s and the dual channel endoscope 867 ± 312 s. In the second task, the EndoSAMURAI in experts' hands took 275 ± 35 s approximately, contrary to the other device, with which no one could complete the task. This clearly shows how the development of NOTES procedures is affected by the effectiveness of endoscopic devices. New innovative devices that

are comparable with laparoscopic tools would bring the possibility of performing new processes and will evolve future surgery methodologies.

5. Discussion and conclusion

The application of NOTES in future depends on several aspects as it was discussed before. Even though complete NOTES procedures have been safely demonstrated in human beings [2], there is still research left. The possibility of using endoscopic robotic technologies would open new solutions to current barriers. Additionally, other technologies that are nowadays used may be included in order to provide better visualization. One possibility would be to include real time images to support the visualization when manipulating the endoscope inside the patient. Interventional angiography systems would be used in surgery if we add a control platform outside to manipulate the endoscopic robot as it can be seen in figure 4. Additional augmented reality images could be combined with X-ray images to make easier the perception of the space inside the peritoneal cavity. There is also another problem that has not been usually mentioned, the relationship between cost and benefits. There are clear improvements when reducing trauma in surgery; it does not mean however, that medical centers will be willing to invest in such technologies. Robots like endoSAMURAI offer good solution but also bring higher costs and specialized training that are not needed in laparoscopy. As a result, pure mechanical devices that decrease cost and bring comparable solutions than laparoscopy should be analyzed. An example is the device "FLEXDEX" design for laparoscopic procedures. It uses the movement of the surgeon's hand to create the same movements in the tip of the tool, which is showed in figure 5[2]. The biggest advantage of this device is that it uses only mechanical transmission mechanisms. Consequently, it is intuitive, the use of electronics is not required and the price is reduced. In this direction, same fundaments might be used to design endoscopic tools with low costs. To conclude, it was shown that by using different entering natural passages, NOTES would be applied in several surgeries. Indeed, there are still several troubles that must be solved but there are also considerable research groups and companies that are working on future solutions.

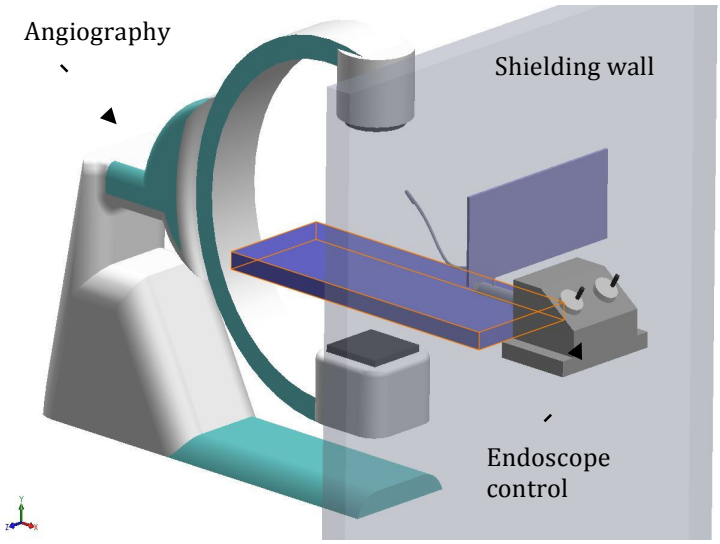


Figure 4. Possible configuration of angiography with robotic endoscopes

Figure 5. FLEXDEX device for laparoscopy[2].

[2] FlexDex Inc, http://www.flexdexsurgical.com

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NEURO ANEURYSMS- DIAGNOSIS AND THERAPY NOW AND IN THE FUTURE

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" The therapies concerning cerebral aneurysms have expeditiously evolved from developing technologies into leading edge therapies utilizing sophisticated diagnosis and minimally invasive devices for the treatment of intricate cerebrovascular lesions. Evolutions in the treatment of patients with aneurysmal subarachnoid hemorrhage with the advent of new diagnostic and therapeutic modalities and devices has been witnessed with the metamorphosis of the technology. "

INTRODUCTION

- Neuro-Aneurysm is an abnormal focal dilation of an artery in the form of a protrusion bulging or sac caused by a weak spot in the vessel wall that balloons out over time.
- Aneurysms may rupture, causing bleeding in the brain structures, which is termed as subarachnoid hemorrhage (SAH) and can lead to a stroke, coma, and/or death.
- Brain aneurysms may form due to inherited tendencies for weak blood vessels, severe head trauma, infection, smoking and high blood pressure.

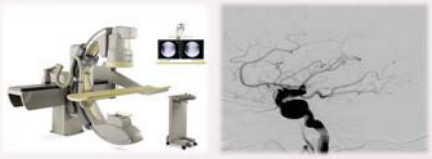
Colored Angiogram of cerebral aneurysm

METHODS

DIAGNOSIS

Diagnostic tests can be used to detect if an aneurysm has or will rupture, and are usually required after a subarachnoid hemorrhage to confirm the presence of an aneurysm.

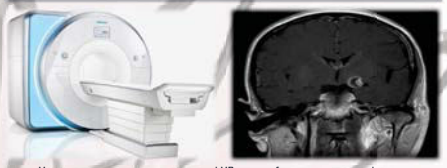
Catheter Angiography and Intra Arterial Digital Subtraction



Digital subtraction angiography setup and DSA image of cerebral aneurysm

- Uses fluoroscopic techniques to visualize blood vessels.
- Images are produced using contrast medium by subtracting a pre-contrast image from later images with time controlled x-rays while injecting contrast medium.
- Access to the blood vessels is gained via the femoral artery using a system of guide wires and catheters.
- Minimally invasive procedure.

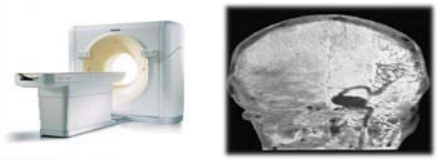
Magnetic Resonance Imaging/Angiography



Magnetic resonance imaging setup and MRi image of aneurysm in carotid artery

- Uses a powerful magnetic field (electromagnetic waves) and a computer to evaluate blood vessels and abnormalities.
- Magnetic resonance signal is generated as the magnetic pulse aligns all the protons in a certain area measuring the amount of time (T1 & T2 relaxation) it takes for those protons to return to their pre-magnetized state.
- May require an injection of a contrast material (gadolinium).

Computed Tomography Angiography



Computed tomography angiography setup and CTA image of aneurysm

- Computer-processed combinations of many X-ray images.
- CT angiography is a thin-section volumetric spiral (helical) CT examination performed with a time-optimized bolus of contrast medium in order to enhance the cerebral arteries.
- The rate and intensity of enhancement of the lumen of interest are then used to create a time density curve and peak of the curve is used to calculate the scanning delay post injection.

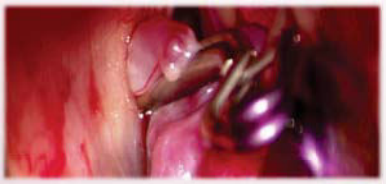
TREATMENT OF NEURO ANEURYSMS

The operative treatment falls into two main categories i.e. Microsurgical treatments and Endovascular techniques.

Microsurgical Treatments

Minimally invasive tools: Surgical clips & clip applicators

- Surgical management is an efficient procedure and involves placement of surgical clip across the neck of the aneurysm.
- Use of high magnification microscope with integrated near infrared indocyanide green videoangiography (ICG-VA) providing real-time data of the vessels and aneurysm sacs.
- To achieve a complete and permanent exclusion of the aneurysm from the circulation.
- Preserves the parent artery and possible perforating arising from the parent vessel.



Surgical clipping of aneurysm

Endovascular Treatments

The purpose of endovascular aneurysm therapy is to exclude the aneurysm from the circulation either by endosaccular occlusion or by flow diversion and parent vessel reconstruction.

Balloon-assisted embolization

Minimally invasive tools: Surgical clips & clip applicators

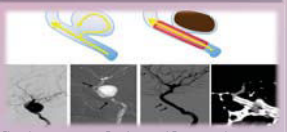
Involves occlusion of wide necked cerebral aneurysms by temporarily inflating a non-detachable balloon in front of the aneurysm neck to avoid inadvertent coil protrusion into the parent artery. Balloon microcatheters shows excellent navigability, ease of retrieval, repeated inflation/deflation of the balloons.

Coil embolization

Endovascular coil embolization and DSA image of coiling

Involves advancing a microcatheter into the aneurysm sac and occlusion with detachable platinum coils of various sizes and shapes. A small needle stick is passed into the femoral artery similar to an in an angiography suite. The coils fill the aneurysm sack, promote thrombosis and exclude the aneurysm from the arterial circulation.

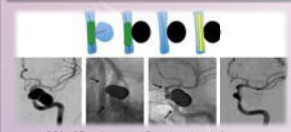
Stand-alone stents: flow diversion



Flow diversion stents: Pre, Intra and Post procedure images

Involves reconstruction by redirecting the blood using stents. Trigger's a set of hemodynamic changes that induce contrast ectasia in the sac and thrombosis of the aneurysm. High metal to surface coverage induces stronger turbulence, flow reduction, reducing vorticity, shear stress and minimizes the water hammer effect.

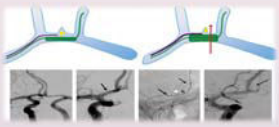
Embolization by liquid embolic agent



DSA of Pre, Intra and Post liquid embolization

Uses a non-adhesive high-viscosity liquid agent (Onyx ev3 Neurovascular, CA, USA) made up of biocompatible ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide (DMSO). Onyx precipitates and solidifies within 10 min post injection and fills the sac. It involves placement of a remodelling balloon covering the aneurysm neck.

Extrasaccural embolization



Extrasaccular embolization & DSA image of the process

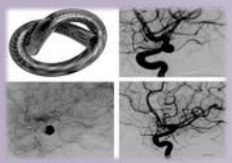
Endovascular coil embolization involves stabilization of the microcatheter in the microaneurysm neck using a remodelling balloon, deploying the coil outside the sac and introducing it by inflating the balloon. This procedure prevents the microcatheter from invading the sac, and minimizes the risk of rupture.

CONCLUSION, RECOMMENDATIONS AND FUTURE PORSPECTIVES

CONCLUSION & RECOMMENDATIONS

- Continuous development of new techniques and materials has offered a significantly wider range of therapeutic possibilities.
- Constant upgradation of methods & procedures is required.
- Suggestive approach towards parent vessel reconstruction:
  - Implantation of Pipeline Embolization Device (PED).
  - Parent vessel configuration, flow redirection & remodelling.

Bioactive coils (Bare coils, Matrix coils, hydro coils)



Pipeline Embolization device: Pre & Post procedure

FUTURE

- Mechanically optimized biologically activated coils.
- Bioactive intraaneurysmal implants.
- Non-metallic materials (e.g., polymers, fibers e.t.c.).
- Pipeline Embolization Device (PED).

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NEURO-ANEURYSMA -DIAGNOSIS AND THERAPY NOW AND IN THE FUTURE

SCIENTIFIC DOCUMENTATION

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December 2015,
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ABSTRACT

The therapies concerning cerebral aneurysms have expeditiously evolved from developing technologies into leading edge therapies utilizing sophisticated diagnosis and minimally invasive devices for the treatment of intricate cerebrovascular lesions. Evolutions in the treatment of patients with aneurysmal subarachnoid hemorrhage with the advent of new diagnostic and therapeutic modalities and devices has been discussed with the metamorphosis from embolization coils, to balloon-assisted embolization, to intracranial stents for assistance in coil embolization, to standalone stents. A review on established devices, currently available treatments, and finally emerging technologies with future perspectives and recommendations are discussed.

KEYWORDS

Aneurysm, Endovascular, Embolization.

ABBREVIATIONS

SAH Subarachnoid Hemorrhage, **CT** Computed Tomography, **MRA** Magnetic Resonance Angiography, **CTA** Computed Tomography Angiography.

1. INTRODUCTION

Neuro-Aneurysma also called cerebral or intracranial aneurysm, is an abnormal focal dilation of an artery in the form of a protrusion bulging or sac caused by a weak spot in the vessel wall that balloons out over time. Cerebral aneurysms have thin, weak walls and a tendency to rupture, causing bleeding into and around vital brain structures. The resultant bleeding into the space around the brain is called a subarachnoid hemorrhage (SAH). This kind of hemorrhage can lead to a stroke, coma, and/ or death.

Subarachnoid hemorrhage (SAH) is often a devastating event with approximately 10 percent of patients dying prior to reaching the hospital while only one-third will have a good result after treatment.[1] Aneurysmal SAH is associated with a high morbidity and mortality. Mortality within the first 30 days approaches 50 percent and is attributed largely to the effects of initial and recurrent bleeding.[2] Medical management is based on the detection and treatment of cerebral and extracerebral complications of subarachnoid hemorrhage (SAH).

The prevalence of intracranial aneurysms by radiographic and autopsy series is 5 percent, or 10 to 15 million people in the United States alone with an incidence that affects as many as 30,000 individuals each year. Aneurysmal SAH occurs at an estimated rate of 3 to 25 per 100,000 Populations with approximately 20 to 30 percent of patients having multiple aneurysms.[1] Almost half of the survivors left are disabled even with modern methods of diagnosis and treatment. Poor outcomes related to subarachnoid hemorrhage (SAH) could theoretically be avoided by preventing the aneurysm rupture, which is the primary goal of aneurysm treatment. All of the treatment options are, however, associated with procedural risks and only a minority of the asymptomatic aneurysms will eventually rupture and cause SAH. The risks associated with potential treatment methods should therefore be carefully evaluated and weighed against the estimated risk of aneurysm rupture prior to initiating aneurysm therapy.

Increasing data suggest that early aneurysm repair, together with aggressive management of complications is leading to improved functional outcomes. These improvements underscore the need to continually reassess which interventions provide the greatest benefit to patients.

2. LITERATURE REVIEW

2.1 OVERVIEW ON NEURO-ANEURYSMA

A brain/neuro aneurysm is a bulge or ballooning inside a blood vessel in the brain. It often looks like a berry

hanging on a stem. A brain aneurysm can leak or rupture, causing bleeding into the brain (hemorrhagic stroke). Most often a ruptured brain aneurysm occurs in the space between the brain and the thin tissues covering the brain. This type of hemorrhagic stroke is called a subarachnoid hemorrhage (SAH). A ruptured aneurysm may become life threatening and requires prompt medical treatment. Most brain aneurysms, however, do not rupture, create health problems or cause symptoms. Such aneurysms are often detected during tests for other conditions.

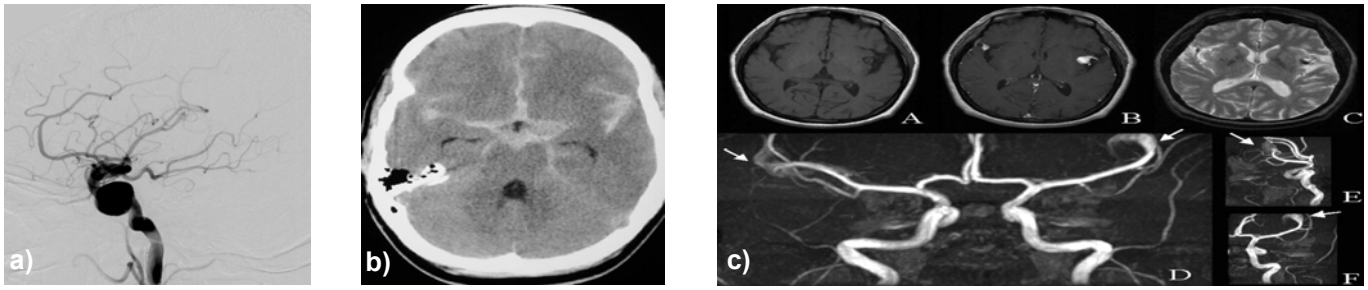

Fig: 1 a) DSA image: Aneurysm of the right internal carotid artery. b) CT image of a subarachnoid hemorrhage. c) MRI images of the areas of the left and right middle cerebral arteries with magnetic resonance angiography images of the circle of willis.[22]

2.1.1 Causes of Neuro-Aneurysms

Brain aneurysms form silently. There may be inherited tendencies for weak blood vessels which may lead to development of aneurysms. However, aneurysms in children are rare, and most aneurysms probably develop from wear and tear on the arteries during life. On occasion, severe head trauma or infection may lead to development of an aneurysm. There are a number of possible risk factors that contribute to the formation of aneurysms which include smoking and high blood pressure.

2.1.2 Epidemiology and risk factors

The epidemiology of cerebral aneurysms differs to some extent from the epidemiology of aneurysmal SAH since most of the intracranial aneurysms never rupture and the annual risk of aneurysm rupture may be as low as 0.05 % in some aneurysms.[3] The estimated prevalence of cerebral aneurysms varies considerably according to study design, study population, and aneurysm characteristics. Combining the data of autopsy and radiological studies, the prevalence of intracranial aneurysms is around 2 % (0.2–9 %) for adults without specific risk factors.[3,4,5]

2.1.3 Classification

Cerebral aneurysms are classified both by size and shape. Small aneurysms have a diameter of less than 15 mm. Larger aneurysms include those classified as large (15 to 25 mm), giant (25 to 50 mm), and super-giant (Over 50 mm).[6]

Saccular aneurysms, also known as berry aneurysms, appear as a round outpouching and are the most common form of cerebral aneurysm.[7] Fusiform dolichoectatic aneurysms represent a widening of a segment of an artery around the entire blood vessel, rather than just arising from a side of an artery's wall and can rupture but usually do not. Microaneurysms, also known as Charcot-Bouchard aneurysms, typically occur in small blood vessels (less than 300 µm diameter), most often the lenticulostriate vessels of the basal ganglia, and are associated with chronic hypertension.[8]

2.2 DIAGNOSIS

There are a number of factors to be considered for finding the best treatment options for brain aneurysm. Diagnostic tests can be used to detect if an aneurysm has or will rupture, and are usually required after a subarachnoid hemorrhage to confirm the presence of an aneurysm. Imaging tests such as magnetic resonance imaging (MRI), computed tomography (CT), cerebral angiogram magnetic resonance angiography (MRA) or computed tomography angiography (CTA) etc. may be used to detect the size, shape and location of the aneurysm.

2.2.1 Warning Signs and Symptoms

Unruptured brain aneurysms are typically completely asymptomatic. However, large unruptured aneurysms can occasionally press on the brain or the nerves stemming out of the brain and may result in various neurological symptoms like localized headache, dilated pupils, cranial neuropathie, chronic symptomatology, blurred or double vision, ischemia, difficulty speaking etc.

2.2.2 Computed Tomography and CT-Angiography

The cornerstone of SAH diagnosis is the noncontrast head CT scan.[9] Clot is demonstrated in the subarachnoid space in 92 percent of cases if the scan is performed within 24 hours of the bleed.[9] Intracerebral extension is present in 20 to 40 percent of patients and intraventricular and subdural blood may be seen in 15 to 35 and 2 to 5 percent, respectively. The head CT scan should be performed with thin cuts through the base of the brain to increase the sensitivity to small amounts of blood. A CT will show if there has been bleeding in the brain. However, a basic CT scan does not usually show the cause of the bleeding. If a contrast dye is injected into a blood vessel, the brain blood vessels will be highlighted and aneurysms can be seen using special imaging techniques. This technique is called a CTA (computerized tomographic angiography).

CT angiography is a fast thin-section volumetric spiral (helical) CT examination performed with a time-optimized bolus of contrast medium in order to enhance the cerebral arteries. In order to visualize the intracranial arteries, the examination includes the region from the first vertebral body up to the vertex. For enhancement of intracranial arteries a contrast medium, that possesses radiopaque properties, is injected intraven ously via a catheter through a small incision in the skin. Intravenous injection of a small test bolus (eg., 10 to 15 ml) of contrast medium at

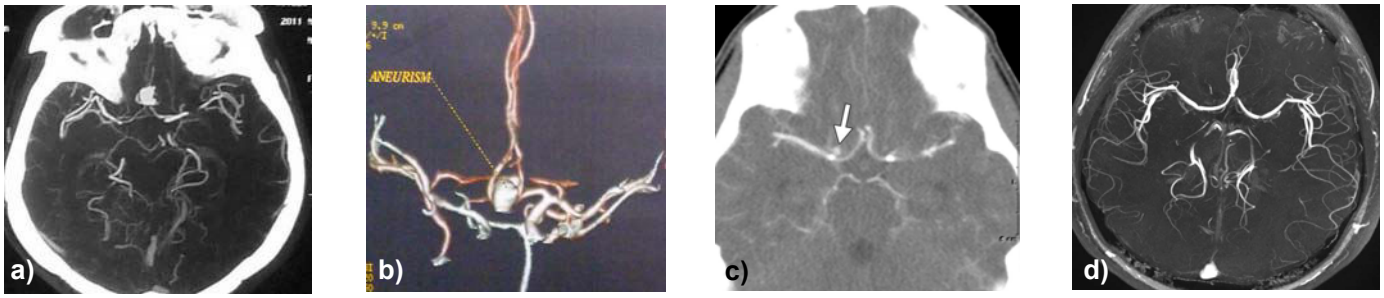

Fig: 2 a) CT angiogram illustrating a focal outpouching at the anterior communicating artery consistent with an intracranial aneurysm. b) 3D volume reformat of CTA shows an anterior communicating aneurysm. c) Normal CT image of aneurysm. d) Time of Flight MRA shows the circle of Willis.[23]

the same rate and through the same access is used for the CTA followed by acquisition of sequential cine CT images at the level of the artery or vein of interest. The rate and intensity of enhancement of the lumen of interest are then used to create a time density curve and peak of the curve is used to calculate the scanning delay post injection. The use of automated or semi-automated triggering software can be carried out based on monitoring of the attenuation within the vessel of interest by the CT scanner following initiation of the full dose of contrast media injection. The CTA is automatically started when the enhancement in the vessel reaches a predetermined operator selected level. For CTV, administration of nonionic contrast medium (iodine, 300 to 370 mg/mL) at a rate of 3 mL sec with a 40 to 50 second prescanning delay, or a 30 second delay after the arterial bolus time, allows adequate opacification of the venous structures minimizing flow artifacts.

Besides the advantages like faster imaging and processing time, increased quality of source images and visibility of aneurysms that are not seen in standard DSA, there are certain limitations to it. When performing CT angiography for the detection and therapy planning of intracranial aneurysms, knowledge about several potential pitfalls is essential. The through-plane resolution requirements causes small perforating arteries with a diameter below 0.5 mm are not visible on CT angiograms.[10] It is often difficult or even impossible to differentiate the infundibular dilatation of the origin of an artery from an aneurysm, which can lead to false-positive results. The time that elapses between the arterial and the venous phase of a contrast material bolus flowing through the intracranial circulation is about 5-6 seconds. Therefore, even with four-row multisection scanners, it is not possible to produce pure arterial phase CT angiography. Thus, the depiction of venous structures cannot be avoided, and when they appear adjacent to arteries they can sometimes be mistaken for aneurysms. Patients with clipped aneurysms represent a specific problem. Beam hardening artifacts produced by the aneurysm clips preclude a clear depiction of nearby intracranial arteries depending on which material the clips are made of.[10] Therefore, CT angiography is of minor value for the postoperative follow-up of patients after aneurysm surgery in most cases. When CT angiography is used for this purpose, it is mandatory to carefully inspect the source images prior to visualization to check for the occurrence of artifacts around the clip.

2.2.3 Magnetic Resonance Angiography

MR angiography (MRA) uses a powerful magnetic field, in the form of electromagnetic waves and a computer to evaluate blood vessels and help identify abnormalities. This exam does not use ionizing radiation and may require an injection of a contrast material called gadolinium. MRA imaging technique uses the signal dependencies on the magnetic properties of the area being imaged, as the magnetic pulse aligns all the protons in a certain area measuring the amount of time it takes for those protons to return to their pre-magnetized state, generates a magnetic resonance signal. With a moving substance, such as blood, the protons aligned during the magnetic pulse move out of the area being imaged and non-magnetized protons take their place. This creates a signal void, which is seen as areas of hypointensity hence contrast agents like gadolinium is used. Flow-dependent angiography is based on blood flow imaging methods that uses time-of-flight MRA (TOF MRA), which exploits that moving spins of the blood experience fewer excitation pulses than static tissue and phase-contrast MRA (PC-MRA) method which utilizes phase differences to distinguish blood from static tissue. Flow-independent angiographic techniques do not rely on flow, but are instead based on the differences of T1, T2 and chemical shift of the different tissues of the voxel. One of the main advantages of this kind of techniques is that we may image the regions of slow flow often found in patients with vascular diseases more easily. Contrast-enhanced magnetic resonance angiography uses injection

of MRI contrast to perform MRA. The contrast medium is injected into a vein, and images are acquired both pre-contrast and during the first pass of the agent through the arteries. By subtraction of these two acquisitions in post-processing, an image is obtained which in principle only shows blood vessels, and not the surrounding tissue. Subtractionless contrast-enhanced magnetic resonance angiography differs from standard subtraction MRA, as it is able to create high quality contrast-enhanced MRA images without subtraction of a non-contrast enhanced mask image. This approach has been shown to improve diagnostic quality,[11] because it prevents motion subtraction artifacts as well as an increase of image background noise, both direct results of the image subtraction.

Its main advantage when compared to CT angiography is that the bone does not disturb the images. The reported sensitivity of MR angiography for the detection of intracranial aneurysms is comparable to that of CT angiography for aneurysms with a diameter greater than 3 mm but is significantly lower for smaller aneurysms.[12] MRA may be influenced by motion artifacts, due to the long acquisition time, making the evaluation quite challenging. This effect is exacerbated if a long field of view needs to be covered. Turbulent flow may also result in signal loss, thus degrading image quality, particularly in large-sized aneurysms. Small-sized aneurysms may not be clearly identified on MRA, particularly if they are located near the skull base or if obscured by motion artifacts.

2.2.4 Catheter Angiography and Intra Arterial Digital Subtraction Angiography

Catheter angiography and intra arterial digital subtraction angiography make use of similar fluoroscopic techniques used in interventional radiology to clearly visualize blood vessels in a bony or dense soft tissue environment. Images are produced using contrast medium by subtracting a pre-contrast image or the mask from later images, once the contrast medium has been introduced with time-controlled x-rays while injecting contrast medium. Access to the blood vessels is gained most commonly through the femoral artery using a system of guide wires and catheters. Catheter-based angiography is not a good initial test for screening as the small risk of this procedure does not justify its use when MRA and CTA are effective in this role. Patients with impaired kidney function, especially those who also have diabetes, are not good candidates for this procedure. Patients with allergic reactions to x-ray contrast materials are at risk of having a reaction to materials that contain iodine.

2.3 TREATMENT OF NEURAL-ANEURYSMS

The treatment of ruptured aneurysms is well grounded for ruptured aneurysm hemorrhage within the first month after SAH. The management of unruptured neural aneurysms is, however, still much more controversial because of incomplete and conflicting data about the natural history of these lesions and the risks associated with their treatment. Many factors (i.e. the location, size, and morphology of the aneurysm as well as the method and often age-specific risks of different treatment modalities) should be evaluated for each patient before initiating any treatment regimen for patients with unruptured cerebral aneurysms. The operative treatment of intracranial aneurysms falls into two main categories, mainly categorized into microsurgical treatments and endovascular techniques.

2.3.1 Microsurgical treatments

Surgical management of cerebral aneurysms is an effective and safe procedure with the evolution of microsurgical techniques. Placement of a clip across the neck of the aneurysm remains the treatment of choice for most aneurysms. Microsurgical operations are performed with the aid of a high magnification microscope, preferably with integrated near infrared indocyanide green videoangiography (ICG-VA) which provides real-time information about the patency of branching vessels and about the aneurysm sac.[13] The goal of microsurgical aneurysm treatment is to achieve complete and permanent exclusion of the aneurysm from the circulation while preserving the parent artery and possible perforating or branching vessels arising from the parent vessel. Pterional, lateral supraorbital, orbitozygomatic, or the interhemispheric approach is used to access aneurysms in the anterior circulation while pterional, lateral suboccipital or subtemporal approach may be used to access posterior circulation aneurysms. The dissection of the aneurysm as well as adjacent vessel branches may be facilitated by the use of temporary clips. Aneurysm clips come in all different shapes and sizes, and the choice of a particular clip is based on the size and location of an aneurysm. The clip has a spring mechanism which allows the two jaws of the clip to close around either side of the aneurysm, thus occluding (separating) the aneurysm from the parent (origin) blood vessel. In the ideal clipping, normal blood vessel anatomy is physically restored by excluding the aneurysm sac from the cerebral circulation.

Microsurgical clipping still represents an efficient treatment for unruptured aneurysms, especially in the presence of a wide neck or if an arterial branch originates from the aneurysm neck.[14] Surgery is the main option of treatment also for many small cerebral aneurysms which are often difficult to treat by endovascular coil embolization. In addition, the development of intracranial-intracranial bypasses is another important advancement

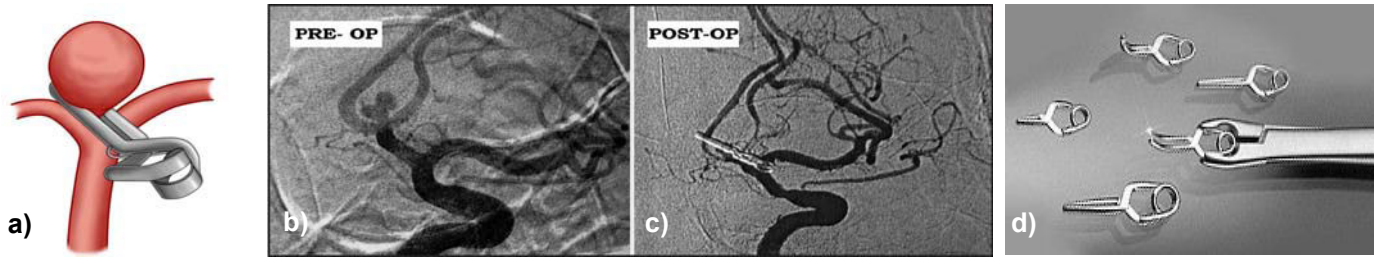

Fig: 3 a) Surgical clipping of cerebral aneurysm. b) The preoperative and postoperative cerebral angiograms of an aneurysmal clipping. c) Different surgical clip designs.[24]

that makes microsurgery a competitive option for the treatment of complex and recurrent cerebral aneurysms. [15] Technological advances (e.g. the development of endoscopic techniques, electrophysiological monitoring of the patient, the introduction of micro vascular Doppler ultrasonography, and the implementation of ICG-VA) have promoted surgical therapy in the same way as new techniques have revolutionized endovascular aneurysm therapy.

2.3.2 Endovascular treatments

The purpose of endovascular aneurysm therapy is to exclude the aneurysm from the circulation either by endosaccular occlusion or by flow diversion and parent vessel reconstruction. The endovascular approach to aneurysm occlusion has the theoretical advantage of avoiding craniotomy and brain manipulation, but is nevertheless associated with numerous challenges (risk of periprocedural aneurysm rupture, occurrence of arterial dissections, reactions to contrast material, and puncture site complications). Endovascular coiling emerged as an alternative to surgery in patients with intracranial aneurysms who were deemed poor surgical candidates due to significant neurologic injury, the presence of severe medical co-morbidities, or difficult surgical access to the aneurysm.

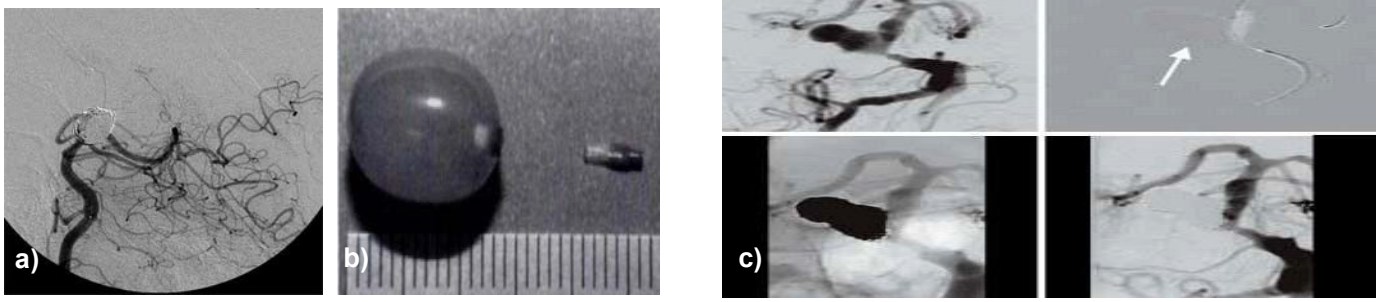

Fig: 4 a) Balloon-assisted technique with an angiogram in the posteroanterior projection performed from a right vertebral catheter position. b) Detachable balloon occlusion. c) Coil embolization with mass of the aneurysm, and its blood flow replaced with platinum microcoils.[1]

2.3.2.1 Coil embolization

In endovascular coil embolization, a microcatheter is advanced into the aneurysm sac and the aneurysm is occluded with very soft detachable platinum coils of various sizes and shapes. Aneurysm coiling is performed through a small needle stick in the femoral artery similar to an angiogram. The procedure is performed in an angiography suite which looks quite similar to an operating room, but has the capabilities for fluoroscopy (Continuous x-ray). Fluoroscopy provides a real-time map of the vessels and aneurysm to guide the catheters and coils into the correct positions. In order to coil the aneurysm, a microcatheter is guided into the aneurysm under fluoroscopy by way of the arteries in the neck (carotid and vertebral arteries). The soft platinum coils are positioned in the aneurysm until the aneurysm is filled with coils and then the catheters are removed. Multiple coils can be placed inside the aneurysm through the same catheter until the aneurysm is densely packed. The coils fill the aneurysm sack, promote thrombosis, and exclude the aneurysm from the arterial circulation, thus reducing the risk of rupture and rebleeding.

2.3.2.2 Balloon-assisted embolization

Endovascular treatment of wide-necked cerebral aneurysms is especially challenging since the coils used in the embolization may tend to protrude from the aneurysm sac into the parent artery. This involves technique to occlude wide necked cerebral aneurysms by temporarily inflating a nondetachable balloon in front of the aneurysm neck during each coil placement. This remodelling technique thus extends the spectrum of endovascularily treatable aneurysms without increasing the risk incurred by the treatment.

Detachable balloon occlusion may provide an alternative therapy for selected cases of direct or difficult aneurysms. The catheter tube is held inside the cylinder by a releasable retainer which permits atraumatic detachment of the catheter tube after placement of the balloon in a lesion. A seal means is installed inside the balloon for sealing the balloon after its placement and inflation. The releasable retainer permits atraumatic detachment by complete separation of the catheter tube from the balloon.

[1] Chiriac A, Baldof J, Dobrin N, Poeata I (2010) Embolic materials for cerebral endovascular therapy. Rom Neurosurg XVII 2:171–181

2.3.2.3 Coil embolization

Although coil protrusion into the parent artery may often be prevented with balloon-assisted remodelling technique, sometimes the introduced coil can prolapse into the parent artery immediately after balloon deflation, necessitating one or more attempts at coil repositioning. It is also possible that the introduction of a new embolization coil could displace a previously detached coil from the aneurysm sac into the parent vessel. Finally, very wide-necked aneurysms or fusiform/circumferential aneurysms oftentimes lack any neck structure at all, making coil placement, even with a balloon remodelling technique, very tenuous or impossible. Additional support or remodelling of the aneurysm neck is occasionally required which can be achieved by deploying a stent over the aneurysm neck before coiling. Stents are tubes made of wire mesh that is capable of expansion. The mesh is made of nitinol, a blend of nickel and titanium. When it is first inserted into a patient's artery, the stent is packed within a wrapper. After advancing the stent to the ideal position, the wrapper is drawn back and the mesh expands to fit snugly against the vessel's inner wall. The use of this type of devices would mean a conceptual advance in the management of cerebral aneurysm because it would enable the treatment of both the aneurysm and the underlying abnormality in the parent artery.[16] These devices are very flexible and navigable, and thus, can easily change their shape to conform to vascular morphology even in curved or very elongated segments. As a result, they are less traumatic, entail lower risk of artery dissection or rupture, and have broadened the indications for the treatment of aneurysms with unfavourable locations. Stents are made of nitinol, so they do not produce any artifacts on MR images. For this reason, MRI can be safely used for follow-up.[17]

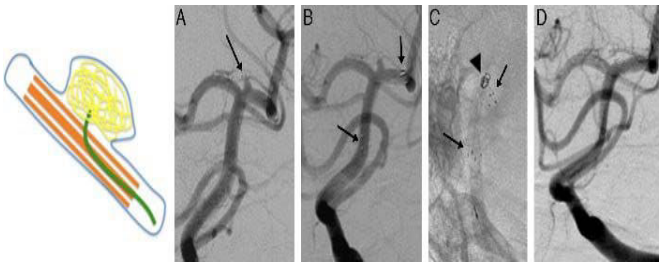

Fig: 5 Incidental wide-necked aneurysm under stent assisted embolization (A) Preoperative digital subtraction angiogram (DSA). (C) Angiography without subtraction in the working projection. (D) DSA at the end of the procedure with good angiographic outcome.[25]

The use of stent-assisted embolization in patients with ruptured aneurysms is controversial because the thrombogenic potential of stents makes it necessary to follow a strict antiplatelet regimen during and after the procedure. In spite of preventing thromboembolic events, antiplatelet agent administration in patients with subarachnoid hemorrhage increases the risk of serious hemorrhagic complications associated with relatively common circumstances in routine practice, such as aneurysm re-rupture, a need again for a surgery after the neuroendovascular procedure and aneurysm perforation during the procedure.

2.3.2.4 Stand-alone stents: flow diversion

Stents have proved to trigger a set of hemodynamic changes that induce contrast ectasia in the sac and thrombosis of the aneurysm, effects that would be influenced both by porosity (proportion of open area with respect to the total area of the stent) and by the geometry of the stent deployed.[18] This flow diversion effect is intensified with flow-diverting stents, which are specifically designed for the endovascular reconstruction of a segmentally diseased artery by redirecting the blood flow away from the aneurysm neck. Flow-diverting stents have dense mesh geometry and a very high metal to surface coverage which induces stronger turbulence and flow reduction than that induced by conventional intracranial stents, potentially inducing thrombosis in the aneurysm sac. The metal surface coverage of a conventional intracranial stent is usually around 10 %, while that of the flow diverting stents is ca. 35 % to 55 % depending on the stent size and parent vessel diameter. The flow diversion stents around aneurysm neck functions to disrupt the inflow jet, reducing vorticity and shear stress on the aneurysm wall and reducing the water hammer effect of chronic pulsatile blood flow on an intra-aneurysmal coil mass. The magnitude of this effect is affected primarily by the amount of metal surface area coverage provided by the stent. Pipeline embolization devices are specifically designed as stand-alone stents, that is, without any other embolization devices for aneurysmal sac filling.[19] These are self-expandable and

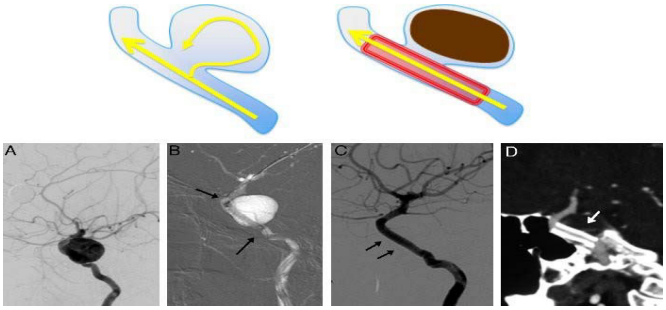

Fig: 6 Flow diversion stents (A) Initial digital subtraction angiogram (DSA). (B) Digital artery map shows the covered stent deployed in the ICA (arrows). (C) DSA after conclusion of the procedure. (D) Follow-up CT-angiogram six months after the procedure.[25]

flexible stents consisting of a mesh of braided microfilaments with significantly lower porosity than that of conventional stents. The special design of these stents promotes aneurysm thrombosis and theoretically permits blood flow through the branches or perforating arteries arising from the artery covered by the stent. Because of this profile, Pipeline and Silk stents are particularly useful for the treatment of aneurysms that are otherwise difficult to treat, such as microaneurysms and large, giant, fusiform or wide-necked aneurysms.[19]

2.3.2.5 Embolization with liquid embolic agent

A non-adhesive high-viscosity liquid embolic agent (Onyx ev3 Neurovascular, Irvine, CA, USA) has also been used to treat cerebral aneurysms. Onyx is a nonadhesive liquid embolic agent made of biocompatible ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO). When it comes into contact with an aqueous solution (blood in this case), Onyx precipitates and forms an initially soft cast, with a peripheral spongy outer layer and a semi-liquid centre. The material solidifies completely 10 min after injection.[20] Onyx embolization involves placement of a remodelling balloon covering the aneurysm neck. A sealing test before the procedure is required to determine whether the balloon is satisfactorily occluding the neck. The test involves the injection of contrast material into the sac while the balloon is inflated to check for absence of leakage to the parent artery or adjacent side branches; the test is then considered positive. Patients with negative sealing test should not be treated with Onyx.[20]

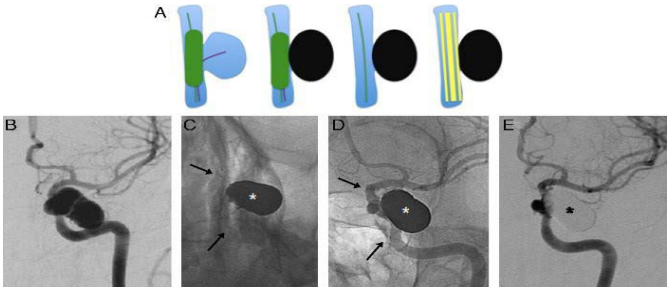

Fig: 7 (A) Onyx embolization requires a previous "sealing test", which involves inflation of a remodelling balloon in the parent artery. After confirming the absence of contrast agent leakage from the aneurysm, the Onyx embolization is performed. (B) Preoperative digital subtraction angiogram (DSA) in the anterior-posterior projection. (C) Angiogram without substraction in the working projection that demonstrates Onyx filling the sac (asterisk) and the stent. (D) Final follow-up angiography without subtraction demonstrates complete sealing of the sac (asterisk). (E) Follow-up DSA one year after the procedure confirms closure stability (asterisk).[25]

Onyx can induce durable aneurysm occlusion in patients with these types of aneurysms, which are always difficult to treat. In fact, other endovascular techniques yield worse results and surgery is associated with significant morbidity. Onyx provides full filling (100%) of the sac (coiling rarely provides a filling rate higher than 30%) and angiographic images with Onyx are more easily subtracted than coil images, which facilitates the treatment when part of the aneurysm overlaps the parent artery in the working projection. Another typical advantage of the Onyx treatment is that it has a lower recanalization rate compared with conventional embolization.

The major disadvantage of neuro aneurysm embolization with Onxy is that it involves a higher technical complexity than conventional endovascular treatment. After the injection, the embolic agent tends to keep advancing through the artery, and unlike coils, it cannot be retrieved if it is placed in an undesired position. For this reason, and taking into account that part of it can travel from the aneurysm sac to the parent artery, embolic material is not recommended in those cases involving perforating arteries in the neck or in its vicinity.

2.3.2.6 Extrasaccural embolization

As with large and giant aneurysms, the management of cerebral microaneurysms (those with a sac ≤3mm in diameter) is difficult both with an endovascular and open surgical approaches. Neurosurgical techniques remain the modality of choice to treat cerebral microaneurysms in many centers because of their high rate of rupture during conventional endovascular procedures. However, clipping such small aneurysms may be impossible due to the low dome-to-neck ratio. Other types of intervention, such as trapping (proximal and distal to the aneurysm), may cause serious neurological sequelae because they involve the occlusion of the main arteries or of potential pathways of collateral circulation. While, on many occasions the clinical condition of the patient does not allow a neurosurgical approach, alternative endovascular techniques are required like extrasaccular embolization, which involves stabilization of the microcatheter in the microaneurysm neck using a remodelling balloon, deploying the coil outside the sac, and introducing it by inflating the balloon. This procedure prevents the microcatheter from invading the sac, and minimizes the risk of rupture.[21]

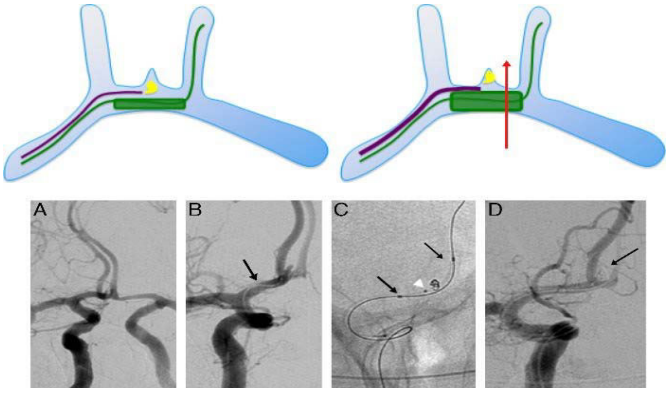

Fig: 8 Ruptured microaneurysm in the anterior communicating artery (ACoA). (A) Preoperative digital subtraction angiogram (DSA) in the anterior-posterior projection. (B) DSA in the working projection during placement of the remodelling balloon (arrow). (C) Angiogram without subtraction during extrasaccural embolization. Inflated remodelling balloon covering the aneurysm neck (arrows). (D) Follow-up DSA after coil delivery shows complete sealing of the aneurysm (arrow).[25]

2.3.3 Limitations of endovascular procedures

In addition to the technique-related limitations of endovascular treatment methods described earlier, there are several additional perspectives that should be considered when evaluating endovascular techniques against microsurgical aneurysm therapy. Firstly, the cost of novel endovascular devices exceeds vastly the cost of microsurgical clips. While the price of a microsurgical

clip is usually at most a few hundred Euros, all of the intracranial stents are priced in several thousand Euros and the price of flow-diverting devices often exceeds 10,000 Euros. Endovascular aneurysm treatment almost invariably necessitates long-term angiographic follow-up. Aneurysm recurrence is common after coil embolization, and routine angiographic follow-up imaging for a minimum of three years after aneurysm embolization is recommended. It is also worth noticing that there is, as yet, no information on long term or lifetime efficacy and safety of stent-assisted embolization, advocating very long clinical and angiographic follow-up after stent-assisted aneurysm treatment.

3. FUTURE PERSPECTIVES AND RECOMMENDATIONS

In the field of interventional neuroradiology the ever increasing pace of technological development is unparalleled, even in the scope of medicine. The continual and rapid advances in material technology and bio-compatible materials, manufacturing processes, biotechnology, and nanotechnology will offer new endovascular treatment options at an accelerating rate, and the role of intracranial stents is becoming ever more important in the management of cerebrovascular diseases. The main focus of aneurysm research and treatment will shift further from reactive treatment of SAH to aneurysm screening and prevention of aneurysm rupture. Although novel endovascular treatment options may solve some of the challenges involved in the treatment of complex cerebral aneurysms, advanced surgical techniques and endovascular procedures will always be complementary. Only multidisciplinary team approach allows the successful management of previously untreatable cerebral aneurysms both now and in the future. The future of endovascular aneurysm treatment will comprise evolutionary and disruptive aspects. Further improvements is expected both in coil and stent technology. The coil technology has come to a mature status and biological activation of the coils optimized mechanically is the logical step ahead. It is also conceivable that coils made of non-metallic materials (e.g., polymers, fibers, natural products) may offer different features. The original idea behind bioactive intraaneurysmal implants combining accelerated thrombus formation and induction of connective tissue formation remains intriguing. Meanwhile with the stent technology, the current available low profile stents come with a limited outward radial force, which needs improvement. The closed cell laser cut stents are notorious for issues like ovalization, poor wall apposition and difficult catheter navigation. All these aspects could be improved. True bifurcation stents with the ability to replace crossing or kissing Y- stenting procedures can find useful clinical applications.

[2] Shapiro, Maksim. "Neuroangio.org." Neuroangioorg. 2015. Web. 16 Dec. 2015.

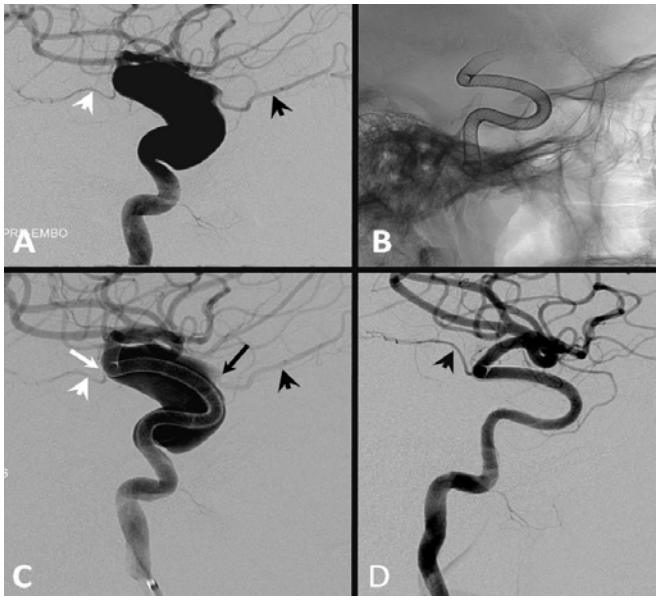

Fig: 9 Curative reconstruction of a fusiform trans-segmental aneurysm with a PED (A). The ophthalmic (black arrowhead) arises from the dome, while the anterior choroidal (white arrowhead) is situated on the tapering segment of the fusiformity. (B, C) The ophthalmic ostium is away from the device (black arrow), while the ostium of the choroidal is situated immediately adjacent to the construct (white arrow). (D) The ophthalmic is closed (asymptomatic, ECA reconstitution), while the choroidal continues to fill.[2]

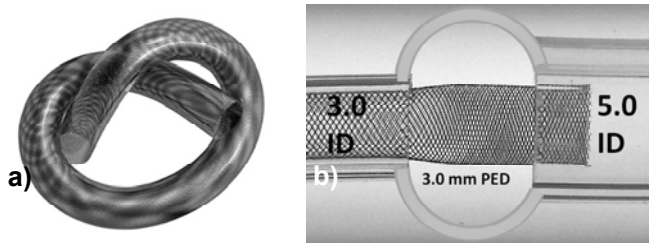

Fig: 10 (a, b) Pipeline Embolization Device (PED, Chestnut Medical, Menlo Park, CA). [2]

Stent assisted coiling could be an ideal scenario for a bioabsorbable stent. Intraaneurysmal flow disruption is a very promising concept.

With the current available technology and future approaches, an implication of the findings can be drawn and valid recommendations can be suggested. One of these suggestions could be an approach towards the parent vessel reconstruction, which represents the most physiological treatment of cerebral aneurysms. With this technique, the diseased parent artery that gives rise to the saccular or fusiform aneurysmal outpouching is primarily reconstructed. This procedure is achieved through the implantation of stents or stent like devices within the parent artery, which function to achieve several important hemodynamic and biological effects like change in parent vessel configuration, flow redirection and biological remodelling. Parent vessel reconstruction can be achieved with Pipeline Embolization Device (PED). During the past years new generation of self expanding, microcatheter delivered, intracranial microstents has been specifically engineered to primarily achieve definitive parent vessel reconstruction of the cerebral arteries giving rise to

the saccular or fusiform aneurysmal outpouching is primarily reconstructed. This procedure is achieved through the implantation of stents or stent like devices within the parent artery, which function to achieve several important hemodynamic and biological effects like change in parent vessel configuration, flow redirection and biological remodelling. Parent vessel reconstruction can be achieved with Pipeline Embolization Device (PED). During the past years new generation of self expanding, microcatheter delivered, intracranial microstents has been specifically engineered to primarily achieve definitive parent vessel reconstruction of the cerebral arteries giving rise to aneurysms. The only such device that has successfully been applied in human patients is the Pipeline Embolization Device (PED, Chestnut Medical, Menlo Park, CA). Parent vessel reconstructive devices, such as the PED, represent a new treatment paradigm for intracranial aneruysms. The existing data suggest that these devices may provide a definitive cure of those lesions that have proven to be the most challenging to treat with the standard, more conventional, endosaccular occlusion techniques. Moreover, the major shortcomings of endosaccular aneurysm therapies like incomplete aneurysm occlusion and aneurysm recurrence are directly addressed through parent vessel reconstruction.

4. CONCLUSIONS

The great advances made in recent years in interventional neuroradiology applied to the treatment of cerebral aneurysms have broadened the indications for the management of aneurysms with unfavourable size and configuration, which have traditionally been treated surgically. The continuous development of new techniques and materials offers a significantly wider range of therapeutic possibilities. At the same time, the personnel involved in the treatment of patients with cerebral aneurysms are required to constantly update their knowledge and reach a high degree of specialization. In the lack of clinical trials that assess systematically the outcomes of new procedures, each case needs to be evaluated on an individual basis in a multidisciplinary session in order to provide each patient with the safest and most effective therapeutic option available at a particular time for each specific case.

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Low Dose versus High Dose Brachytherapy – Dose management, Imaging needed for these procedures, Pros and Cons & Future Growth

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"Brachytherapy is effective and safe cancer treatment, providing a good alternative to surgical removal of the prostate, breast, and cervix, while reducing the risk of certain long-term side effects using primarily two different techniques: Low Dose Rate uses a lower strength radioactive source & High Dose Rate uses a higher strength radioactive source"

Background

Introduction

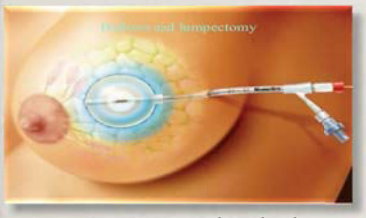
•Greek words for short distance (brachy) and treatment (therapy).
•It is sometimes called seed implantatio.In this radioactive "seeds" are carefully placed inside of the cancerous tissue and positioned in a manner that will attack the cancer most efficiently.

Dose Rate

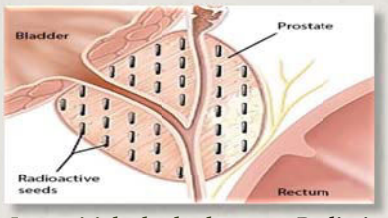
▪The dose rate of BT refers to the level or intensity with which the radiation is delivered to the surrounding medium.
- LDR brachytherapy radiation dose < 2 Gy·h⁻¹
- HDR brachytherapy radiation dose > 12 Gy·h⁻¹

Techniques

There are many techniques used in Brachytherapy

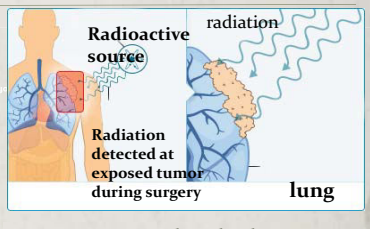


During Intracavitary brachytherapy, the radioactive source is placed in a cavity in the body, such as the rectum or uterus. It is use in the treatment of locally advance cancer



Interstitial brchytherapy Radiation can be delivered from material placed inside the prostate gland & seed applied either in a permanent manner, or temporary manner.

Figure 1: Radioactive seeds about the size of grain of rice



Intraoperative brachytherapy is the application of therapeutic levels of radiation to the tumor bed while the area is exposed during surgery.

Low dose rate & High dose rate brachytherapy Treatment procedure

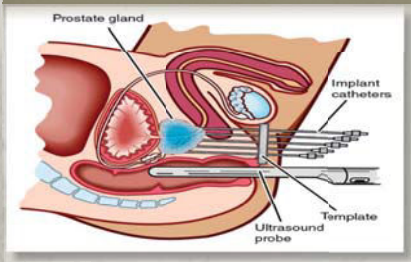


Figure 2 : High dose rate brachytherpy

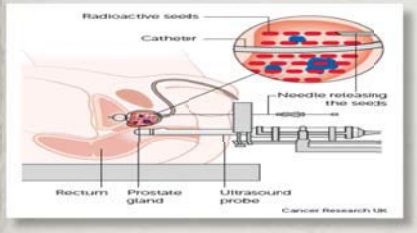


Figure 3: Low dose rate brachytherapy

Internal radiotherapy may involve two sessions : 1) A planning session 2) A treatment session

•The planning session :
A general anesthetic or spinal anesthetic for a short time given & doctor uses a trans rectal ultrasound scanner to find the exact size and shape of the prostate gland. The scans give a three dimensional model to help doctors for planning how many seeds need and exactly where to put them.

•Treatment session :
The treatment team plans treatment and radiation doses. doctor puts an ultrasound probe into rectum. They put a plastic template with holes in it in front of the skin between legs.

•For High dose rate brachytherapy:
The doctor positions the tubes inside the prostate. Radioactive material is inside the tubes. A computer monitors the time the treatment should take. After the tubes have been in position for the right amount of time, the doctor takes them out. So when patient wake up, the treatment is all done.
➢There is no radioactive material left in prostate.

•For Low dose rate brachytherapy:
Doctor pushes needles containing the seeds into place inside the prostate. They carefully pull the needle out .
➢seeds are left behind in prostate.

Advantages & Disadvantages

Advantages
➢HDR therapy is One-time procedure, Minimally invasive, No surgical risks & No hospital Stays require.
➢LDR prostate brachytherapy is flexible quick treatment and reduces side effects.
Disadvantages:
➢Pain or swelling in the area between anus and scrotum for some time after treatment.
➢Radiation that used to kill cancer cells will diminish the prostate's normal Productivity & May be forced to strain urine in case of pellets moving.

Future Development

•Atec biopsy device is safe, accurate & effective. system is Simple one minute set-up and clean-up. No software required for user to program or operate.
•Proton therapy is alternative option offers greater precision in focusing radiation on the prostate, with fewer negative side effects.
•Hdr monotherapy for localized prostate patients.
•Breast device: SAVI & Clear Path device.

Figure 4: ATEC device, Clear Path device & SAVI device.

Conclusion

•Therapy is Safe, Effective & cost saving
•Faster therapy compare to EBBT.
•Treatment with precision deliver of radiation doses to the target area
•Ensures optimal accuracy and reduced toxicity by reduction in radiation exposure to healthy tissue
•Very convenient methods for patient therefore they can go home at the same day of treatment.
•Gives comfort excellent and good cosmetic outcomes.

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Low Dose versus High Dose Brachytherapy- Dose mangagement,imaging needed for these procedures,pros and cons & quality assurance

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ARTICLE INFO

Keywords:

Brachytherapy
breast cancer
prostate cancer

ABBreviations:

APBI-Accelerated Partial Breast Irradiation
WBI-Whole Breast Irradiation
LDR-low dose rate
HDR-high dose rate

ABSTRACT

Brachytherapy is a precise,effective, state-of-the-art radiotherapy option. Radiation for breast cancer can be delivered by either Whole Breast Irradiation (WBI) or Accelerated Partial Breast Irradiation (APBI). HDR brachytherapy can be used for a wide range of prostate stages, PSA values, and tumor grades. The components and dosages are modified for those with low, intermediate, or high risk prostate cancer. This paper includes types of dose rate medium , brachytherapy treatment procedure, limitations and advantages-disadvantage. Additionally, a comparison among LDR & HDR brachytherapy and quality assurance of brachytherapy for treatment of cancer. This paper provides evidence which establishes brachytherapy as a patient-centered treatment option in the management of early breast cancer & prostate cancer with future direction

1. INTRODUCTION

Brachytherapy (from the Greek word βραχύς brachys, meaning "short-distance"), also known as internal radiotherapy, sealed source radiotherapy, curietherapy or endocurietherapy.This is applied either in a permanent manner,or a temporary manner (sometimes called seed implantation),often through the use of catheters into which the radioactive sources are placed inside the body, and positioned in a manner that will most effectively treat the disease.[1] low dose rate brachytherapy or LDR ,whereby the patient lies in bed for several days while the radioactive sources treat the disease,or in an out-patient setting. while (high dose rate brachytherapy,or HDR,whereby the patient usually undergoes several treatments of radiation in a short period of time[2] There are many methods used in Brachytherapy like Intracavitary brachytherapy (ICBT).It is Suitable for tumors located in a body cavity,Interstitial brachytherapy (ISBT) where radioactive sources are surgically implanted,Intraluminal brachytherapy (ILBT) in which tumors surrounding a luminal organ is accessed via the lumen.This is an advanced and effective treatment for cancer which is commonly used as Cervical, Prostate, Breast, and Skin cancers and also used in other part of tumor area.It is also used to treat coronary artery disease to prevent restenosis after angioplasty.Now a days most oftenly used Brachytherapy in breast & prostate cancer by Surgeon.prostate brachytherapy usually involves an out-patient procedure for either permanent seed implantation or HDR brachytherapy to the prostate gland. It has been shown to have comparable 10-year survival rates to radical prostatectomy and has fewer side effects including a lower incidence of impotence and incontinence.[3]Treatment of breast cancer with brachytherapy usually involves a five-day treatment course with either LDR (in-patient) or HDR (out-patient) brachytherapy, rather than six weeks as with traditional radiation treatment following a lumpectomy. This offers excellent cure rates without the need for a mastectomy.

2.0) Dose Managment

2.1.) Background of Dose Rate

The dose rate of BT refers to the level or 'intensity' with which the radiation is delivered to the surrounding medium. The dose rate of BT is defined in Grays per hour (Gy/h). In clinical practice, commonly used BT dose rates are Low-dose rate (LDR) brachytherapy Involves implanting radiation sources that emit radiation at a rate of less than 2 Gy per hour.LDR brachytherapy is commonly used for cancers of the oral cavity and oropharyngeal carcinomas,soft tissue sarcomas and prostate cancer.Medium-dose rate (MDR) brachytherapy is Characterized by a dose delivery rate ranging between 2 Gy to 12 Gy per hour High-dose rate (HDR) brachytherapy: The dose rate is more than 12 Gy per hour. The most common applications of HDR brachytherapy are gynecological cancers, esophageal carcinoma, lung and prostate cancers.Pulsed-dose rate (PDR) brachytherapy Involves short pulses of radiation, typically once an hour, to simulate the overall rate and effectiveness of LDR treatment.Typical tumor sites treate by PDR brachytherapy are gynecological and head and neck cancers. [4]

3.0)Theory

3.1.) Overview of Breast cancer

The most common type of breast cancer is ductal carcinoma, which begins in the cells of the ducts. Breast cancer can also begin in the cells of the lobules and in other tissues in the breast. Invasive breast cancer is breast cancer that has spread from where it began in the ducts or lobules to surrounding tissue Each year there are about 2,300 new cases of breast cancer in men and about 230,000 new cases in women.[6] The signs and symptoms referable to the breast, such as a change in skin color texture, lump, nipple discharge, or skin dimpling[7].Types.of breast cancer are two very early types called ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS),Invasive breast cancer (NST),Invasive lobular breast cancer and Inflammatory breast cancer.[13]

3.2) How Brachytherapy works in breast cancer

There are two types of brachytherapy that can be used to treat breast cancer, Low dose rate (LDR) brachytherapy and High dose rate (HDR) brachytherapy.LDR brachytherapy uses radiation sources that give out a low level of radiation, while HDR sources give out a higher level of radiation. HDR brachytherapy is much more commonly used than LDR brachytherapy After surgery, radiotherapy is commonly used to kill any remaining cancer cells. [25].HDR brachytherapy can be given after the whole breast has been treated using external beam radiotherapy, known as whole breast irradiation (WBI).Brachytherapy provides a 'boost' of radiation just to the area where the tumor was.HDR brachytherapy can be used as radiotherapy after surgery,known as accelerated partial breast irradiation (APBI)[11].In this radiation dose just expose to the area around where the tumor was and can be completed much more quickly than WBI.Brachytherapy also involves placing a radiation source within or close to the cancer.[10] The sources of radition is gernerally in the size of pencil lead.The radiation dose intensity falls off rapidly by just a short distance away (millimeters). In this therapy the seeds are precisely positioned in the tissues containing residual cancer cells with less radiation scatter to the nearby healthy tissues such as lung, heart, ribs, and skin by using Specialized treatment planning programs and image guided delivery systems which allow the radiation dose to be placed internally to achieve highly conformal radiotherapy.

3.3) Treatment Procedure

Three main stages of procedure` a) planning, b) treatment delivery and c) postprocedure` monitoring. Treatment planning ammography` (X-ray) ltrasound` scan` Computerised Tomography (CT) scan. The scan provides an accurate picture of the tumor and its position. This image helps the doctor knows about radiation position and amount of radition dose is needed to treat the cancer.Before planning process stimulation and intracavitary implant process will start.Before each treatment the exact location of the implant is verified on simulator.

The implants may be Placed at lumpectomy or may occur post-surgery.The patient is then moved into the brachytherapy treatment room. The ends of the applicator or treatment catheters that protrude outside the body are connected to "transfer" tubes which are then connected to the after loader.The programmed instructions suggest to afterloader where to direct the source and how long the source will stay in each dwell position.The patient is alone in the treatment room while the treatment is being given, but the therapists and nurses are continually observing the patient through an intercom and TV monitors. The time the source spends in the implant is about 10 to 15 minutes. The entire treatment process takes about 30-60 minutes.These time is depending on the size and complexity of the implant and on the activity of the source. When the treatment is completed, the radiation source is retracted back into the HDR afterloader.There is no radiation left behind in the patient. After the implant has been placed, simulating either CT or special x-ray films are taken by the radiation therapists to determine the exact location of the Implant in the body and the relationship to surrounding tissue.These films assures that the implant and nearby organs are visualized clearly. Reviews these films and makes final adjustments to the implant if necessary.[10]

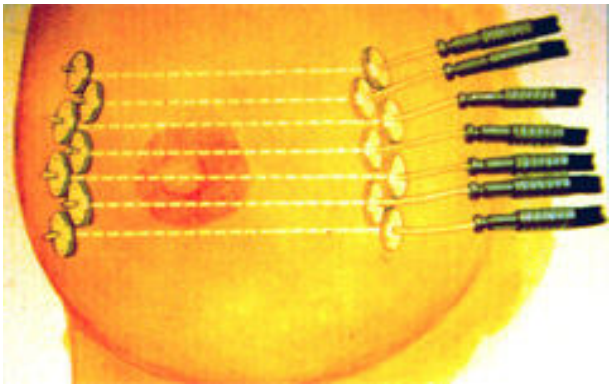

Figure of : Tube and Button Applicator Insertion Procedure

3.3.1)Treatment planning

The CT images or X-RAY films are given to the dosimetrist to enter into the treatment planning computer.The computer does calculation but the dosimetrist who customizes the radiation doses to Conform to the target volume while minimizing the doses to healthy tissues.After the treatment plan has Been approved by the physician, the computer transfers the treatment plan instructions to the HDR remote afterloader.[10]

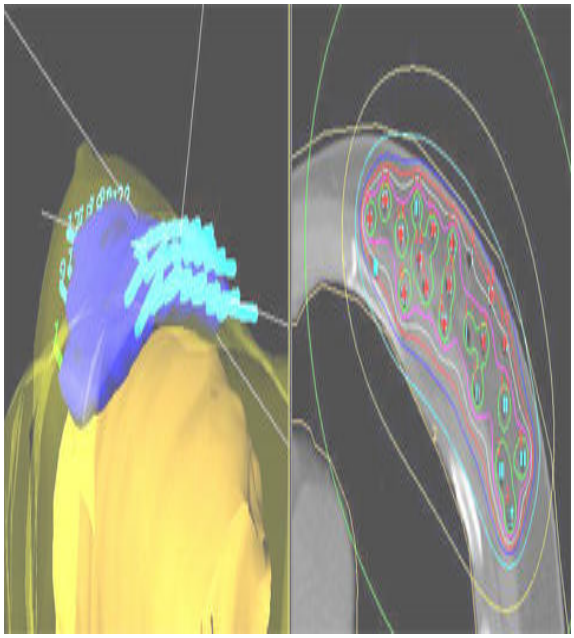

Figure: 3D computer simulation a conformal radiation dose cloud: left of image representation of the implant Catheters (light blue), the 100% radiation dose "cloud" (blue) the underlying lung (yellow)and the skin (Transparent yellow).Right of image represent transverse CT cut showing the levels of radiation dose [10]

3.3.2) Treatment Delivery

(Applicator placement process.) There are two main ways in brachytherapy Applicators (which will carry the radiation sources) can be placed. Interstitial multicatheter brachytherapy used for both boost and Accelerated Partial Breast Irradiation (APBI) and intracavitary brachytherapy Normally reserved for APBI.Both techniques have demonstrated excellent efficacy, Toxicity and cosmetic Results.

3.3.3) Interstitial multicatheter brachytherapy

This therapy is firstly used in brachytherapy for breast cancer, it has the longest period of follow-up. over 20 years ago first used as a boost therapy used for Whole Breast Irradiation (WBI).This therapy has key Efficacy and safety outcomes with interstitial multicatheter brachytherapy for boost. Modern interstitial Techniques use 3D planning and imaging to define the planning treatment volume (PTV). Multiple, specially designed catheters are then inserted in the breast to cover the PTV with high conformity and Accuracy. Once correct placement is verified, then the radioactive source is delivered to the internal catheters via a remote afterloading device. The entire procedure is normally carried out in an outpatient setting, and the catheters are removed following delivery of the last fraction.[12]

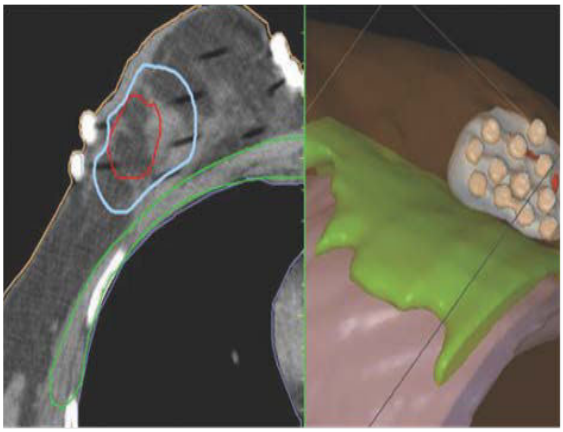

Figure : Interstitial multicatheter brachytherapy imaging and planing.

3.4) Intracavitary brachytherapy

Intracavitary devices were developed with view to matching the high conformity achieved with Interstitial multicatheter brachytherapy using a simplified deliver process via a single catheter or Multi channels,which is inserted into the tumor cavity via a single puncture site. After insertion, placement is verified to conform to the treatment volume, and an HDR source is delivered to the catheter using a remote afterloader.[12,13,14]

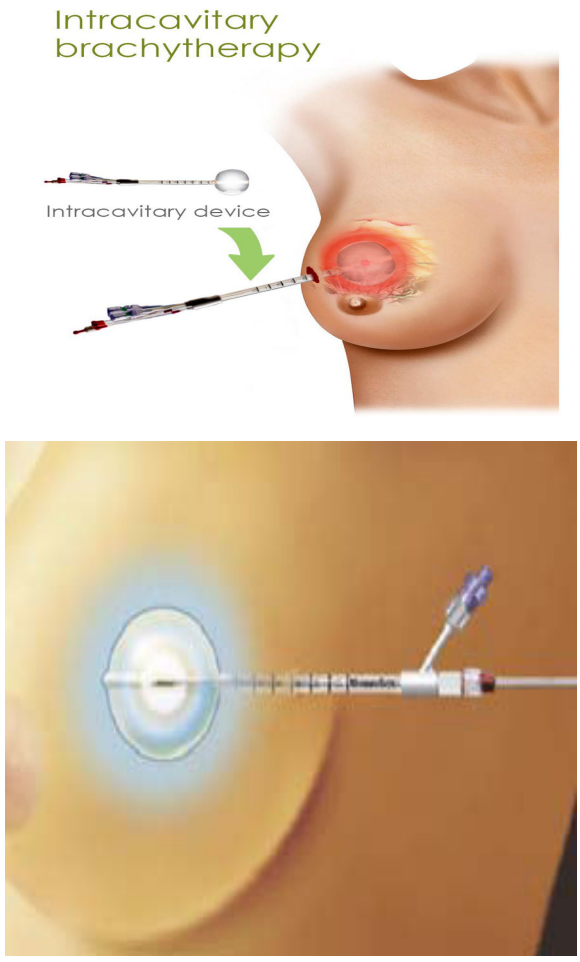

Figure Intracavitary balloon brachytherapy

3.4.1) Radiation delivery

The applicators are then attached to a computer controlled machine, known as an afterloader. The afterloader sends a small radiation source down the catheters to the treatment site in the breast and it is left in place for a predetermined period of time.The computer is programmed to control very accurately where the radiation is delivered and how long it remains in or next to the breast tissue. This ensures that a very Precise and accurate dose of radiation is delivered to the tumor. This precision reduces the risk of healthy Surrounding tissues or organs being damaged by the radiation.After the set period of time, the radiation source is transferred back out of the applicator and into the afterloader. [20]

3.4.2) Post-procedure monitoring

A follow-up appointment will be scheduled a few weeks after the procedure.This appointment is to check that the treatment is going well and monitor for any possible side effects.[20]

3.5)Benefits of Intersitial &Intracavitary brachytherapy

Boost therapy has the benefit of survival rates comparable efficacy to external beam radio therapy (EBRT) boost,When used to deliver the boost dose to the tumor area,then brachytherapy offers some advantages of surrounding tissue so treatment time for boost therapy can be decreased to 1–2 days using by brachytherapy to where it is needed that means less toxicity/damage to surrounding healthy breast tissue, skin and other organs,Excellent efficacy rates for this brachytherapy are coupled with low toxicity rates and high 'excellent to good' cosmetic results with good cosmetic outcomes. In APBI Therapy,Excellent long- term tumor control and survival rates which high 'excellent to good' cosmetic results with good outcomes.Excellent conformity.Amount of radiation delivered to non-target tissue and organs is significantly less using Interstitial multicatheter brachytherapy than other forms of radiotherapy.Good cosmetics outcome can have an impact on patient satisfaction with treatment,toxicities is low and quality of life. while in Intracavitary Brachytherapy is less extensive to intersitial multicatheter brachytherapy and gives toxicity outcomes with few complications and excellent results compare to intersitial brachytherapy[15,16,17]

3.6) Advantages of HDR brachytheraoy in breast cancer

HDR brachytherapy limits radiation exposure to healthy surrounding breast tissue, reducing side effcts associated with standard radiation. It delivers a precise, highly concentrated dose of radiation directly to the breast tumor area, The treatment takes few minutes, rather than days ompare low-dose brachytherapy. After treatments,the catheters are removed and no radioactive seeds left in the body.Ability to shape the radiation dose to fit the tumor, Conserves the breast and yields excellent cosmetic results.

3.6.1) Advantages of LDR brachytherapy

LDR is a one-time procedure, and enjoys a long-term follow-up database supporting its excellent outcomes and low morbidity. while in other brachytherapy the modulatingsource (dwell time and position) is needed which is absent in LDR brachytherapy.

3.7) Side Effects of brachytherapy in breast cancer :

All treatments for breast cancer carry a risk of side effects. Patient responds to treatment in different ways.Some side effects may appear in the short time (acute side effects) or may appear several months later(long-term side effects).Some women have experienced minor bruising, redness and discomfort. All of these side effects are common in breast surgery.Acute side effects are Tiredness,slight changes in skin color of breast and Infection in the placement of the applicators (in the case of catheter or balloon delivery) & Long term side effects are Fibrosis.It means the breast tissue can change in texture and feel a little firmer after treatment. The risk of developing fibrosis depends on the dose of radiation received. Treatment is tailored to reduce the risk of fibrosis from occurring and second one is Fat necrosis.It means Radiation can cause some Of the fat tissue within the breast to break down, causing local irritation of the tissue ,only about 2% of Patients are affected by this.[20]

3.8) Reason for brachytherapy suitable in breast cancer:

There are other kind of therapy also used in breast cancer but among that brachytherapy mostly prefer by Women who have breast cancer because who have received brachytherapy (either as a 'boost' dose of radiation after whole breast irradiation (WBI), or as accelerated partial breast irradiation (APBI) show that the vast majority of women continue to remain free of breast cancer many years after treatment.[20] Cancer often affects organs and other esential structures so it is very neccessary in radiation treatment to be tightly focued on tumors to minimize serious side effects. HDR or LDR brachytherapy is highly targeted radiotherapy it places the radiation directly at the treatment site compared to EBRT (where the radiation has to travel from outside the body).

4.0) Overview about Prostate & prostate cancer

Men have a small gland about the size of a walnut called the prostate gland. The prostate is below the Bladder. It surrounds the first part of the tube (urethra), which carries urine from the bladder to the penis. The same tube also carries sex fluid (semen). The prostate gland is divided into 2 lobes, to the left and the right of a central groove.Its main purpose is to produce fluid that forms part of a man's semen, which is used to protect and transport sperm as it travels out of the penis.Prostate glnd produces a thick clear fluid that is an important part of the semen. The growth and function of the prostate depends on the male sex Hormone testosterone, which is produced in the testes. Some treatments for prostate cancer work by Lowering the levels of testosterone.[14]

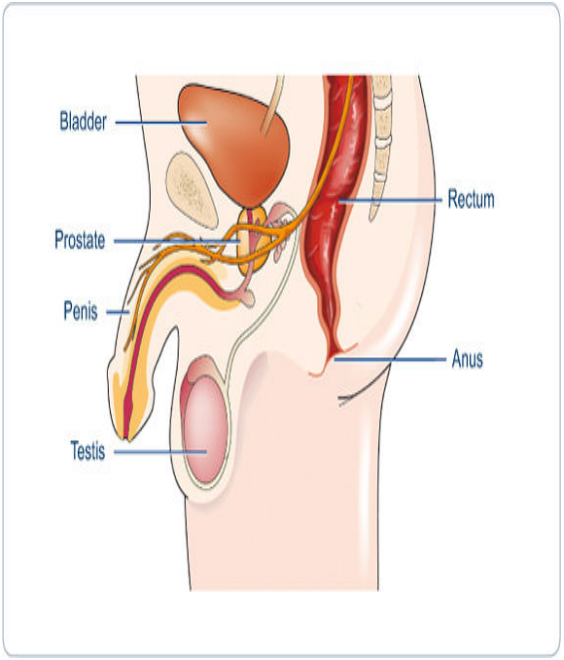

Figure of prostate

Prostate cancer occurs when abnormal cells develop within the prostate tissue.Prostate cancer occurs when Abnormal cells develop in the prostate gland, usually after the age of about 45.[6]

4.1) Symptoms of Prostate Cancer

Very early prostate cancer generally does not cause any symptoms at all. Many prostate cancers start in the outer part of the prostate gland,which is away from the urethra. If a tumor is not large enough to put much pressure on the tube that carries urine out of the body (the urethra).First symptoms are from prostate cancer which has spread to your bones but this is not common and this Prostate cancer cells in the bone may cause pain in Back, Hips,Pelvis,Other bony areas and weight loss, particularly in elderly men. The other symptoms are Greater urgency in passing urine,Passing urine more often than usual, especially at night,Difficulty passing urine including straining to pass it or stopping and starting, not being able to completely empty the Bladder,and Blood in the urine or semen.[19]

4.2) Risk Factors

Men's age is more likely to develop prostate cancer if they are over 45 years old. A family history of cancer like if your father or brother diagnosed with prostate cancer then you are 2 to 3 times more likely to get prostate cancer yourself, compared to the average man. Men have also a higher risk of prostate cancer if their mother has had breast cancer. This increased risk is mainly caused by an inherited faulty Gene called BRCA2. also Men who have a fault in the BRCA2 gene can have a risk of prostate cancer that is 5 times higher than men in the general population and 7 times higher under the age of 65.[22] Genes is also a reason for prostate cancer if People with Lynch syndrome have inherited faulty genes.Ethinicity is also a risk factor.Prostate cancer is more common in black Caribbean and black African men than in white or Asian men.This difference seems to be due to a mixture of inherited genes and environmental factors and Physical exercise and Diabetes Mellitus can protect against developing prostate cancer.

4.3)Prostate cancer Treatment option: Treatment for prostate cancer depends on the stage of the disease and the patient's age and overall health. Medical treatment e.g waiting/active surveillance,Hormon therapy, Brachytherapy e.g Radioactive seed implantation. External radiation treatment (XRT),surgical treatment and Natural treatment and support Nutrition Supplements.Low Dose Rate (LDR) brachytherapy also referred to as'seed therapy', 'internal radio-therapy' &High Dose Rate (HDR) brachytherapy used to treat prostate cancer[14]

4.4)Low dose rate (LDR) Brachytherapy

Low dose rate brachytherapy (seed therapy) LDR is commonly used to treat low risk prostate cancer. Tiny radioactive seeds, about the size of a grain of rice, are permanently placed inside the tumor.The seeds give out low levels of radiation for a few months for killing the cancer cells. LDR brachytherapy is very effective treatment for prostate cancer. LDR procedure is in three stages: Planning, Treatment delivery and Post Procedure monitoring Planning.[14]

4.4.1) the Planning stage

The detailed planning of the brachytherapy procedure can be 'pre-planned', or take place in 'real-time.In Pre-planned procedure a scan is taken the day before the treatment delivery.This involves scan such as Ultrasound scan,Computerised Tomography (CT) scan, Computer Axial Tomograahy (CAT) & Magnetic Resonance Imaging (MRI) scan. Thease scan provide an accurate picture of the tumor and its position in relation to the prostate gland, as well as surrounding healthy tissues. This image helps the doctor calculate how much radiation is needed to treat prostate cancer and radiation position in to the prostate.When it is completed then patients normally stay in hospital overnight and have the treatment Real-time planning is not available in every hospital.[14]

4.4.2.2) Treatment delivery

In this a general anesthetic or a spinal anesthetic is given before the delivery of the treatmentfor avoiding discomfortness.Using the plan the doctor will place the radioactive seeds inside or near to the tumor by using a series of fine needles (catheters).Then, these needles are inserted into the skin between the scrotum and the anus and delivered into the prostate.The needles are then carefully Removed & leaving the seeds in place. Ultrasound is usually used to enable the doctor to see where the Needles and seeds are being placed. This helps ensure that the treatment precisely targets by radioactive source particular in the tumor.After the seeds have been implanted, a CT or MRI scan can be used instead of ultrasound.This whole procedure takes about one hour.

4.4.3) Post-Procedure monitoring

Once the seeds have been implanted, they will give low radiation over the course of several monthsTo kill the cancer cells. The radiation dose is localized to just the prostate.It does not make the patient Radioactive. After that a follow-up appointment will be in 4 to 6 w eeks after the procedure to check that the Treat ment is going well and monitor for any possible side effects, over time the radiation dose by see ds will reduce to at which point the seeds becom e inactive. [14]

4.5) High dose rate Brachytherapy

Radiotherapy is an important therapeutic modality for the treatment of patients with localized or locally Advanced prostate cancer. For localized prostate cancer radical prostatectomy, external beam radiotherapy (EBRT) and low dose rate (LDR) brachytherapy these therapies are traditionally used and considered to have similar efficacy for prostate cancer. Thus, factors such as the impact on quality of life, treatment time, convenience and cost will all play increasingly important role in deciding which therapy are suitable for patient in prostate cancer. The past new decade have seen significant advances in

radiation techniques, and in particular high dose rate (HDR) brachytherapy.The role of HDR brachytherapy in the treatment of prostate cancer advantages over LDR brachytherapythree-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT).HDR brachytherapy involves the temporary placement of a radioactive source to treat thecancerous treatment. HDR brachytherapy has been shown to be an effective treatment for intermediate and high risk prostate cancer .It is often given in combination with external beam radiotherapy (EBRT), as it can provide an additional dose of radiotherapy to help prevent the cancer from returning.HDR brachytherapy is very effective and quick treatment, making it very convenient for many patients.The technological advances in real-time ultrasound image guidance for high dose rate (HDR) prostate brachytherapy places thistreatmentofinnovationinradiotherapy.
This brachytherapy as a highly conformal method of dose delivery and safe dose escalation to the prostate, in additionally it has radiobiological advantages over low dose rate and external beam radiotherapy and with good outcome data and or the future.

4.5.1) the dose–response for prostate cancer

Local tumor control is directly related to the radiation dose that it receives. While clinical studies show that Minimum 70 Gray dose is needed to control prostate cancer also shows that dise ase control rates for intermediate- to high-ri sk disease can be improved with higher doses of EBRT. Subgroup analysis suggested that the benefit of dose escalation was greater for those with a pre-treatment PSA level >10 ml/mg

4.6) Procedure of HDR brachytherapy

There are a number of sophisticated treatment planning systems and remote afterloaders available that allow real-time image-guided HDR prostate brachytherapy

A typical real-time image-guided HDR procedure is carried out under local anesthetic with the patient in the dorsal lithotomy position. Under Transrectal ultrasound, guidance needles are inserted into the prostate via transperineal implantation Through a grid, as shown in figure. Transrectal ultrasound provides real-time imaging, good image quality of the prostate boundary and clear visualization of the needles.

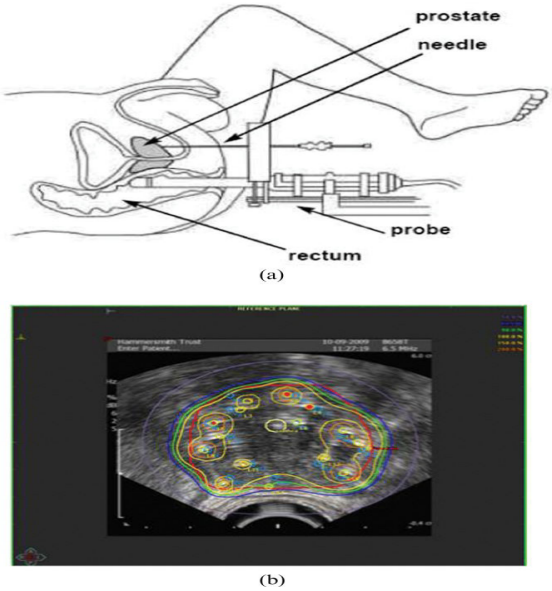

Figure - (a) Needle insertion is carried out via transperineal implantation under ultrasound guidance.

b) Typical high dose rate dose distribution

CT and MRI also available, can provide suitable images for brachytherapy planning unlike they are not Real time. Needle positions are chosen prior to their insertion in the form of a pre-plan.Typically between 12 And 20 needles will be needed to cover prostate gland volumes of 25–60 cm3,and the exact needle configuration will depend on the individual prostate anatomy. In order to ensure coverage of the base of the prostate, the needles are over inserted and therefore pushed beyond the prostate base, typically to a fixed Depth (1.2–2.0 cm). Radioactive Source positions and dwell times are determined using inverse planning Algorithms for provide an optimal dose distribution to the prostate gland while minimizing the dose

to critical structures such as the bladder, urethra and rectum, as shown in Figure 2b. Under ultrasound guidance each needle is tracked into the planning system during insertion, and therefore any deviations from the pre-planned ideal paths is design. When all of the needles have been tracked and thei tr true Locations entered into the planning system, source positions and source dwell times are recalculated and modified when necessary.This information is then transferred to the remote afterloader, which delivers the source to the appropriate needles in turn, for the dwell positions and dwell times determined in the live plan.[20]

4.7)Advantages & Disadvantages of HDR & LDR brachytherapy in prostate cancer

Using HDR brachytherapy no hospitalizat-ion stays or surgical risk, Less radiation damage to healthy tissue (nerves,bladder, rectum),One time treatment,Low risk of urinary incontinence (1to2%),Minimally invasive. while LDR brachytherapy offers quick treatment and fairly quick recovery compared to other prostate cancer options. Men with bowel problems such as irritable bowel syndrome (IBS) often tolerate brachytherapy treatments well. A key benefit of this method over LDR prostate brachytherapy is its flexibility. Under real-time ultrasound guidance dwell positions and dwell times can be modified to provide truly precise, dynamic, real-time image guide brachytherapy,suggesting that HDR prostate brachytherapy offers improved dose Distributions and better dosimetric selectivity while sparing critical structures

Disadvantages are radiation that is being used to kill cancer cells will diminish the prostate's normalproductivity so prostate will not produce the same amount or quality of semen untill it has the chance to recover and it will decrease in their amount of ejaculation.Pain or swelling in the area between Anus and scrotum for some time after treatment & lead to bruising of the patient's sexual organs, as well as the inner thighs.The radiation treatments can also affect the vessels that supply the blood necessary for an adequate erection a patient's age and health can also result in problems with erectile dysfunction. May be forced to stay away from children and pregnant women due to the internal radiation and strain urine in case of radio active source (pellets) moving Can cause bowel, urinary, and erectile issues,No post-treatment staging information, Less favor option for men with intermediate-or high-risk disease. some time Urinary retention, urgency create.Side effects may appear in the short-term & long-term side.side effects Soreness or localized bruising around the perine,Blood in urine and/or semen, Discomfort when passing urine, Bowel discomfort & Erectile dysfunction.Since the radiation seeds are confined to the prostate, this is little impact on the bladder, urethra or rectum.Brachytherapy is associated with a reduced risk of side effects compared to other treatment options for prostate cancer.

4.8) Comparison of LDR & HDR Brachytherapy

LDR is limits prostatic volume (<55 cc) while HDR treat small & large prosates. Probability of non symmetric distriughout in LDR,but in HDR uniform radiation distribution throughout the whole prostate HDR no radioactivity exposure. seeds are permanently inserted in the prostate during LDR while HDR no radioactive material left in the prostate. LDR therapy chance for migration and the other side no seed migration. In LDR prolonged acute urinary & Bowel side effects & increased late complications while in HDR short acute effects &b appericable decrease of late complications.[9]

4.9) Quality Assurance

Using Ultrasound imaging for Visualization of the prostate and other critical structures with the ability to identify the locations of the inserted seeds is necessary for good quality implants, so quality assurance of The ultrasound sused for prostate brachytherapy .this will specific focus on tests applicable to image guidance during a prostate implant procedure. The test covers visibility, depth of penetration, axial and lateral resolution. A trained member of staff repair the instrument who has aware of both technique ultrasound and prostate brachytherapy.for all implants technique users verify the alignment of the electric grid overlay on the ultrasound system with the treatment planning system grid template. Treatment planning system (TPS) is Computersized treatment planning plays a crucial role in prostate brachytherapy. Production of clear and accurate treatment plans results in smooth implantation. Which in turn in good Implants. TPS is established to confirm the continuing accuracy of dosimetric calculations & this programmed should be designed to check on the individual plans.TPS that check is made on the seed source data to ensure the integrity of the system.This seed source data check source type,activity of the seeds .this can be achieved by using a standard plan visually verifying computed isodose curves to the commissioning baseline. TPS which include verification that dosimetric algorithm compute dose correctly verifiy that plan evaluation tools,including dose volume calculationsfunction correctly and compare dose volume histogram parameters using standard plan that performed at commissioning Verification of geometric accuracy of the imaging modality used for post implant dosimetry using specially designed phantoms consisting of targets at know positions.for example,the Baltas phantom. if image Registration is utilized then testing functionality must be included. This system is used for intraoperative procedures.[22]

5.0) Future Directions of brachytherapy

One of the main practical attractions of HDR over EBRT is the shorter treatment times, and thus more recent work has focused on HDR MONOTHERAPY. At present this approach is not recommended routinely, but should the long-term outcome data become favorable, this will help to establish HDR monotherapy as a credible option for localised prostate patients.This treatment requires multiple fractions/implants. Thus, although the number of hospital visits is lower than with EBRT, they are more intense and Require inpatient stay. While the results are not as mature as with HDR boost.Monotherapy studies have reported freedom from biochemical relapse rates of 89–100% in low- and intermediate-risk patients, which compare favorably with findings with LDR brachytherapy. There is recognition that approximately 25% of all patients failing EBRT will have recurrent disease confined to the prostate. These patients are normally candidates for local salvage therapies, such as cryoablation and high-intensity focused ultrasound, which were designed to replace salvage prostatectomy because of its adverse toxicity profile and the technical difficulty in removing the prostate after EBRT. Although these techniques gives good figures for biochemical control, all are still associated with high risks of urinary incontinence, erectile dysfunction and recto-urethral fistula .LDR brachytherapy has also producing similar biochemical progression-free survival data, but with urinary and rectal complications. Limitations of LDR is also include the inability to reliably implant the seminal vesicles or allow for extra capsular extension, the inability to reposition seeds once implanted and variable seed migrat.HDR can potentially overcome these imitations, and in particular decrease the dose to the urethra (the dose-limiting structure for LDR)while maintaining adequate coverage to the prostate. Although it is technically more difficult to implant a smaller prostate gland in

which there is already fibrosis from previous EBRT, there are emerging data with better biochemical control and decreased toxicity than cryotherapy or LDR. The development of stereotactic radiotherapy using Cyber Knife technology is based on the principles of HDR brachytherapy, automatically track, detect and correct for intrafraction prostate movement,non-invasive and does not Require transperineal catheters, the requirement is only a urinary catheter or hospital admission.It has also ability to recapitulate HDR dosimetry.At present there are no durable outcome data, with relatively few centers in the UK able to provide this service, it is not recommended for more advanced disease such as extra capsular extension or seminal vesicle involvement.[22] There is Several competing radiation therapy technologies have been also introduced recently that have affected the market for prostate seeds.Intensity-modulated radiation therapy(IMRT) coupled with image-guided radiation therapy (IGRT).These modalities are being utilized in conjunction with prostatectomy to improve patient outcomes. Proton therapy is another option that has become more widely available as an alternative to prostate seeds implants.This therapeutic modality offers greater precision in focusing radiation on the prostate, with fewer negative side effects compared with traditional external-beam radiation. However, it is considerably more expensive.New breast brachytherapy device is Cianna's SAVI(strut-altering variable-irradiation)employs multiple parallel tubes, which act as struts around a longitudinal core. The core can be retracted in a controlled fashion, forcing the struts outward to expand in the resection cavity. The acronym SAVI is descriptive of the mechanism. An irradiated wire (iridium-192) is passed through the individual struts progressively in a timed sequence,which distributes the radiation in the resection cavity. This provides more accurate control of the radiation than MammoSite and reduces the risk of overexposure in critical areas. other one is Eviva breast biopsy system.Designed with enhanced technology compared to the ATEC breast biopsy device, this system combines better patient access with seamless integration for a compassionate, minimally invasive breast biopsy. Designed for both prone and upright systems, the Eviva breast biopsy system offers multiple device options to reach the broadest spectrum of patients with care. other one is North American Scientific's ClearPath device has two rows of longitudinal tubes. The outer row of tubes or struts expands outward to shape the resection cavity when the core is retracted. However, the inner row of tubes is used to conduct the radiation source. This allows somewhat more separation of the radiation source from the skin. The Clear Path device allows the use of palladium seeds, which can be inserted in the inner row of tubes for low-dose therapy. This allows more freedom for the patient because an afterloader and vault room are not required to deliver the radiation.Xoft's Axxent device is also a new device for breast brachytherapy.[21]

6.0) Conclusion

Brachytherapy is as a safe therapy and prefer for many patients in breast cancer & Prostate cancer. The primary reason a woman would select breast brachytherapy over standard external beam radiation is Time, external beam Radiation requires over six weeks of daily treatment, but Breast Brachytherapy is faster can be completed in one week by using APBI treatment. So it is an effective therapy compare to standard external beam therapy.Brachytherapy is a flexible treatment with Precision delivery of radiation doses to the target area via innovative treatment planning and delivery

and systems also ensures optimal accuracy and reduced toxicity by reduction in radiation exposure to healthy tissue. This is a cost saving treatment option & it is Also allowing to patients to get back to their everyday lives quicker. For Prostate cancer, Brachytherapy delivers the most conformal high dose radiotherapy possible to the prostate, using either a low dose rate (LDR) or high dose rate (HDR) technique,specially low dose rate (LDR) is a traditional therapy which seed implants remain in the prostate permanently but the radiation levels given out by the seeds are very low and gradually decrease after about 9 months. Choosing between HDR or LDR Brachytherapy depends on several factors like tumor size and what treatments are available at your center and etc. For both low dose rate and high dose rate brachytherapy procedures, treatment will be done under anesthetic and so it shouldn't hurt.patient & does not feel some discomfort afterwards. Both low dose rate and high dose rate brachytherapy are usually provided as outpatient procedures, therefor it is very convenient methods for patient therefore they can go home at the same day of treatment. Prostate brachy-therapy is an excellent treatment modality for localized prostate cancer because of it is not affect a man's level of fertility but only major side effect is temporary urinary symptoms. Recent technological advances in HDR brachytherapy have increased application of this approach for patients with localized prostate cancer. Current treatment methods allow administration of a high dose of radiation that tightly conforms to the targeted volume while minimizing radiation exposure to adjacent healthy organs. an impressive therapeutic outcome, with a low rate of adverse events, can be achieved with HDR brachytherapy, because of the ideal radiation dose and also improve patient comfortness. Brachytherapy gives comfort excellent and good costmetic outcomes also.

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Endovascular Aneurysms : Diagnosis and Treatment Now and Future

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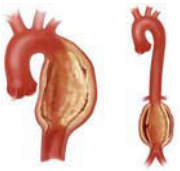
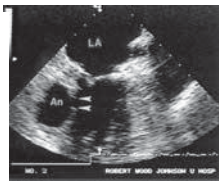
Introduction and Diagnosis Methods

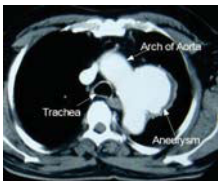
An Aneurysm occurs when part of a blood vessels swells either the blood vessel is damaged or there is a weakness in the wall of the blood vessel. The pressure of blood passing through can force part of a weakened artery to bulge outward. If an aneurysm ruptures, the patient must be treated immediately to have a chance of survival.



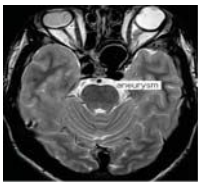
Aneurysms in Aorta



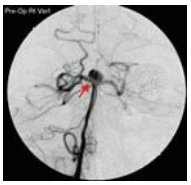
(1) Diagnosis with US



(2) Diagnosis with CT



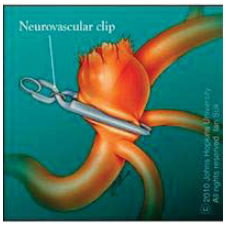
(3) Diagnosis with MRI



(4) Diagnosis with Angiogram

Treatment Methods

(1) Microsurgical Clipping

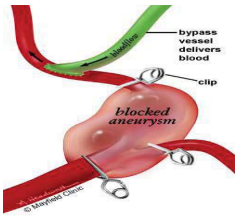


- Surgical Method
- Blood supply clipped by Metal Clip

(2) Endovascular Coiling

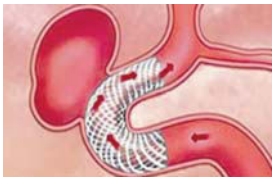
- Minimal Invasive Technique
- Blood flow blocked by coiling

(3) Artery Occlusion and Bypass



- Combined Two method
- Microsurgery and Endovascular Coiling

(4) Flow Diversion with Stent



- Endovascular Technique
- Stent diverts Blood Supply

Future Prospects in Diagnosis and Treatment

Diagnosis

- Development in Imaging modalities that provides information about growth prospects of Aneurysms.
- Detection of Biological markers that provides characteristic behavior of AAA.
- The future of AAA imaging lies in the combination of anatomical and molecular imaging techniques.
- Blood markers which can be used to screen for AAA and contribute to risk stratification.
- Prognostic markers which can better stratify patients with clinically important AAAs.
- Markers useful for guiding medical therapy of small AAAs.

Treatment

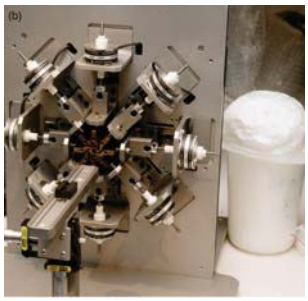
(i) Smart Forms

- Shape memory polymer form is turned into secondary stage by heated bladed machine and again is turned to its original shape when heated by laser diode hence blocks blood supply to Aneurysm Sac.
- The foams material has several advantages over Platinum
- Complete and faster occlusion of Sac., low stress to Aneurysm wall, Tissue like mechanical property,
- Bio-Absorbable material which helps in healing Aneurysms

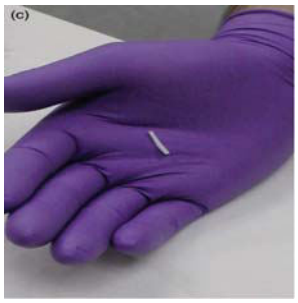
(ii) Embolization Device

- Broad Neck Aneurysms are difficult to treat with clip and aid of Stent with Coil
- The new endovascular devices attack the aneurysm by remodeling the parent artery and restoring natural blood flow.

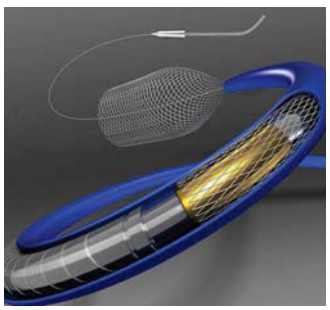
Foam is in its original shape



Heat Bladed modifies its shape



Foam is in its secondary shape



Covidian Pipeline Embolization Device

Conclusion

It is concluded that in successfully management of Endovascular Treatment involves profound knowledge of Anatomy as well as characteristics behavior of Aneurysms in different environments. In Addition Development of Imaging modalities that combines Anatomy as well as Molecular approach also crucial in understanding of Aneurysms Growth which results in perfect Diagnosis. It is imperative that, as we continue to develop our knowledge of cerebral aneurysms and their management, we remain focused on the optimal treatment for the individual patient, doing not only what can be done, but what should be done

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Endovascular Aneurysm: Diagnosis and Therapy Now and in the Future

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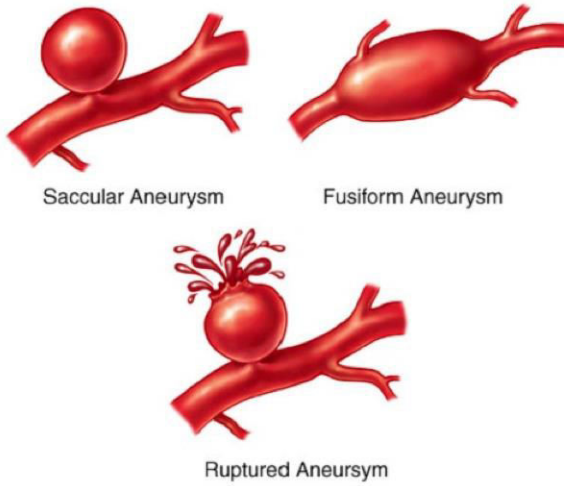
ABSTRACT

Unruptured aneurysms may cause symptoms mainly due to a mass effect, but the real danger is when an aneurysm ruptures, leading to a subarachnoid hemorrhage. Most aneurysms are asymptomatic and will not rupture, but they grow unpredictably and even small aneurysms carry a risk of rupture. Endovascular aneurysms are diagnosed and monitored with imaging including intra-arterial digital subtraction angiography, computed tomography angiography, magnetic resonance angiography, and recently transcranial Doppler ultrasonography has been proposed as a potential modality. Treatment options include observation, endovascular coiling, and surgical clipping. This documentation emphasizes on the current diagnosis and Treatment procedure for Endovascular Aneurysms and rivals the insight in future diagnosis and treatment procedure we might have.

Index Terms
Endovascular Aneurysms, Future of Aneurysms Treatment, Diagnosis of AAA

1. Introduction

An Aneurysm occurs when part of a blood vessel (artery) or cardiac chamber swells either the blood vessel is damaged or there is a weakness in the wall of the blood vessel. It is a permanent ballooning in the wall of an artery. The pressure of blood passing through can force part of a weakened artery to bulge outward. Aneurysms in any of places are serious, while those in other locations such as the leg are often less hazardous. The most serious threat an (Hemorrhage). If an aneurysm ruptures, the patient must be treated immediately to have a chance of survival. [1] Given below are different forms of Endovascular Aneurysms in Fig. 1



[Fig. 1 Different forms of Aneurysms]

2. Types of Aneurysms

There are mainly three types of Aneurysms.

Aortic Aneurysm: The aneurysm is located in the aorta. They can be associated with the buildup of plaque caused by hardening of the arteries or atherosclerosis. Aneurysms may also be an inherited condition or a complication of high blood pressure or smoking. It is depicted in Fig.2 (a)
AAA - Abdominal Aortic Aneurysms.

Cerebral aneurysm: Also known as a berry aneurysm, this occurs in the wall of a blood vessel in the brain. Smoking increases a person's risk of developing a cerebral aneurysm.
It is depicted in Fig. 2 (b).

Ventricular aneurysm: This is a ballooning out of part of the wall of the heart. A previous heart attack most commonly causes ventricular aneurysms. In rare cases, severe chest trauma can also cause a ventricular aneurysm. [2-4]

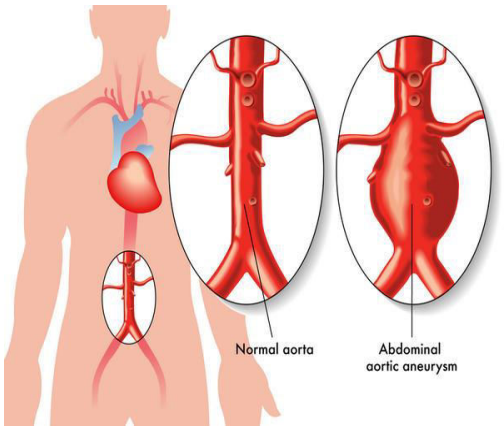


Fig. 2 (a) Aortic Aneurysm

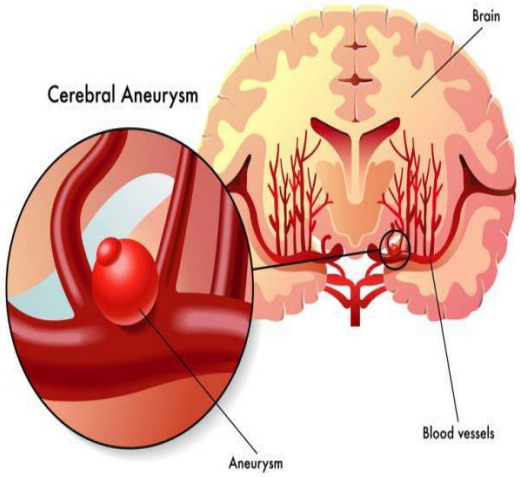


Fig. 2 (b) Cerebral Aneurysm

3. Diagnosis of Aneurysms

More often, doctors find aneurysms during tests done for other reasons, such as chest or abdominal pain. In the case of an AAA, doctor may hear rushing blood flow instead of the normal whooshing sound when listening to abdomen with a stethoscope. The type of diagnostic testing performed depends on the location of the aneurysm.

I. Ultrasound and Echocardiography

Ultrasound and echocardiography (echo) are painless tests that use sound waves to create pictures of the structures inside body. These tests can show the size of an aortic aneurysm, if one is found.

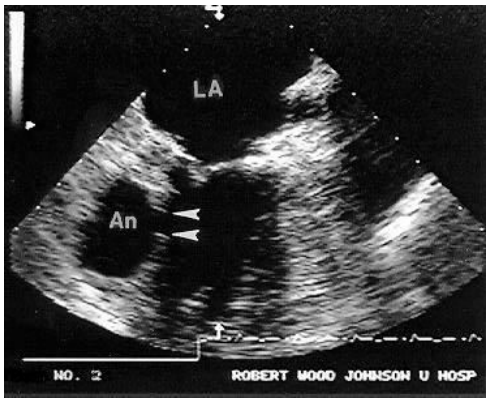


Fig. 3 (a) Aneurysms Diagnosis with US

II. Computed Tomography Scan (CT scan)

It is a diagnostic imaging procedure that uses a combination of x-rays and computer technology to produce cross-sectional images (often called slices), both horizontally and vertically, of the body .The dye makes arteries, including aorta, visible on the CT scan pictures clearly. This is the best test in case of AAA (Abdominal Aortic Aneurysm or a thoracic aortic aneurysm (TAA).

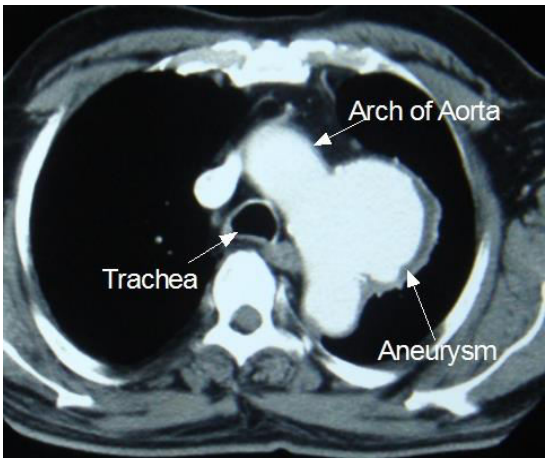


Fig. 3(b) Aneurysm in CT scan

III. Magnetic Resonance Imaging and Angiography (MRI/MRA)

Magnetic resonance imaging (MRI) works well for detecting aneurysms and pinpointing their size and exact location. Sometimes it is also done with Angiography that known as MRA (Magnetic Resonance Angiography).

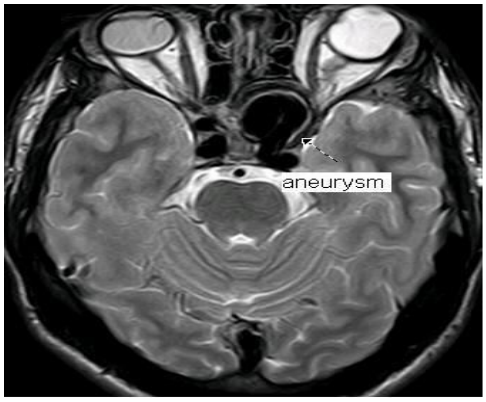


Fig.3 (c) Aneurysm in MRI

IV. Arteriogram (Angiogram)

It is an x-ray image of the blood vessels used to evaluate various conditions, such as aneurysm, stenosis (narrowing of the blood vessel), or blockages. Contrasts agent (Dye) is used in this test to visualize blood vessels clearly.

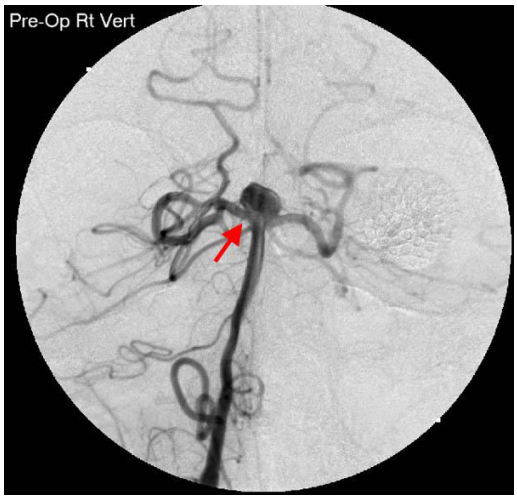


Fig.3 (d) Angiogram showing Aneurysm

4. Current Treatment for Aneurysms

There are several techniques that are performed for the treatments of Aneurysms. These are as given below.

I Microsurgical Clipping
Ii Endovascular Coiling
Iii Artery Occlusion and Bypass for Aneurysms
IV Flow Diversion with Stent

I Microsurgical Clipping:

Microsurgical clipping is a technique in which the blood supply to the aneurysm is clipped using a metal clip. The first aneurysm ever treated by surgical clipping was performed at Johns Hopkins Hospital by Dr. Walter Dandy on March 23, 1937.

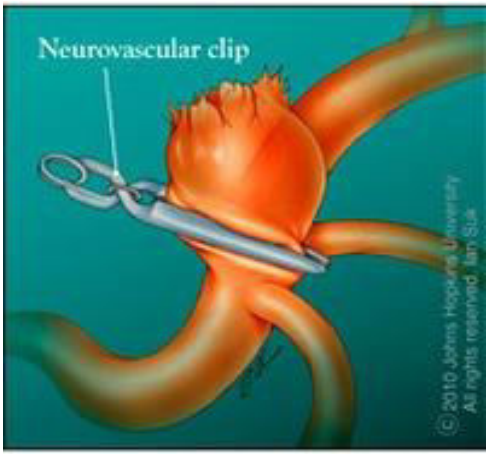


Fig 4 (a) Clipping of Aneurysm by Metal Clip

How is it performed?

A craniotomy is performed to create an opening in the skull to reach the aneurysm in the brain. The clip is placed on the neck (opening) of the aneurysm to obstruct the flow of blood, and remains inside the brain. [Link 2]

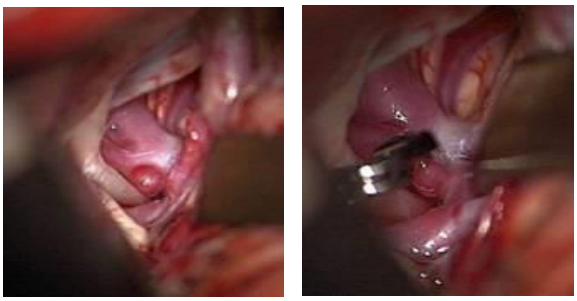


Fig 4 (b) Procedure of Microsurgical Clipping

Ii. Endovascular Coiling

Endovascular coiling is a procedure performed to block blood flow into an aneurysm. Endovascular coiling is a minimally invasive technique. A catheter is used to reach the aneurysm in the brain. [10]

How is endovascular coiling performed?

A micro catheter is inserted through the initial catheter over Hip through a Femoral Artery. When the micro catheter has reached the aneurysm and has been inserted into the aneurysm, an electrical current is used to separate the coil from the catheter. The coil seals off the opening of the aneurysm. The coil is left in place permanently in the aneurysm. Depending on the size of the aneurysm, more than one coil may be needed to completely seal off the aneurysm. The coils used in this procedure are made of soft platinum metal, and are shaped like a spring.

Fluoroscopy aids in this procedure to guide the catheter to the aneurysm's location in the brain... The catheter, which is inserted into an artery in the groin, is guided by a small wire inside of the catheter along the length of the blood vessel to reach the area of the aneurysm.

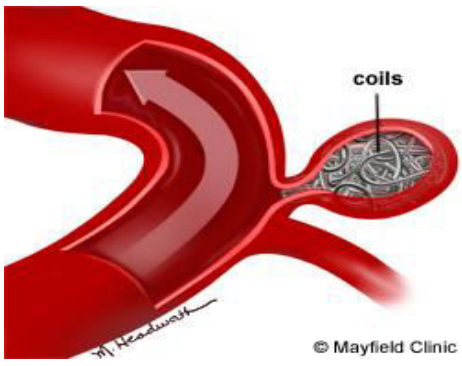


Fig 4 (c1)
Aneurysm packed

Some aneurysms with a wide neck or unusual shape require a stent to help hold the coils in place. The stent is positioned in the normal artery next to the aneurysm. The stent remains in the artery permanently holding the coils in place.

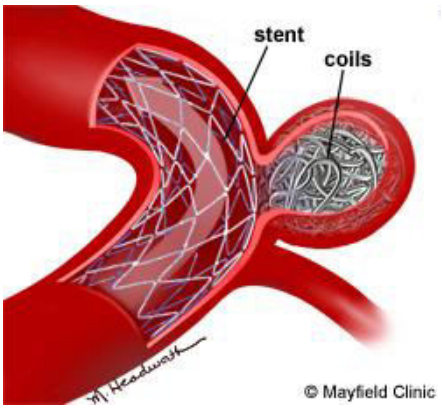


Fig 4 (c2) Placement of stent with coil for broad neck Aneurysm[1]

By injecting contrast agent, the doctor inspects the coils to ensure that blood is no longer flowing into the aneurysm. This technique also verifies that the coils are inside the aneurysm and not narrowing the main artery.

Once the coils have been placed, the catheter is removed. Pressure is applied to the groin area for about 10 to 15 minutes so that the artery won't bleed. A bandage is tightly applied to the incision. [12]

Iii. Artery Occlusion and Bypass for Aneurysms

Artery occlusion and bypass is a two-part procedure combining open microsurgery and endovascular coiling**.** The purpose of this procedure is to coil the entire diseased portion of the blood vessel and then bypass the blood flow to the specific location in the brain. The difference between this procedure

[1] http://www.mayfieldclinic.com

and endovascular coiling is that this procedure closes down **(***occludes***)** the whole vessel rather than just putting coils in the aneurysm sac.

How Occlusion and Bypass performed?

Bypass the first part of the procedure, in which blood vessels as conduits to flow blood from one part of the brain into another.

A previously identified donor vessel is detached from one end of its normal location and rerouted into the brain at a position beyond the aneurysm. The donor vessel is then reconnected to the parent vessel to ensure that blood continues to flow to the part of the brain that needs to receive it.

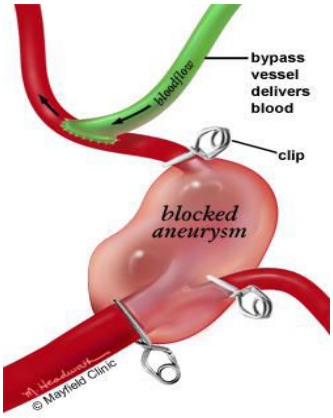


Fig 4 (d) Occlusion and Bypass of Artery

After the blood vessel has been bypassed, the next step is to close (occlusion) the diseased portion of the blood vessel containing the aneurysm using an endovascular technique called coiling**.** To close down the diseased vessel, coils are inserted into the vessel until it is completely filled. These coils will remain inside the brain permanently. [Link 4]

Artery occlusion and bypass may be performed to treat aneurysms that cannot be closed with standard methods.

iv. Flow Diversion for Aneurysms with Stents

What is flow diversion?

Flow diversion is an endovascular technique whereby instead of placing a device inside the aneurysm sac, such as with coiling, the device is placed in the parent blood vessel to divert blood flow away from the aneurysm itself.

How is flow diversion/Pipeline™ performed?

During a flow-diversion/Pipeline™ procedure, a microcatheter is navigated past the aneurysm without having to enter the aneurysm. Then, the flow-diverting device (Pipeline™ Embolization Device) is deployed across the neck of the aneurysm in the parent blood vessel where the aneurysm is present.

Almost immediately the blood flow to the aneurysm is reduced, and the complete closure of the aneurysm occurs between 6 weeks to 6 months after the procedure.

A flow diversion procedure may be performed to treat an unruptured brain aneurysm. Flow diversion is one method that removes the need to enter the aneurysm, which is the most dangerous part of endovascular treatment of aneurysms. The risk of rupturing the aneurysm during surgery is greatly diminished by not placing a device inside the aneurysm.

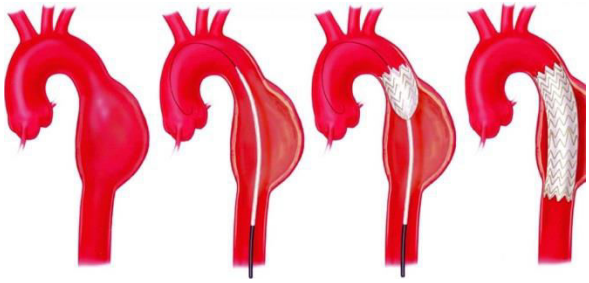


Fig 4 (e) Procedure of Flow Diversion[2]

5. Some factors that create difficulties in the treatment of some kind of Aneurysms. Those are as follows:

Factors that make Microsurgical Clipping procedure undesirable:

[2] http://www.cardiachealth.org

Elderly patients, Patients in poor neurological or medical condition, Patients presenting with cerebral vasospasm, difficult location, calcified neck, multiple aneurysms requiring multiple operations**.**

Factors that make Endovascular procedure undesirable

Fusiform aneurysms, Blister-like aneurysms, Complex aneurysm configuration, Thrombotic aneurysms, Giant aneurysms, Very small aneurysms.

6. Future Perspectives:

About Diagnosis

Currently only Anatomical Imaging is used for the diagnosis of Aneurysms. This imaging may not always be feasible as variations in patient characteristics such as obesity or renal impairment may prove prohibitive. [16] In the other hand imaging assessments do not provide complete data to identify which AAAs are most likely to continue to increase in size and be at risk of rupture. Small AAAs with similar initial diameter can vary in growth pattern significantly. A more complete ability to predict AAA progression may allow significant streamlining of current management practice which involves prolonged intermittent imaging. [17]

There is significant current interest in the detection of biologically relevant markers which can be used to better characterize AAA behavior. Biological information about the AAA could potentially highlight therapeutic targets for non-surgical intervention, and provide a means to assess the physiological response to such medications.

The coming decade promises considerable change in the management of AAA including:

1 Blood markers which can be used to screen for AAA and contribute to risk stratification

2 Prognostic markers which can better stratify patients with clinically important AAAs

3 Improvement in the methods to monitor AAA following repair or receiving other therapy

4 Markers useful for guiding medical therapy of small AAAs

In order for this promise to be fulfilled carefully planned hypothesis-led and more global screening studies are required with large scale validation of putative biological markers identified. The considerable interest in this area suggests that despite significant challenges, successful identification of clinically useful biomarkers will occur. [13]

When clearly identified new biomarkers can potentially form part of standard blood tests or be used for targeted or functional imaging. [16]

The future of AAA imaging lies in the combination of anatomical and molecular imaging techniques, which are largely complementary rather than competitive. There are many challenges, as well as many areas that deserve extensive investigation, in molecular imaging of AAA in the future.

About Treatment

Lawrence Livermore researchers are collaborating with colleagues from the University of California (UC) at Davis's Center for Bio photonics, Science, and Technology and from UC Berkeley to develop safer, faster, and more cost effective treatments for patients with cerebral aneurysms.

"SMART" Foams

To address these shortcomings, Maitland's team developed an alternative treatment that isolates an aneurysm from the rest of the vascular system with one implanted device—a "plug" made from shape-memory-polymer (SMP) foam. SMPs are a class of polymeric

materials that remember their primary (original) shape after being molded into a secondary (temporary) shape. Depending on the type of SMP, it can be altered from one shape to the next using heat, moisture, pH, or electric or magnetic fields. The Livermore-developed SMP foam plug is altered with heat.

Researchers first cut a plug out of the foam material to match the contours of an aneurysm. Then a crimping machine with heated blades compresses the foam plug into a stable secondary shape that can be fed through catheters via a fiber-optic cable to the aneurysm sac. Once the plug reaches the sac, it is heated with diode laser light through the fiber-optic cable. Heating time could range from as little as 10 seconds to several tens of seconds, depending on the temperature at which the foam plug is designed to fully expand to its primary shape. As the plug expands, it absorbs blood, which congeals and forms clots to stop blood flow inside the aneurysm.

Fig. 6 (a) 10 mm SMP Foam in its original Shape

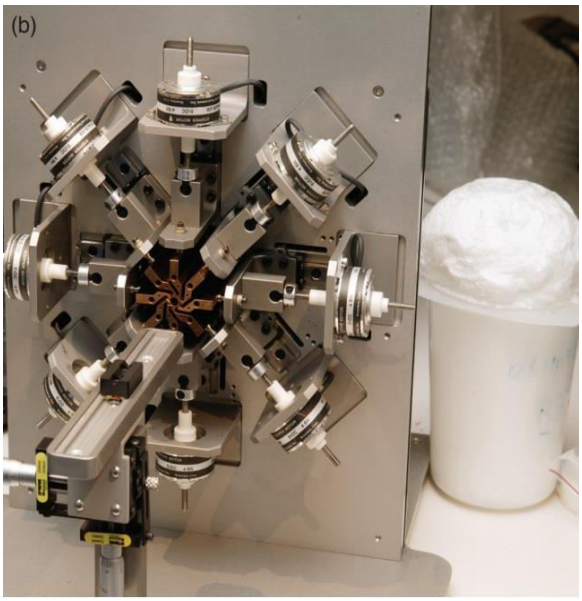


Fig 6 (b) An eight-blade cylindrical crimping machine with heated blades

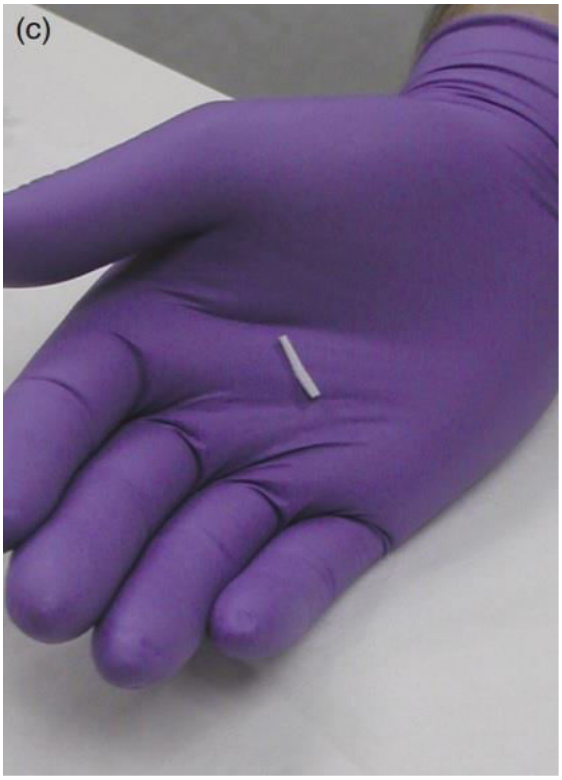


Fig 6 (c) Foam in its secondary shape[3]

[3] Lawrence Livermore National Laboratory

Foam versus Platinum

If Livermore's foam-plug procedure is approved for clinical trials, it could lead to a new, nonsurgical treatment option for patients. It is optimistic because the foam plugs offer several advantages over platinum coils, including faster and more complete occlusion of the aneurysm and lower and more uniform stresses to the aneurysm wall, thereby decreasing the risk of hemorrhage. If the coils become compacted, the already vulnerable aneurysm wall may be reexposed to blood flow.

The foams are softer and have more tissue like mechanical properties, so they are less likely to injure surrounding arterial tissue. In addition, unlike platinum coils, Livermore's foam plugs could be made from bio-absorbable material, which could help to heal the aneurysm.

They are also trying to develop a foam plug that can biodegrade into small molecules and be safely absorbed. It is hoped that the device would essentially disappear and be replaced by human tissue. [20]

Advanced Technology for Better Surgical Outcomes

Surgical clipping is an open procedure that involves cutting off the aneurysm's blood flow. Neurosurgeons at IU Health Neuroscience have access to a sophisticated fluorescence technology called INFRARED 800 to improve success rates and minimize risks. INFRARED 800 enables quick visualization of blood flow with the aid of fluorescence technology, which provides neurosurgeons with real-time images during surgery. Any problems can be immediately identified and corrected, allowing neurosurgeons to have a higher degree of certainty with fewer complications. [Link 3]

Breakthrough Treatment for Broad-Neck Aneurysms

In the case of wide-neck aneurysms, which are considered the most difficult aneurysms to treat, the opening is less like a balloon and more like a bowler hat. This makes it nearly impossible to clip and challenging to treat with coiling—even with the aid of a stent.

The new endovascular devices attack the aneurysm by remodeling the parent artery and restoring natural blood flow. The Covidian Pipeline Embolization device is the first-such device to be approved by the FDA.

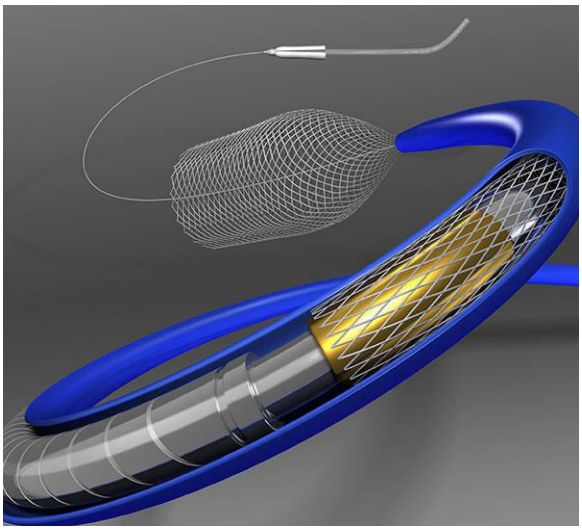


Fig. Covidian Pipeline Embolization Device [4]

It's a whole new way of approach aneurysm treatment. During an endovascular procedure, a flexible, mesh, stent-like device is placed over the opening of the aneurysm and acts as scaffolding to the parent artery. The device is made up of 48, very tightly braided strands of metal and is less porous than traditional stents. It diverts blood flow downstream, restores natural blood circulation and allows the aneurysm to thrombose. [13]

The latest breakthrough in endovascular treatment has just become available to us in the United States. In selected patients with aneurysms that are unsuitable for coil treatment

[4] http://www.medgadget.com

or in whom previous treatment has failed to occlude the aneurysm, Onyx treatment offers an endovascular alternative. Onyx is a liquid ethylene vinyl alcohol polymer suspended in dimethyl sulfoxide (Micro Therapeutics, Inc., Irvine, CA) that adheres to itself and solidifies slowly from the outside in, allowing conformation to the aneurysm sac with subsequent occlusion. [18]

The most important limitation of this technique is the relatively poor control of migration of the liquid embolic agent into the parent artery. The use of a microballoon across the neck of the aneurysm, a microstent deployed across the neck of the aneurysm, or the deposit of GDCs into the aneurysm allowed faster and more complete filling of the aneurysm with Onyx.[19]

Conclusions

Our understanding of the etiology, anatomy, natural history, and treatment of aneurysms continues to evolve. New technology and innovation have given us more tools in our armamentarium but have certainly complicated our choices of management. It is imperative that, as we continue to develop our knowledge of cerebral aneurysms and their management, we remain focused on the optimal treatment for the individual patient, doing not only what can be done, but what should be done. This last decade has seen extraordinary changes in the treatment of ruptured and unruptured aneurysms alike, and we fully expect that theses paradigms will continue to shift as new randomized studies and long-term follow-up data on endovascular treatment becomes available

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[20] Duncan Maitland (979) 458-3471 (djmaitland@tamu.edu) or Thomas Wilson (925) 422-5519 (wilson97@llnl.gov).

Links:

1.http://www.brainaneurysm.com/symptoms

2. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2666114/

3. http://iuhealth.org/knowledge/detail/treating-brain-aneurysms-the-latest-advances-and-treatment-options/

4. http://www.vascular.surgery.ucsf.edu/conditions--procedures/abdominal- aortic-aneurysm.aspx

5.https://www.vascularweb.org/vascularhealth/Pages/endovascular-stent- graft.aspx

"DEEP BRAIN STIMULATION" (DBS)- A surgical therapy for neurological disorders

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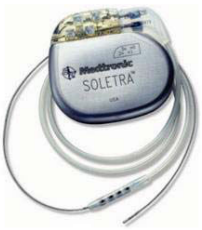
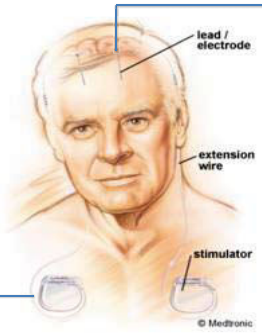
Introduction to a DBS (Brain Pacemaker) system

Three main parts of DBS System

- Neurostimulator-It is a programmable powered pacemaker that creates electric pulses[3].
- Lead/Electrode-It is a coated wire with one or more electrodes at the tip that deliver electric pulses to the brain tissue[3].
- Extension wire-It is an insulated wire that connects the lead to neurostimulator[3].



DBS Hardware system (Source: megadget.com)



DBS Hardware implanted in a patient (Source: mayfieldclinic.com)

DBS Lead with Platinum electrodes (Source: cabellhuntington.org)

- It is placed inside the brain.
- It is quadripolar[3].
- It connects to the extension wire through a small hole in the skull[3].

DBS Extension wire (Source: professional.medtronic.com)

- These run subcutaneously through the skin.
- It runs from scalp behind ear, down the neck to the chest[3].

DBS Neurostimulator (Source: businesswire.com)

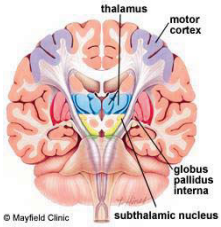
- It is the titanium unit containing the electronics and power supply.
- It is placed under skin of the chest below collarbone.

DBS Procedure and Surgical Methodology

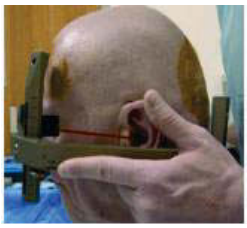
The first step of planning involves identification of specific targets and their trajectory in the brain which is done by CT or MRI scans taken after the head is attached to a stereotactic frame[1]. The skin is anesthetized locally and hair is shaved[2]. Using a drill, blurr holes are made for electrode to pass through. A recording electrode is then inserted to a precise angle and depth from calculations of the CT/MRI scans. It's position accuracy is tested many number of times. Once the exact nerve cells are located, recording electrode is replaced by DBS lead followed by implantation of neurostimulator by a small incision made near the collarbone[5]. Few days after the surgery, the neurostimulator will be programmed and the medication dosage will be adjusted. The patient can control the stimulation by turning it on or off, selecting programs and strength of stimulation with the help of a hand-held patient controller. DBS batteries last 3 to 5 years depending on the settings and are usually replaced on an outpatient basis[3].

DBS Target sites and Effects of therapy [2]

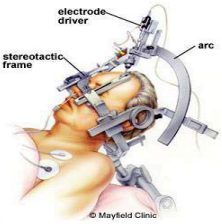
DBS SITE	EFFECT OF THERAPY
Thalamus	Reduction in tremor
Globus Pallidus internus (GPi)	Reduces tremor, rigidity, bradykinesia, gait problems, dyskinesia
Subthalamic Nucleus (STN)	Reduces tremor, rigidity, bradykinesia, gait problems, dyskinesia



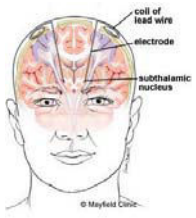
Identification of specific targets in brain



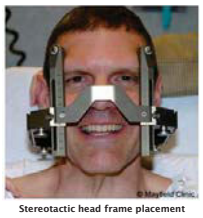
Planning trajectory of electrode by brain-imaging study[5]



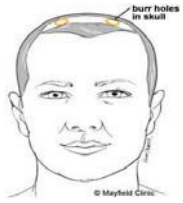
Electrode insertion into the brain



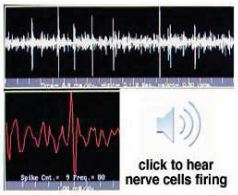
Stimulation of brain cells after electrode tip is precisely placed followed by implantation of stimulator



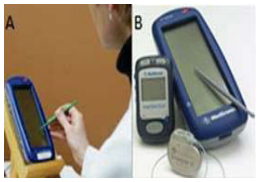
Stereotactic head frame placement



Skin and skull incision



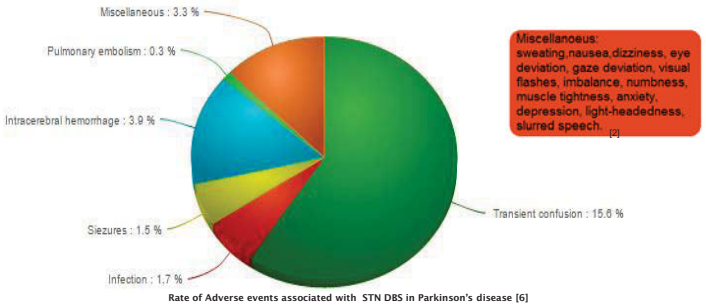
Electrical waveforms of nerve cells detected by recording electrode(Source:mayfieldclinic.com)



(A)Programming and settings adjustment(B)Patent controller and clinician programmer(Source: dbsprogramming.org)

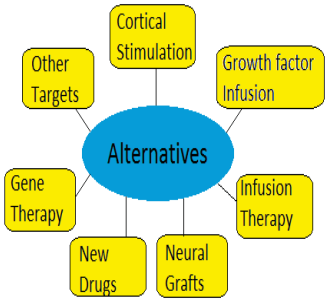
Risks, Problems and Alternatives

The complications are surgery-related, hardware-related and stimulation-related.



Rate of Adverse events associated with STN DBS in Parkinson's disease [6]

- Lead migration occurs when the electrode has moved away from the optimal target site[4].
- Fracture, disconnection or damage of the connecting wire leads to serious consequences.
- Malfunction or injury to the neurostimulator is a major technical problem[4].
- Misplacement of the brain electrode occurs even with the best equipment and skills[4].



Alternatives suggesting better solutions to drawbacks of DBS

Conclusion and Future Outlook

DBS directly changes brain activity in a controlled manner. It's effects can be reversed compared to other lesioning techniques. It is riskier for people above 70 years age who are prone to stroke. A major future challenge is selective stimulation of motor parts of thalamus[5]. All hardware components need to be redesigned, miniaturised, made more biocompatible and compact. Recharcheable stimulators eliminate the need for battery replacement[5].

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INTERVENTIONAL NEUROLOGY- DEEP BRAIN STIMULATION

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Abstract— **Deep Brain Stimulation (DBS), also known as the "brain pacemaker" is an invasive surgical therapy procedure that is approved by the U.S Food and Drug Administration (FDA) for controlling the symptoms of various neurological diseases, especially Parkinson's disease, essential tremor and dystonia. Just like a cardiac pacemaker helps to maintain an appropriate cardiac rhythm, DBS is presumed to help modulate dysfunctional circuits of the brain so that the brain can function more effectively. It is a procedure that involves the placement of electrical wires on certain areas of the brain through which electrical stimulation is delivered to relieve certain symptoms. For people with Parkinson's disease (PD), DBS can reduce tremors and significantly improve slowness and stiffness. For people with Essential Tremor (ET), DBS can make the tremors disappear, allowing them to eat and drink without spilling. For people with dystonia, DBS can relax the muscles, improve abnormal postures caused by muscle contractions and improve their quality of life. In other words, it is a life-changing therapy that can allow people to do simple things they had been unable to do for years. Although it is proven to be helpful for many patients, there is also a potential for serious complications and adverse side effects including apathy, hallucinations, hyper sexuality, cognitive dysfunction and depression. However, these may be temporary and related to correct placement and calibration of the stimulator and so are potentially reversible. For over 50 years DBS has been used for relieving a variety of intractable pain syndromes including neuropathic pain, phantom limb pain, low back pain and cluster headache pain.**

Keywords— ***Deep brain stimulation (DBS), Parkinson's disease (PD), sub thalamic nucleus (STN), Globus Pallidus internus (GPi), Magnetic Resonance Imaging (MRI)***

I. INTRODUCTION

Neurological diseases comprise movement disorders that affect the ability to control movement. The basal ganglia of the brain comprises of a group of interconnected deep brain nuclei, Globus pallidus (GP), substantia nigra (SN), sub thalamic nucleus (STN) that through their interconnections with the thalamus and the cortex influence the movement and muscle tone. Disruption of this complex circuitry causes movement disorders like Parkinson's disease, essential tremor, dystonia and other gait difficulties. Deep Brain Stimulation (DBS) has been a popular surgical treatment for such neurological diseases since the past decade and its application is extended to even treat neuropsychiatric problems like pain, depression and obsessive compulsive disorder (OCD) [2]. It involves continuous high-frequency stimulation of certain brain regions using chronically implanted electrodes [4]. Although the mechanism of action of DBS is not clearly understood, it has gained widespread acceptance as the preferred surgical treatment for a variety of neurological diseases especially PD due to its remarkable improvements in motor function and subsequently for improving the quality of life of PD patients who suffer sustained long-term disorders.

The first report of human cortical stimulation appeared in 1874. In the 1930s, electrical stimulation was used to map cortical function but the effects of stimulating deeper structures of the brain were not investigated by neurosurgeons until stereotaxic devices were developed in the early 1950s [1] [2]. In 1964, it was reported that high-frequency stimulation (100Hz) of the ventro-lateral thalamus could diminish tremor. In 1966, Sem Jacobsen developed a method of implanting a bundle of multiple electrodes deep in the brain and leaving it in place for weeks during which stimulation was delivered. Although the goal was lesion guidance and targeting in the early 1960s, there emerged shortly thereafter the use of chronic stimulation therapeutically for treatment of pain, movement disorders and epilepsy. In 1976, Cooper published the report of chronic cerebellar stimulation studies for cerebral palsy where stimulation was delivered transcutaneously through inductive coupling devices to electrode implanted on the surface of the cerebellar cortex. After the development of fully implantable cardiac pacemaker in the 1960s, this technology was later combined with the chronically implanted deep brain electrodes for long term stimulation of the brain in the 1990s [1]. The first widespread use of DBS in United States and Europe came with treatment of tremor in PD or ET. Benabid and his colleagues in 1991 reported the efficiency of stimulation of the ventral intermediate nucleus of the thalamus (VIM) for treating tremor. The use of DBS in PD was first reported in the mid-1990s. Stimulation in different sites of the brain results in different clinical effects in PD. In 1993, positive reports of DBS for medically generalized dystonia involved the thalamus and the internal segment of the Globus Pallidus (GPi) [1]. There have also been reports of DBS for

treating Tourette syndrome where the centromedian-parafascicular part of the thalamus has been targeted. Patients who have undergone such treatments are reported to have shown a significant degree of tic reduction.

II. DBS SYSTEM

A deep brain stimulator system has three parts that are implanted inside the body:

- Neurostimulator- It is a programmable battery-powered pacemaker device that creates electric pulses. It is placed under the skin of the chest below the collarbone.
- Lead or Electrode- It is a coated wire with one or more electrodes at the tip that deliver the electric pulses to the brain tissue. It is placed inside the brain and connects to an extension wire through a small hole in the skull.
- Extension- It is an insulated wire that connects the lead to the neurostimulator. It is placed under the skin and runs from the scalp, behind the ear, down the neck and to the chest [6] [17].

The neurostimulator is the titanium unit containing the electronics and power supply of the DBS system. Different types of neurostimulators are available worldwide: single channel, dual channel, rechargeable and non-rechargeable models. Single channel neurostimulators deliver stimulation to only one DBS lead while dual channel stimulators provide to two separate leads [19]. The DBS lead is quadripolar with four platinum/iridium electrodes encased in polymer based insulation. Extensions which run subcutaneously through the skin are available in different lengths to accommodate different body sizes and the placement of the neurotransmitter in the chest or the abdominal area [19]. The hardware is secured to the skull with a plastic cap, metal plate or cement. The patient uses a handheld controller called patient programmer to turn the DBS system on or off, change therapy programs and check battery status. The doctor programs the stimulator settings with a wireless device called the clinician programmer. The stimulation settings include data like percentage of time the stimulator is on, recharge periods, low-battery periods, battery voltage and electrode impedance which can be adjusted as a patient's condition changes over time [19]. Because the left side of the brain controls the right side of the body and vice versa, DBS is commonly performed on both sides. It represents an advance on previous other treatments which involved pallidotomy, ie. surgical ablation of the GP or thallotomy, ie. surgical ablation of the thalamus. Instead, a thin lead with multiple electrodes is implanted in the globus pallidus, nucleus ventralis intermedius thalami or the sub thalamic nucleus and electric pulses are used therapeutically. The lead from the implant is extended to the neurostimulator under the skin in the chest area which is done invasively.

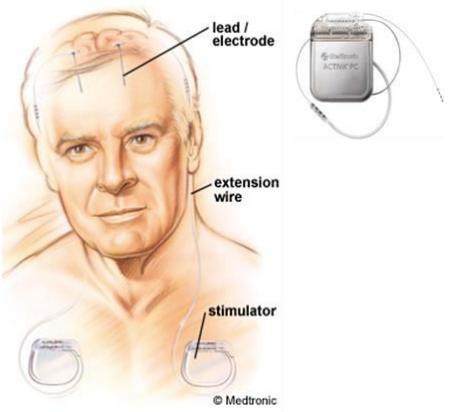

Fig.1. DBS Hardware as implanted in a patient and DBS system showing the neurostimulator, the extension wire and the lead (Rezai *et al.* [8])

III. DBS PROCEDURE

A. *Pre-operative steps*

DBS is used only for patients whose symptoms cannot be treated by medications. However, it is limited to patients who actually show some degree of improvement after taking medications. In general, the whole procedure can be distinguished according to preoperative planning, surgical procedure and postoperative follow up. The surgical procedure is discussed in detail in the next chapter.

The first step of planning is aimed to identify specific targets in the brain and the trajectory to reach this target. These are planned on preoperative anatomical images. In general, markers are introduced into the skull of the patient with the help of a stereotactic system, an example of which is seen in Fig. 2. in order to introduce a reference to the system. The neurosurgeon uses MR-Imaging or CT scanning to identify brain locations where surgical intervention can be done. Some surgeons use microelectrode recording which involves a small wire that monitors the activity of the nerve cells in the target area, to identify the precise area to be stimulated. Generally these areas are thalamus, STN and GP [7]. MRI is the best imaging modality to visualize anatomic targets. The sequence used depends on the chosen target structures- T1 or proton density weighting is especially used for the targeting of GP, T2 imaging for STN targeting and inversion recovery images are best suited for targeting of GPi and STN [8].

The time of image capture can vary in different centers according to different procedural styles, different clinical centers, imaging modalities and targeting techniques. Some centers acquire stereotactic MRI the day of implantation just before surgery, while others perform surgery the day before the surgery and reposition the stereotactic frame the day of surgery. More often, an MRI is acquired some days before the implantation to be merged with a stereotactic CT of the day of the surgery [8].

- Targets for DBS

It is important to understand the brain circuitry in terms of neural networks for various neurophysiological interactions in order to define specific relay ―nodes" that may be targeted by electrical perturbation by DBS. For patients with PD, STN is mostly taken as the target or ―node", and the GPi is taken in case of PD as well as for dystonia. For ET, the VIM of the thalamus is taken as current target [6] [24]. All these targets are shown in Fig. 3.

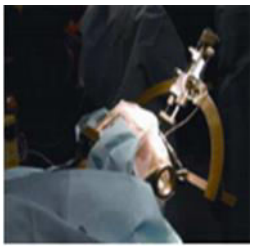

Fig.2. Leskell stereotactic frame (Rezai *et al.* [8])

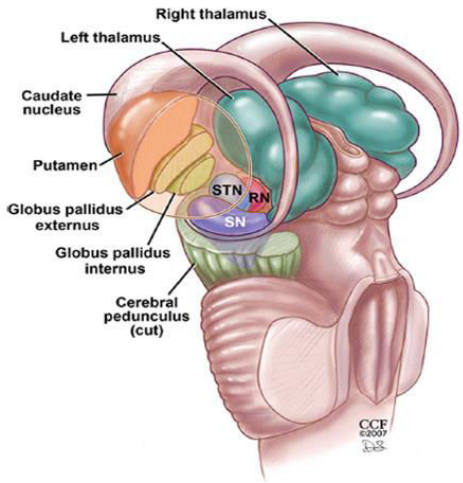

Fig.3. Targets for DBS (Rezai *et al.* [8])

It is interesting to note the existence of different cortico-striato-pallido-thalamo-cortical (CSPTC) circuits, each linked to a specific area in the striatum. Different circuits exist for limbic, associative and motor functions [8] [24]. These circuits maintain some degree of anatomical separation. However, they are not totally isolated as there are some interfaces seen between them as in the case of primates, allowing more limbic circuits to influence more dorsolateral motor circuits [24]. This allows for a link between emotion and motivation with cognition and planning which finally manifests with a motor output and behaviour. The most commonly described loop is the motor circuit and it is implicated in pathogenesis of PD. Abnormal activity patterns in the motor circuit are correlated with the appearance of Parkinsonism [24]. The loss of dopaminergic substantia niagra pars compacta (SNc) cells in the CSPTC loop is the best known pathological feature of PD. Therapeutic effects can be achieved by electrical stimulation to the specific critical points along the anatomical pathway of these circuits and the three different sites for DBS therapy are summarized in Table I.

TABLE I. Effect of Therapy in the three DBS sites [7]

DBS Site	Effect of Therapy
Thalamus (VIM)	Reduces tremor but not the other symptoms of PD
Globus Pallidus internus(GPi)	Reduces tremor, rigidity, bradykinesia, gait problems, dyskinesia
Subthalamic Nucleus(STN)	Reduces tremor, rigidity, bradykinesia, gait problems, dyskinesia

- Targeting techniques

In general, there are two types of targeting techniques; namely ―direct targeting" and ―indirect targeting" [8]. When the planning is done with the definition of the entry point, the trajectory and target point with the help of high definition MR and/ or CT and MR data alone, it is called direct targeting [24]. When surgeons prefer the use of anatomical brain atlases created from dissected brains and superimposing them on MRI to improve the identification of the nuclei in the thalamus or basal ganglia (e.g. STN, GPi) or other invisible structures of deep brain, it is called indirect targeting [24]. Modern versions of these atlases are available for computer use and as 3D image reconstructions. The former method is more often considered inferior to the latter in terms of predicting the optimal contact position. However, the main challenge in planning this step is that the patients' anatomy doesn't always match the atlases and the brain can move and shift in the skull during surgery. Probabilistic atlases are being employed for overcoming this problem [23] [24]. Fig.4. shows high resolution MRI images obtained from the direct targeting technique. The anatomical location of the STN is anteroposterolateral to Substantia niagra pars reticulate (SNR) and the Red nucleus (RN) [24]. The nodes or critical target points in the brain circuitry can be targeted for lesioning or DBS implants with sub millimeter accuracy using modern imaging and neurophysiological stereotactic surgery [24].

B. Postoperative follow up and care

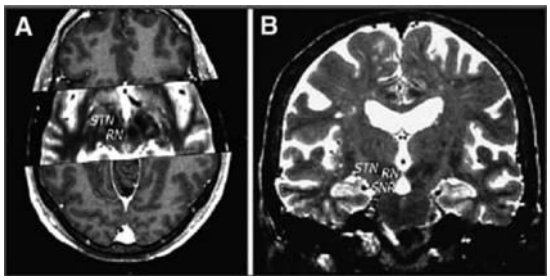

Fig.4. Axial (A) and Coronal (B) T2 weighted MRI scans showing STN (Rezai *et al*. [8])

The patient normally leaves the hospital 2 days after the surgery. After 1-2 weeks, the patient visits the hospital again for suture removal and check of incisions. The postoperative pain is assessed and monitored along with surgery complications or side-effects. Testing all electrodes for efficacy occurs one month after the surgery. A postoperative MRI or CT may be obtained to merge with preoperative MRI to confirm lead placement. The medications can be continued as taken prior to surgery unless troubling side-effects are experienced [5]. The medications need to be adjusted as required when the stimulation is maximized. To program the stimulator, additional visits to the doctor are needed the first three months. These visits decrease to once or twice per year depending on the patient's condition. DBS batteries last 3 to 5 years depending on the settings and are usually replaced on an outpatient basis. Once the DBS has been programmed, the patient is sent home with instructions for adjusting his own stimulation. The handheld controller allows him to turn the stimulator on and off, select programs, and adjust the strength of the stimulation [19]. Most patients keep their DBS system turned on 24 hours day and night. Some patients with essential tremor can use it during the day and turn off the system before bedtime. The doctor may alter the settings on follow-up visits if necessary. If the DBS has a rechargeable battery, the patient will need to use a charging unit. On average charging time is 1 to 2 hours per week [4]. The patient will have a choice of either a primary cell battery or a rechargeable unit and the patient should discuss this with his surgeon prior to surgery. Just like a cardiac pacemaker, other devices such as cellular phones, pagers, microwaves, security doors, and anti-theft sensors will not affect the stimulator. The patient is asked to carry his Implanted Device Identification card when flying, since the device is detected at airport security gates [4] [5]. If patients undergo any surgery, only bipolar cautery may be used. Monopolar cautery, using a Bovie, is contraindicated. If skin cancer surgery is required within three inches of any of the DBS components (battery, extensions, leads) a DBS-surgeon should be involved in the case.

IV. SURGICAL METHODOLOGY OF DBS

The surgical technique of implantation of a DBS device consists of two stages: the first stage is the DBS- electrode placement which was discussed in the previous chapter, the second stage is the DBS- battery placement. Both these stages can be done in the same occasion or in two different occasions [24]. The operative methodology of DBS is the similar to ablative stereotactic neurosurgery, excluding the final stage of electrode implantation. If the patient decides to pursue Deep Brain Stimulation (DBS) therapy, the next step will be planning and preparation of the surgery and recovery. It is important to understand the need to select a center that has a staff of experts who specialize in DBS therapy for the treatment of Parkinson's disease. Once the patient has been referred to a DBS center, he or she plans to bring a family member or friend with him or her for the appointments [7]. The patient needs to make sure that he meets with the movement disorders neurologist, neurosurgeon, neuropsychologist, psychiatrist and nurses who will be involved in his care. In many cases a physical therapist, occupational therapist, and speech therapist will be necessary members of the team. The patient is prepared to ask questions about DBS, and make sure that they are answered to his satisfaction before the procedure takes place. The staff is even asked if there are other patients who have had the surgery performed, and if the patient can speak to them about their positive and negative experiences. How the surgery is performed in the awake and asleep conditions is discussed below [7].

A. Awake microelectrode-guided DBS

- Anesthetization

  First, the skin is anesthetized with a local anesthetic. A stereotactic head frame as in Fig.5. (A) is then fixed to the patient's head and a brain imaging study is made with the frame in place. An arc-shaped device is attached to the frame to plot the coordinates and drive the electrode to exact location and depth in the brain as shown in Fig.5. (B). With the images of the brain and the frame, the position of the desired brain target is calculated. The instruments are guided to that target with minimal trauma to the brain. In the operating room, an intravenous sedative is given with the stereotactic frame fixed rigidly to the operating table. The scalp is made completely numb after a patch of hair on top of the head is shaved and the scalp is washed. Then an incision is made on top behind the hairline and a small opening is made in the skull [6]. If both the sides of the brain are to be implanted, the skull opening is made on both sides before sedation is stopped and the patient is fully awoken.

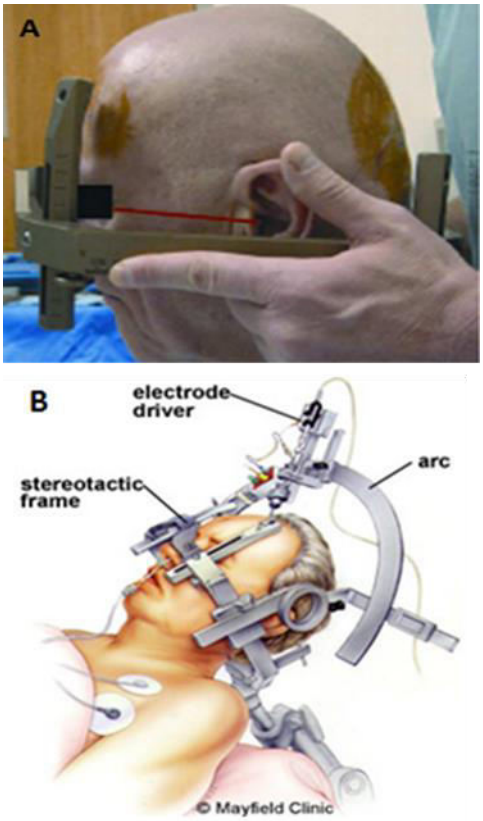

Fig.5. (A) Stereotactic head frame placement (B) An arc-shaped device attached to the frame (Rezai *et al.*[8])

- Brain mapping

  Brain mapping is done during the procedure with hair-thin microelectrodes to record brain cell activity in the region of the intended target to confirm the correctness of the target position or to make very fine adjustments of 2 millimeters or so to try and find the optimal location. During this mapping the patient must be calm, cooperative and silent or else the procedure must be stopped. The surgical team can listen for distinctive patterns of neuronal activity that indicate the location of the recording electrode as the brain's electrical signals are played over a speaker. This can take around 30 minutes to 2 hours for each side of the brain depending on the patient's brain anatomy. Tremor patients, although typically awake in the operating room, do not require this mapping procedure as with patients with PD and dystonia, and they can proceed directly to the implantation and testing phase.

- DBS Electrode insertion and Testing

  Once the correct target site is confirmed with the microelectrode, the permanent DBS electrode is inserted and tested for about 20 minutes. The testing is intended to focus on unwanted stimulation-induced side effects rather than on relief of motor symptoms. This is because the therapeutic effects of stimulation may take hours or days to develop but the unwanted side effects will be present immediately. For the testing phase, the device is deliberately turned to a higher intensity than normal so as to produce unwanted side-effects induced by stimulation. These may include tingling in the arm or the leg, difficulty in speaking, a pulling sensation in the tongue or the face or a sensation of flashing lights. All of these induced sensations produced at high intensities of stimulation are experienced as strange but not painful.

B. *Asleep Interventional-MRI-guided (iMRI) DBS*

It is now possible for DBS electrodes to be implanted with the patient asleep in an MRI scanner instead of awake in the operating room. This has been successfully proved by the department of Neurological Surgery at University of Pittsburg who became one of the first ten programs in the world to offer such a procedure. Patients suffering from PD and dystonia may now undergo surgery without having a frame fixed on their heads and without having to be awake. This is especially beneficial for children and adults with severe dystonia who have difficulty in tolerating surgery. This new procedure is potentially appropriate for:

a) Patients in which STN or GPi is the target

b) Patients who are too dystonic to undergo an awake surgery

c) Patients who are too frightened or too anxious to undergo awake surgery

d) Pediatric movement disorder patients

It is important to note that routine MRI or CT is not permitted following DBS surgery because it can cause brain damage or injury with lead migration or even heating of the electrode. However, MRI of the head can be done with very specific scanning equipment under the supervision of a highly experienced DBS team. Diagnostic ultrasound is safe and so is cardiac pacemaker along with DBS as long as they are placed 10 inches apart to avoid interference between the two devices [7].

V. PROBLEMS AND ALTERNATIVES

A. *Surgery-related risks and complications*

No surgery is without risks. General complications of DBS surgery involving placement of DBS lead include seizure, infection and a 1% chance of bleeding in the brain. Other complications include blood clots, breathing and balance problems, worsening of movements, dyskinesia, slurred speech, nausea and heart problems [9]. The risk of death is less than 1%. There is a small risk of stroke of around 2-3% [7]. The risk of infection at the surgery sites in the brain, scalp or chest is about 5 to 20% [7]. Possible side effects after surgery are anxiety, depression, confusion, hallucinations, dizziness, tingling or an electric jolting sensation etc. [7]. Many of these unpleasant effects can be almost immediately improved by turning off the stimulator with the handheld patient controller or patient programmer [4] [5], seen as the black device in Fig.6 (B). An adjustment of stimulation settings by the neurosurgeon

on the clinician programmer, the blue device as in Fig.6 (A) should take care of these effects [18]. The patient must give frequent visits to the neurosurgeon to get the settings adjusted.

B. *Hardware-related complications*

Reasons for which one might need additional surgery include breakage of the extension wire in the neck; parts may wear through the skin; and removal of the device due to infection or mechanical failure [10]. Technical problems associated with DBS devices can be summarized as:

a) Lead migration, when the electrode has moved away from the optimal target site [10].

b) Fracture, disconnection or damage of the connecting wire [7].

c) Malfunction or injury to the neurostimulator [7].

d) Misplacement of the brain electrode[10]

Even with the best equipment and skills, there is a chance of electrode being misplaced. Anything that puts direct pressure on the implantable devices must be avoided. Also, twisting and pushing of implanted parts of the DBS system must be avoided. Manipulations can damage the system and cause skin erosion or infection [13]. In some instances, the treatment has to be discontinued or the stimulator and related hardware has to be fully removed.

C. *Stimulation-related complications*

Possible side effects of stimulation are motor contraction, eye deviation, gaze deviation, visual flashes, nausea, dizziness, sweating, imbalance, numbness or tingling sensations, muscle tightness of the face or arm, light-headedness etc. [7] [20].

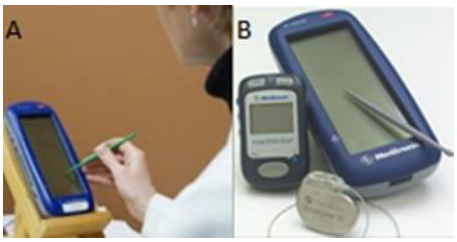

Fig.6. (A) Settings adjustment (B) Patient controller and clinician programmer [19]

All these adverse effects are generally reversible and can be alleviated by adjusting the settings. However some effects might occur with the progressive increase in voltage necessary to adequately control parkinsonian features. A good indicator of accurate electrode placement is stimulation-induced dyskinesia, and it can be reversed by decreasing the voltage, the drug dose or both [18].

D. *Alternatives to brain stimulation*

Other targets- Clinical trials are underway to reassess old targets and to asses new targets like radiation prelimniscalis, caudal zona incerta and pedunculopontine nucleus. The exact anatomical structure to be stimulated is still under debate but experimental findings suggest that DBS of the mostly cholinergic pedunculopontine nucleus, which degenerates in PD, could improve gait-related motor function if stimulated at low frequency (20-25Hz) [20]. This adds to the benefits of STN high frequency stimulation (STN-HFS) by improving gait, but on its own cannot recreate the positive effects given by STN-HFS on motor symptoms of PD [14]. Ablative methods have also been proposed to solve the problems of cost but its high rate of severe complications suggest that better solutions to drawbacks of DBS must be sought [3].

Cortical stimulation- Experiments have shown that there is an improvement in PD symptoms when the motor area of monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonism were assessed for chronic cortical stimulation. However, there have not been reports of results of such trials in humans although clinical trials are still being done.

Gene Therapy- With the development of effective gene delivery systems, viral vector technology has made great progress in effective targeting of neuronal populations in cluster of brain nuclei that are responsible for symptoms of PD. These vectors can transfer genetic information to the brain and allow for long term exposure to factors that would otherwise not cross the blood-brain barrier. By their continuous expression of enzymes involved in dopamine synthesis, fluctuations in brain dopamine can be avoided.

Growth factor infusion- Introducing a growth factor into the brain of patients may be a future treatment for diseases like PD. Dr. Steven Gill, a neurosurgeon in Bristol assessed the efficacy of using a glial-derived neurotrophic factor (GDNF) into the putamen area of the brain. Improved motor function was seen in five patients with advanced PD. Therapeutic effects of GDNF are seen in rats and monkeys. Intraventricular injections have not been so effective due to lack of penetration into the correct area of the brain [16].

New drugs- Levodopa is the first effective medication taken to treat PD [23]. It is converted into dopamine by brain and stored in the neuron until needed by the body for movement. Pharmaceutical companies are working intensively to bring out a new drug that would deliver the beneficial effects of levodopa without the major complication of dyskinesia.

Infusion therapy- Continuous infusion of dopamine agonists such as lisuride and apomorphine produces a more stable and regular dopamine concentration in the brain rather than pulsatile administration of levodopa that results in a loss of optimum response by striatal dopaminergic receptors [12]. Although it induces cutaneous nodules at the site of injection, it clearly decreases dyskinesia.

Neural grafts- This approach is still experimental and not currently available to patients. There is immense research on grafting methods to check for clinical improvement, evidence of dopaminergic reinnervation of the striatum, good survival of the grafted neurons, efficient production of dopamine and increased tyrosine hydroxylase immunoreactivity which is the rate limiting enzyme in dopamine production. Stem cells have been investigated widely due to its better immunological tolerance. Other types of cells that have been used are adrenal gland, mesencephalic fetal grafts and more recently, epithelial retinal cells.

VI. CONCLUSION AND FUTURE OUTLOOK

DBS is generally well tolerated and does not damage nerve cells like other surgical treatments for Parkinson's disease. Many patients report significant improvement in their symptoms after having this treatment. However, most of them still need to take medication, although at lower doses, which improves their quality of life [19]. This surgery, and surgery in general, is riskier in people over age 70 and those with health conditions such as high blood pressure and diseases that affect blood vessels in the brain. The patient and the doctor should carefully weigh the benefits of this surgery against the potential risks. The DBS procedure can be reversed, if needed [19].

From a systems neuroscience point of view, the overall causal and interventional nature of DBS is very exciting [21]. It directly changes brain activity in a controlled manner and its effects are reversible compared to other lesioning techniques [23]. It is also the only neurological method that allows blinded studies whereby one can unravel the fundamental mechanisms of human brain function by mapping the effects of this causal intervention. There are new researches going on for the possibilities of more sophisticated stimulators, including demand-driven stimulator technologies. In order to make DBS a more widely available surgical treatment especially in countries where healthcare systems are developing, cost of equipment and duration of surgery must be significantly lowered [11]. Each DBS surgery can cost from 30,000 to 50,000 dollars or even more; which patients find hard to afford. More selectivity is needed at both the topographic level with newly designed electrodes and rechargeable batteries, and at the level of stimulation with the pulse sequence or waveform as well as the targets. Hardware manufacturers have developed rechargeable stimulators that eliminate the need for battery replacement [11]. All hardware components need to be redesigned, miniaturized, and made more biocompatible and more compact, and designed to suppress cables and distant pulse generators via nanotechnology. Additionally, an important future challenge is to selectively stimulate only the motor part of STN so that unwanted side-effects like depression can be avoided [22]. There is also a global consensus on timing of the surgery proposing it to be done at an earlier stage of the disease, as soon as the symptoms cannot be adequately managed by drugs and when the risk to benefit ratio has become reasonable. However, this is yet to be proved by large multicenter studies.

Although DBS is used to treat various neurological disorders, new applications are being investigated to treat obesity, choreoathetosis including Huntington chorea and in vegetative state [11]. It essentially relies on open loop continuous stimulation with little dynamic possibility for adjustment to the individual. However, the possibility of recording of signals from the DBS electrode opens prospects for development of more sophisticated closed loop variable DBS that is customized to the morphology and anatomy of the target. Such closed loop systems with sensors that detect local neuronal activity and a processing system to interpret this data with multiple output electrodes might allow it to precisely modify neuronal activity thereby making DBS a first line therapy for various neurological disorders [11]. The development of such devices require a thorough understanding of the normal oscillatory brain activities which may be provided by neuroimaging studies or computer models of neural activities. This research opens up the possibilities of advanced brain-computer interfaces, which comes useful for patients with pathological conditions [21]. For example, patients with spinal cord injuries can learn to control their limbs or prostheses. In future, DBS-driven brain-computer interfaces might help in modulating brain activity in vegetative or minimally conscious states [21]. Finally, the mechanism of action of DBS and whether it has a neuroprotective effect needs to be addressed both by basic research and clinical trials along with clinical and metabolic assessment of its effects on disease progression, stability or even regression in a precisely quantitative manner [15]. This is the only way to find out if this theoretical, yet controversial concept has any validity and use in clinical situations.

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Telemanipulation System for XR and MRI

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Introduction

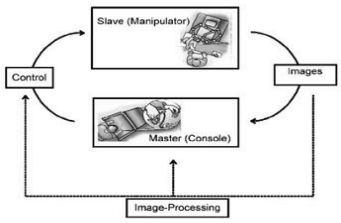

Fig.1.Workflow of surgical telemanipulator with centralized control [1]

Motivation :

- Surgeon needs stability, repeatability and accuracy during intervention
- Intraoperative integration with real time MRI and XR to provide real time visualisation to surgeon
- Minimal trauma to the patient
- Protection from ionising radiations
- Increase in accessibility

Idea :

Master -Slave Telemanipulation based on intraoperative images for precised remote intervention

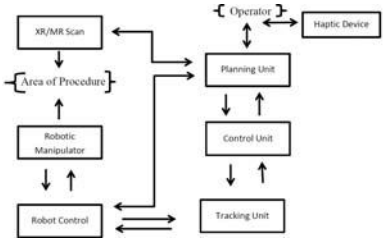

Fig.2.System Module

System Review

- Telemanipulation system is divided into three major parts : a master device, a slave device and communication channel.
- Physician gives command through master console and slave device perform the task.
- Many current network topologies such as Integrated Services Digital Network (ISDN), Transmission Control Protocol (TCP)/Internet protocol(IP), User Datagram Protocol (UDP) and Asynchronous Transfer Mode (ATM) are available and evaluated as communication channel for telemanipulation.[7]
- For design purpose system can be further divided into different units shown in Fig2.Image processing, data visualization, segmentation and registration is performed under planning and control unit .Tracking unit involves localization of spatial position and orientation of anatomy and tools. Haptic devices (mostly admittance controlled) are used by operator to give commands[6](See Fig.5). System translates the hand movement of operator into small and precised movements and robotic manipulator executes the command.

System Pipeline
Sense → Process → Perceive

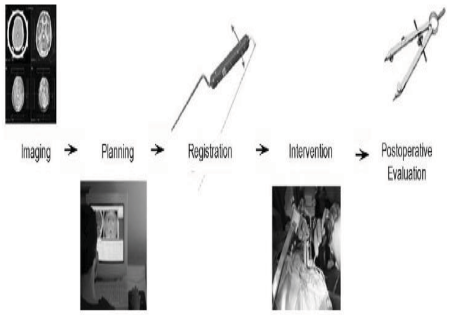

Fig.3.Sequence of surgical telemanipulation process with surgical robot [1]

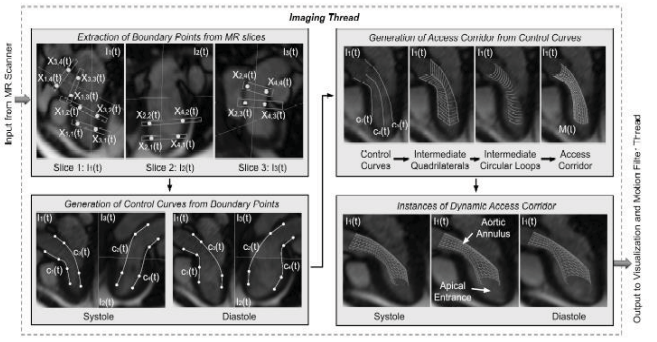

Fig.4.Image acquisition using MR and processing for intracardiac intervention [2]

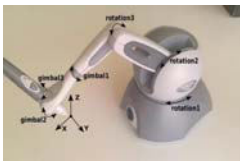

Fig.5.PHANTOM Omni Haptic Device with 6 DOF [www.cooperative haptics.com]

Fig.6.Operator working remotely using haptic device [www.waaaat.welovead.com]

System Evaluation

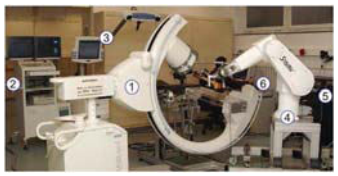

Fig.7.View of 3D Telemanipulator set up where operator is sitting away from source of radiation. 1.Fluroscopy device, 2. Fluoroscopy workstation, 3. Surgical navigation system, 4. RX 90 Robot, 5. Robot controller unit. 6. Controller PC [3]

Merits :

- Surgical operation from remote with precision
- Protection of medical staff from ionising radiation
- 3D,real time images
- Miniaturisation, small incision, decreased blood loss, speedy recovery as a result shortening length of stay in hospital

Demerits :

- Telecommunication delay/Latency
- Kinesthetic coupling and Tactile feedback[5]
- Extra time needed for navigation, robotics setup
- Additional surgical training required to operate the system
- High cost

Main Challenges :

- To find a common language for the interdisciplinary work of engineers and surgeons
- User (surgeon and patient) acceptance

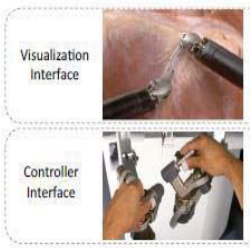

Fig.8.Combination of end effector and hand control (Haptic feedback) enable more natural interaction between surgeon and machine in Telemanipulation system [www.intuitivesurgical.com]

Conclusion and Future Scope

Telemanipulation system are still in it's stages of development but potential clinical impact of this modality is already clear. In various surgical operations such as spine surgery, heart surgery, long bone fracture reduction[2][3][4] telemanipulation with XR and MRI provides real time road map of patients anatomy and thereby more accurate surgical outcome. In future, further research, implementation of current network topologies and use of force feedback through servo motors may enable to overcome limitations of latency and tactile feedback to obtain better results[7].

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Telemanipulation System for XR and MRI

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I. Abstract

Telemanipulation systems for XR and MRI are still in its stages of development but potential clinical impact of this modality is already clear. In various surgical applications such as spine surgery, heart surgery and long bone fracture reduction, telemanipulation with advanced imaging modalities plays an important role. This review presents current applications, future potential and limitations of the telemanipulation system using diagnostic imaging tools in medical field. The aim of this work is to develop a better understanding of this concept in order to contribute to the advancement of telemanipulation based surgeries.

Keywords Telemanipulation system, Master slave model, Imaging modality.

II. Introduction

Since early ages, variety of devices have been invented to extend the human reach. This extension has led to the term telemanipulation. In 1943, when danger of working with radioactive material was better comprehended, the remote handling tongs were adapted for use behind shielding walls, using mirror to view operating field. The difficulties arising with this method of manipulation, initiated the research of modern Telemanipulator.

"Telemanipulation system is a scheme in which a slave robot arm, normally located in a remote or dangerous environment, tracks the motion of the master manipulator. In general, telemanipulation is divided into two strongly coupled processes - the interaction between operator and master device, and the interaction between remote slave and its environment" [1].

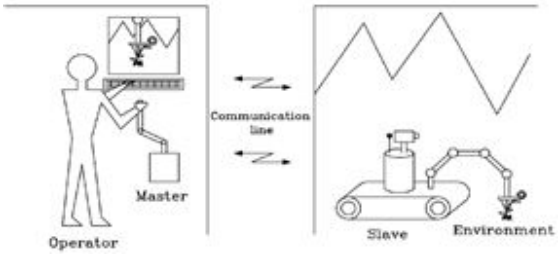

Figure 1 : General overview of the Telemanipulator System [8]

Telemanipulator was first developed by National Aeronautics and Space Administration (NASA) for the purpose of space exploration [2]. However, the medical telemanipulation system of present generation is a brainchild of the U.S. Army through the Defense Advanced Research Project Agency (DARPA) with a desire to decrease war casualties by developing telemanipulated surgery.

The master slave Telemanipulator concept was developed for medical use in early 1990's. The first recorded robot surgical procedure was CT guided brain biopsy which took place on 11 April 1985, at the Memorial Medical Center, Long beach CA, USA [2] An industrial robot, a Unimation PUMA (Programmable Universal Manipulation Arm) 200, was used to place a probe for brain biopsy using CT guidance. In these types of procedures, robots act as a Telemanipulator under the

control of surgeon. Although the first clinical trial was performed in 1985 itself, because of the high cost of its development, maintenance and purchase, surgical telemanipulation using diagnostic imaging is still in the early stages of evolution. Da Vinci Surgical System is currently widely available telemanipulation system in medical field.

Telemanipulators rely on intraoperative images, with the application of XR/CT and MR imaging devices it is possible to acquire 2D, 3D intraoperative images. Use of Telemanipulator during surgery can assist the surgeon in complex tasks with accurate and precise outcome, and it also prevents surgeon from exposure to the ionizing radiations. Telemanipulation system combines the element of robotics and cutting edge communication technology with which bits of information can be transmitted across telecommunication lines in milliseconds. In telesurgical application, surgeon performs the movement based on the images obtained from CT/MR scans. These movements of the surgeons are replicated by robotic arm using end-effector and manipulator to perform actual surgery on patient. The field of surgical Telemanipulator system is currently undergoing massive transformation and the future looks even brighter. Telemanipulation system for XR and MR can be termed as a system 'extending and enhancing human capabilities'.

Mutual understanding among surgeons, engineers, entrepreneurs and healthcare administrators is a very important factor for complete utilization and further development of this promising technology. On the clinical side, this starts with an open mind towards resolving the unmet clinical need or the unsolved clinical problem with a willingness to evaluate innovative technologies as a means for achieving resolution [3].

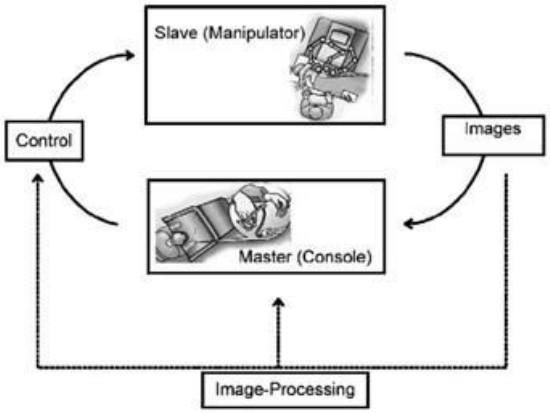

Figure 2 : Workflow of surgical Telemanipulator with centralised control [9]

III. System Review

Telemanipulation system is divided into three major parts: a master device, a slave device and an information transmission channel as shown in figure 2. Master device creates the connection between environment and machines. It is placed far away from the sources of radiation. Surgeon gives commands through master console. Mater device also has ability to perform functions such as delay compensation, modelling of remote and local dynamics. Slave device does the work at remote environment. It executes the task planned by operator. In Telemanipulation system, surgeon operates up to five robotic arms with the controller in console. Planning of robotic arm movement is based on the images obtained from traditional laparoscopic, endoscopic imaging. System translates the hand movement of surgeon into small (up to 5X reduced) and precise movements. Feedback from the sensory system such as fibre optics pressure sensor is transmitted to human operator through the information transmission channel between master and slave device. But with the implementation of advanced

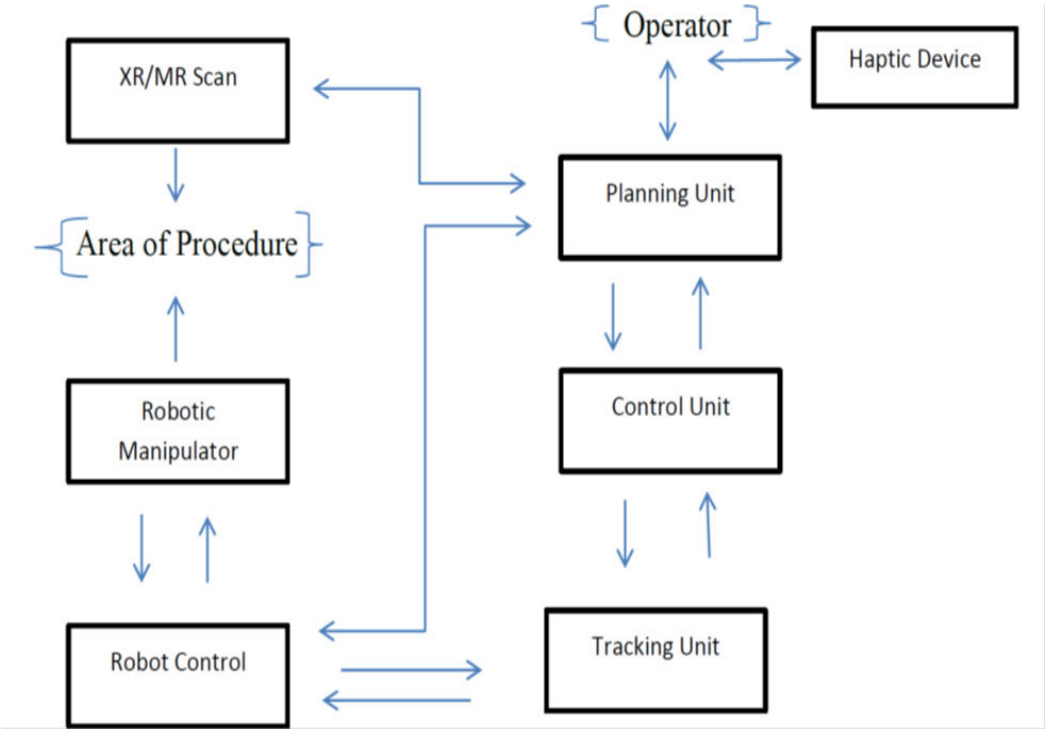

Figure 3 : System Modules

imaging modality such as XR/MRI in telemanipulation system, it is possible to resolve issues such as depth perception, spatial orientation which may affect surgical performance. In advanced 3D imaging, complete scanning from different orientation is achievable without having the patient move from treatment couch.

In Telemanipulation based on XR/ MRI, work of human operator is highly dependent on imaging data but imaging is quite a time consuming activity and time is a very important factor during any surgery. However, at the same time, accurate guidance is possible by introducing imaging modalities in the system. These two competing issues results on the control of current number of imaging sessions. Decision on required number of imaging sessions based on surgeons instinct or preference, no specific scientific optimization methods are available for it.[6]

In medical procedures such as discography, bone biopsy, radio frequency ablation, and vertebroplasty, a needle like instrument is utilized to pin point in the spine, for that it is important to have preplanning based on intraoperative images, good hand eye coordination of the medical staff and precise tracking of needle tip position. As a solution to these issues, imaging based telemanipulation system, to be precise, CT has been proposed for such applications.

For design purpose basic telemanipulation system can be divided into several modules as shown in Figure 3.

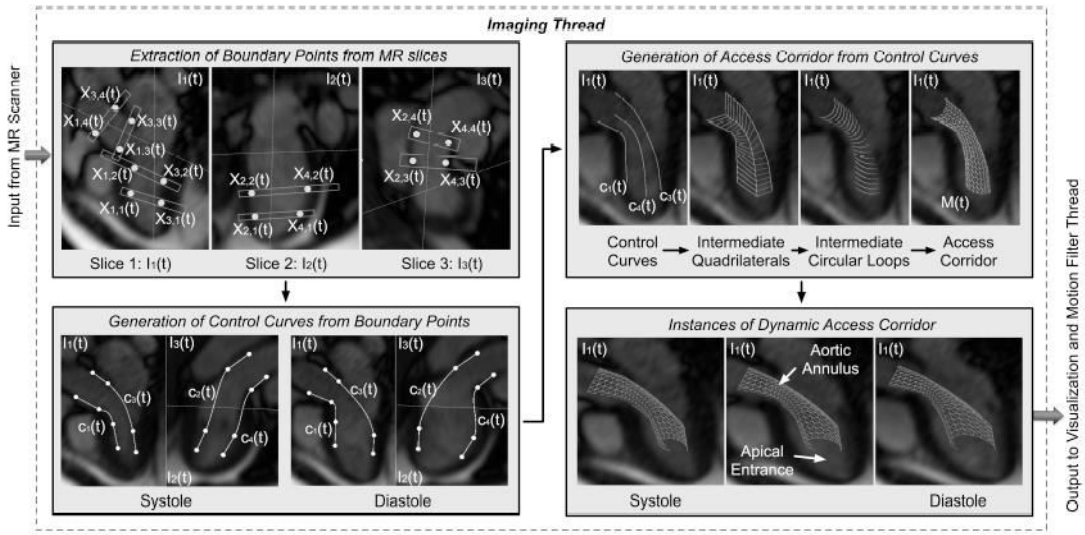

Figure 4 : Image acquisition using MR and processing for intracardiac intervention [13]

Working principle of the system follows three basic steps, which are:

Sense → Process → Perceive

Module description of the system

System shown in figure 3 has units as described below

Planning Unit

Planning unit plays a vital role in the performance of the overall system. It consists of an image processing station and a robot desktop station. It is the interface between environment and operator. It performs the operations such as intraoperative image processing and motion planning, under the control of operator. It gives physician necessary information for planning the movement of robot and giving commands to control unit. Some information from robot control is also fed to physician via planning unit in order to give him/her details for planning further commands.

Trajectory planning for surgical robot is based on information gathered from preoperative images. Therefore planning unit is synchronised with imaging modality (e.g. CT/MR). In many operations, images from the imaging tool are transferred to the planning unit by DICOM (Digital Imaging and Communication in Medicine) server which is an application protocol that uses TCP/IP to communicate between systems. Selection of imaging modality depends on the area of application. For excellent soft tissue discrimination, MR is preferred over CT. Planning unit updates the images obtained from scanner permanently at the user interface without losing previous commands.

For image processing, each image is collected and transmitted to image processing station where boundary points are extracted and based on that control curves are created. These control curves are further utilised for generating access corridor. Extraction and visualisation of access corridor, trajectory planning is important to reach the targeted anatomy as shown in figure 4 [13].

Registration is also an important process for spatial and temporal alignment of separate data stream. Various methods are incorporated for registering preoperative data to intraoperative data.

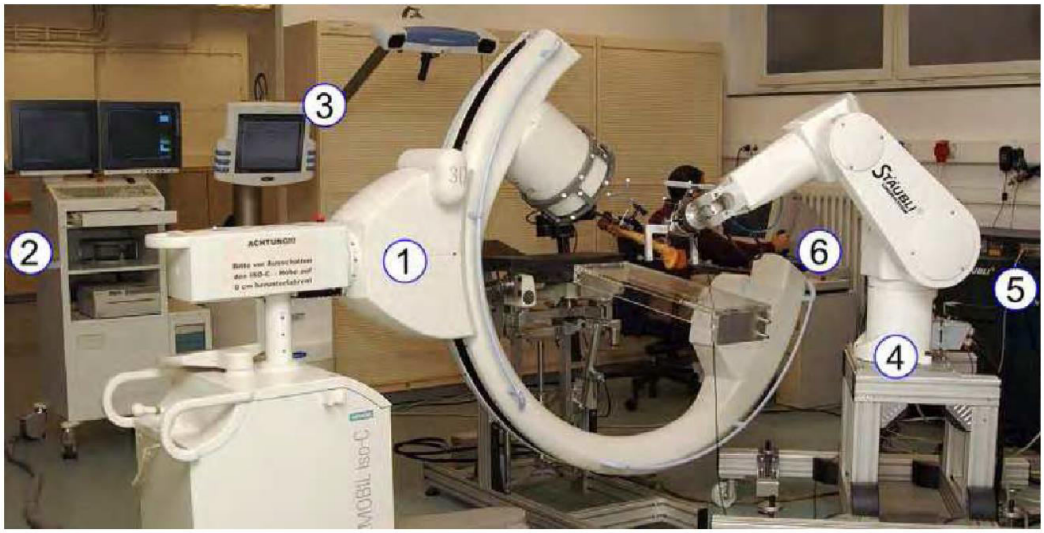

Figure 5 : View of 3D Telemanipulator set up 1.Fluroscopy device, 2. Fluoroscopy workstation, 3. Surgical navigation system, 4. RX 90 Robot, 5. Robot controller unit. 6. Controller PC [4]

For CT based registration, placing fiducial markers (titanium marker) on the patient as 'artificial landmark' prior to image acquisition is a common technique. Such markers exhibit strong contrast in acquired CT scan and get identified easily. For MRI registration, nonlinear inter-subject registration (Woods AIR 3.0), Landmark based registration techniques are used [3].

Control Unit

Control unit perform the task of execution of planned actions. This unit also reads the force sensor feedback obtained from tracking unit and performs the task of controlling other functional modules. It uses controller area network (CAN) bus to communicate with other modules. In some applications it uses USB interface or for communicating with planning unit. If planning unit runs under Windows XP which is not real time system, then such a limitation imposes the use of additional algorithm to have better performance and transition of information [6].

Tracking Unit

This unit consists of force feedback and robot control unit. It provides the current position and orientation of operating tool. It also gives information required for exact positioning of the robotic manipulator in order to perform required operation. Tracking unit also measures the deviation between the planned and actual positioning of surgical tool. Robot control unit controls the kinematic coupling of robotic manipulator by tracking current robot position. There are different tracking procedures such as optical tracking (line of sight requirement), electromagnetic tracking (no line of sight requirement). Selection of tracking method is application dependent.

For several decades, X-ray fluoroscopy has been widely used intraoperative imaging tool despite the concern about radiation exposure. Now due to the application of telemanipulator in fluoroscopy radiation exposure is minimised. Set up of fluoroscopy based 3D Telemanipulator is shown figure 5

Types of Haptic Devices

Large numbers of haptic interfaces are commercially available today due to their ability to allow user to touch, feel and manipulate three dimensional objects in virtual environment. Haptic devices track the user's physical manipulation and produces realistic touch sensation in coordination with on screen event. They can be distinctly classified as impedance controlled device (displacement in, force out) and admittance controlled device (force in, displacement out). Admittance controlled haptic devices are appropriate for master-slave application for working of complex end effector with high degree of freedom. Example of haptic devices comprises force feedback joystick, steering wheel, gloves, exoskeletal device, PHANTOM device, Haptic Master and so on [14].Widely used PHANTOM omni haptic device is shown in figure 6.

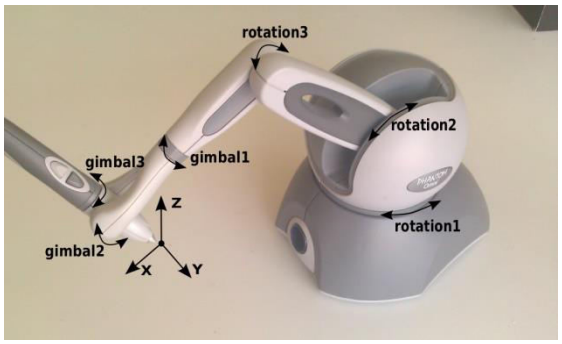

Figure 6 : PHANTOM Omni Device with 6 DOF [www.cooperative haptics.com]

IV. System Evaluation

Telemanipulation system can be evaluated for various advantages and limitations as listed below,

Advantages

Increase in the accessibility – It is possible to control telemanipulation devices from different places by force feedback or remote control devices. It increases possibility of patient in medically remote areas would have the option of receiving an operation performed by renowned surgeon even though the surgeon and patient may be kilometers apart.

In telemanipulation for XR/MR, intervention is performed under the control of intraoperative 3D imaging due to which surgeons get easy access to the body parts where direct access is difficult.

Increased precision – Robotic manipulators used in telemanipulation system are designed to be rigid and stiff. Degree of freedom (DOF) of these manipulators is often good which results into more flexibility and improvement of overall outcome by increasing the accuracy and precision of the procedure and reducing collateral damage and healing time [9].

Redundancy – By using Redundant robotic manipulator which has actuation redundancy and kinematic redundancy a larger workspace, increase in the dexterity and avoidance of configuration singularities can be achieved

Protection from ionising radiation – Less exposure to the ionising radiation is the preliminary need of operating staff. Utilization of Telemanipulation system for telesurgical process allows the use of ionising radiations as well as radiotherapy without causing much radiation exposure to the medical staff.[9]

Real time visualization – Utilization of high quality three dimensional intraoperative images transfers the real world (patient) into virtual world. With this system it is possible to process virtual

and real information in bidirectional manner which can provide more immersive experience for surgeons.

CT scanner allows multiplaner, real time visualization and also permits rapid alteration between imaging planes without complex equipment movement or projection realignment. For soft tissues, real time functional MRI provides information with better resolution. It is widely used for cardiac applications.

Limitations and possible remedies

Telecommunication Delay/Latency – Latency can be defined as the delay between surgeon's hand motion initiation and movement of manipulator device. It is the main hindrance to the implementation of this technology. This delay is inevitable and consequence of the propagation speed of electromagnetic radiation [10]. One more cause of time delay is TCP/IP (Transport Control Protocol/ Internet Protocol) which is packet switched protocol. In packet switch protocol driver divides data into packets before it is transmitted. These packets are then transmitted individually through different routes to the destination. Once all packets needed to data arrives at destination, they are recompiled to form original data. During this transmission process some packets get lost and receiver repeatedly ask driver for lost packet which causes the time delay in process. To tackle this problem new technology ATM (Asynchronous Transfer Mode) based on packet switching as well as on circuit switching is implemented for telemanipulation processes. Besides that various approaches such as Smith Predictor, delay modelling and control system design [17], Supervisory control [18], Virtual coupling impedance with position error correction method [19] are proposed to handle problem of telecommunication delay.

Kinesthetic Coupling and Tactile Feedback – Kinesthetic coupling and tactile feedback are important factors for precise manipulation and perception of skills. Kinesthetic coupling is defined as coupling giving the operator a feeling of manipulating the environment without feeling the dynamics of teleoperation. If kinesthetic coupling is limited then human cannot observe the result of his/her action on environment. A real time FEM (Finite element method) based model is implemented to impose the motion of device as the input boundary condition and generate kinesthetic (e.g. force) and tactile feedback. In this approach, low impedance robot arm for large workspace is used [12].

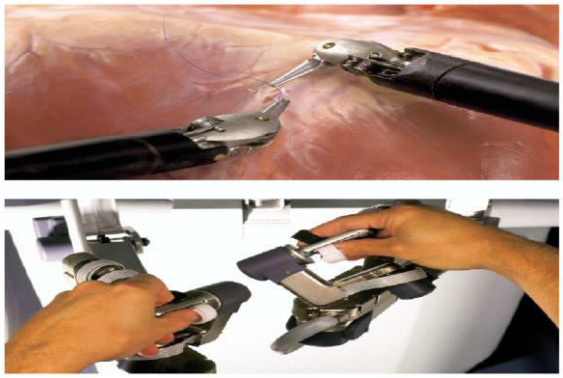

Figure 7 : Combination of end effector and hand control enable more natural interaction between surgeon and machine in Telemanipulation system [www.intuitivesurgical.com]

Cost – Overall system is expensive considering the individual cost of telemanipulation system and advanced imaging modalities. As an example, the cost associated with Da Vinci system is indicated as $ 1-2.3m with an annual service agreement of $ 100-180k and instrument and accessories of $1.3-2.2k per procedure [11].Because of its high cost access to the Telesurgery is limited to the minority hospitals.

XR and Magnetic Resonance Compatibility constraints – In telemanipulation system it is important to consider XR and magnetic resonance compatibility in order to avoid artefacts. Most important aspect during real time tracking of target position is that the robotic manipulator should be able to maneuver, even during imaging. Movement of robotic manipulator should not imply any adverse effect on imaging, at the same time, imaging should not get affected due to any motion artefacts. This requires the robotic manipulator to be made up of paramagnetic material. In addition to all, robots must be MR safe. It should not be responsible for any unintentional magnetic attraction and adverse electromagnetic side effects (e.g. leakage of, heating by, eddy current and RF pulses).[7]

Operation time – Operating time of the process will decrease with the use of robotic manipulator, which will result into two main benefits. First, need of anaesthesia for shorter time which will reduce the stress of the patient. Second, from economical point of view it is beneficial to shorten the time of operation in order to reduce the overall cost. However, time required for modern surgical procedures like navigation, robotics set up is also crucial. This time increases the overall operating time of the procedure. Telemanipulator assisted tracking takes more time and led more error while working on moving target such as beating heart surgery. Telemanipulator tracking becomes more difficult and time consuming with the increase in motion frequency.[20] .By reducing the time requirement of navigation system and robotics set up total operating time of telemanipulation procedures can be reduced.

V. Future Scope

Although Telemanipulation system using XR and MR is still in its early stages of development, it has wide future scope due factors such as improved accuracy, precision, reliability, ability to perform certain part of delicate procedure and decreased fatigue. Parameters like decrease in communication delay, high cost and improvement of end effector to perform multiple operations without changing instrument should be taken into consideration for future development.

Parameters listed below should be taken in to account for future development of the telemanipulation system

Control design considerations for system stability analysis – Control design of the system is one of the major factors of consideration. Direct force feedback reflection control and position error based reflection control are two classical methods for the stability analysis of telemanipulation control. However these methods suffer from poor performance in terms of low reflection gain with remained stability. To overcome these limitations, new improved methods such as Shared compliance control and Impedance control are proposed to improve performance of Telemanipulation system.

In shared compliance control, low pass filtering of force sensor output is performed using signals to alter reference command to slave controller. In case of impedance control approach possibility to generate desired force characteristics based on Cartesian position addressed [15].

Bandwidth – It is considered that transparency of the telemanipulator can

be characterised by bandwidth of the forward channel (master to slave) and reverse channel (slave to master). Bandwidth of forward channel is required to be comparatively higher to perform particular task with precision and bandwidth of reverse channel must be minimum 300 Hz [16].Use of electromagnetic actuator which are comparatively clean, quiet and with high efficiency provides high linearity and high bandwidth.

Improvement of force feedback – Implementation of high fidelity force sensor has ability to improve force sensation which is comparatively better than those sensed by human hand. This improvement will be similar to the use of microscope and microphone in order to improve the vision and hearing capacities.

Miniaturization – Implementation of MEMS (Microelectrical mechanical system) technology to operate miniature sensors, actuators on an even smaller scale can play an important role in the future field of telemanipulator. It will allow to sense, control and actuate on microscale level as a result it will be possible to obtain force feedback with a micro force sensor.

Gravity Compensation – Static balance of telemanipulator is an important factor in minimising operator fatigue and hence probability of error.

Ethical and liability issues – One more important challenge is the interdisciplinary work of engineers and medical staff to develop a common language [17]. Only then both communities will be able to understand each other's needs and constraints in order to pave the path for further development of the current system of telemanipulation and imaging intervention, ultimately enhancing patient care. In future, the surgical workstation can be connected to the network of other expert in the field via low latency, high speed network to get assistance or advice in occurrence of critical situation. For the time being lack of companies and patent restriction hinder a faster progress of mentioned technology. Process of approval by U.S. Food and Drug Administration (FDA) or in Europe by Medical Device Directive (MDD) for safety and regulation should be optimised to speed up the market availability of the system. In next future new companies can join the club to enable this promising system getting near to clinical use.

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CRYOTHERAPY

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Introduction

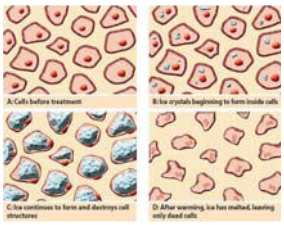
Cryotherapy is the use of extreme cold in surgery to destroy abnormal or diseased tissue. Cryosurgery has been historically used to treat a number of diseases and disorders, especially a variety of benign and malignant skin conditions. Liquid nitrogen or argon gas to destroy diseased tissue .

The physician is demonstrating correct cryoprobe and ultrasound transducer positioning during a cryoablation procedure.

Mechanism of cell

- Cryosurgery destroys tumors by freezing and thawing them.
- The destructive effect of the cryosurgery on tumors is due to two major mechanisms.
  - **Immediate cell destruction**
  - **Delayed cell destruction**
- Two factors that induce a greater destruction of targeting tissue:
  - Recrystallization or fusion of small ice crystals.
  - The extracellular compartment becomes briefly hypotonic

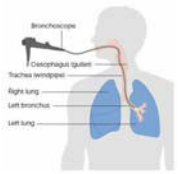
How cryotherapy works



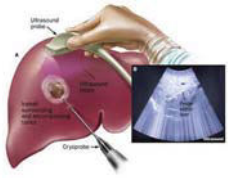
Clinical Applications And Procedure

Warts, moles, skin tags, solar keratoses, Morton's neuroma and small skin cancers are candidates for cryosurgical treatment. Several internal disorders are also treated with cryosurgery, including liver cancer, prostate cancer, lung cancer, oral cancers, cervical disorders and. Soft tissue conditions such asplantar fasciitis (Jogger's heel) and fibroma(benign excrescence of connective tissue) can be treated with cryosurgery. Cryotherapy is also used in cardiac ,ophthalmology and also in physiotherapy treatments.

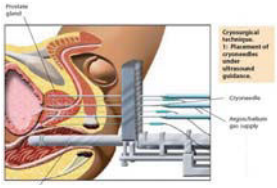
Cancer Treatment:



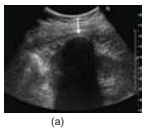
Cryosurgery for lung cancer: Inserting cryoprobe down the bronchoscope



A) Cryosurgery of liver cancer B) Ultrasound image showing the cryoprobe



Cryosurgical ablation of the prostate cancer

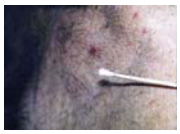


(a)

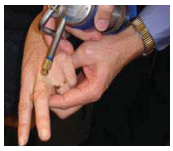
(b)

Kidney cancer: (a)Grey-scale US image during the ablation (b)ice ball formation

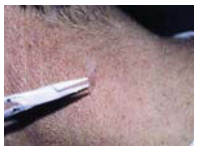
Dermatology:



A cotton-tipped applicator is used to treat benign lesions

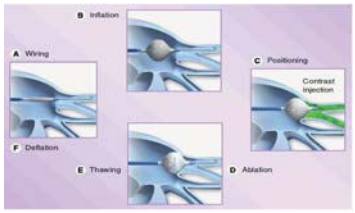


Spraying viral warts

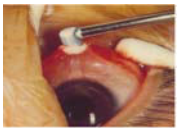


Forceps or clamps can be used to concentrate the freeze and to prevent collateral damage.

Cardiology:



Ophthalmology:



Cryotherapy done in left eye with cryoprobe

Advantage, Disadvantage, Limitation and Future outlook

Advantage:

- Complete destruction of the selected volume of biological tissue
- Access to unhealthy tissues, subject to cryodestruction, is realized with minimal trauma to healthy tissues
- Cryodestruction enables quick healing, practically without leaving scars, while providing excellent cosmetic effect.
- Minimal traumatic consequences and short time of operation.
- Cryotherapy is less costly and results in fewer side effects than open surgery.

Disadvantage:

- Bleeding may result from the puncture and the freezing of tissues.
- Complications like headache, pain, blister formation, hemorrhage, infection, excessive granulation tissue formation, scarring, and hypopigmentation can occur .
- If freezing occurs near the diaphragm, fluid can accumulate in the space around the lungs.
- Completely frozen nerves can cause motor weakness or numbness in the area supplied by the nerves.

Limitation :

- Cryotherapy is considered a localized therapy.
- It can only It can only treat disease only at a single site.
- It cannot treat cancer that has spread to other parts of the body.

Future outlook:

Although its use in the bone, kidney, liver and lung and especially in heart is promising, percutaneous cryotherapy research is ongoing to determine longer term clinical outcomes.

Conclusion

Cryotherapy is a technique that employs freezing to destroy undesirable tissue. Developed first in the middle of the nineteenth century it has been recently corporate with new imaging technologies and is a fast growing minimally invasive surgical technique. It is anticipated that cryosurgery, especially percutaneous cryosurgery, will become a practical and effective modality for treatment of a variety of early and advanced cancer.

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CRYOTHERAPY

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ABSTRACT

Cryotherapy also known as cryosurgery, cryoablation or targeted cryoablation therapy, is a minimally invasive treatment that uses extreme cold to freeze and destroy diseased tissue, including cancer cells. Cryotherapy is mainly used in dermatology (for lesions, warts etc.), for cancer treatments (liver, kidney, lungs etc.) in and in ophthalmology. Different equipment like ultrasound, computed tomography (CT) or magnetic resonance (MR) imaging, a cotton swab, spray device, cryoprobe and bronchoscope are used for cryotherapy treatments. Cryotherapy uses liquid nitrogen or argon gas to destroy diseased tissue. This review paper mainly deals with the clinical application, systems, advantage and disadvantage and the limitation of the cryotherapy.

1. INTRODUCTION

Cryotherapy is the use of low temperature in medical therapy. It is mainly used to treat variety of benign and malignant tissue damage known as **lesions.** Cryotherapy is a Greek word where cyro means cold and therapy means cure. The main aim of cryotherapy is to decrease cell metabolism i.e. cell growth and reproduction, increase cellular survival decrease inflammation, pain and spasm and promote vasoconstriction and using extreme temperature to destroy the cell by crystallizing the cytosol(intra cerebral fluid). Cryotherapy is also known as **Cryosurgery or cryoablation.**

1.1. HISTORY

In early 2500 BC the Egyptian used cold to treat injuries and inflammation. In the years 1845 Dr. Arnott described the benefits of cold treatment for numerous conditions including headaches and neuralgia. He used salt solution with cursed ice at temperature of -18° to -24°C to freeze breast, cervical, and skin cancers [1].

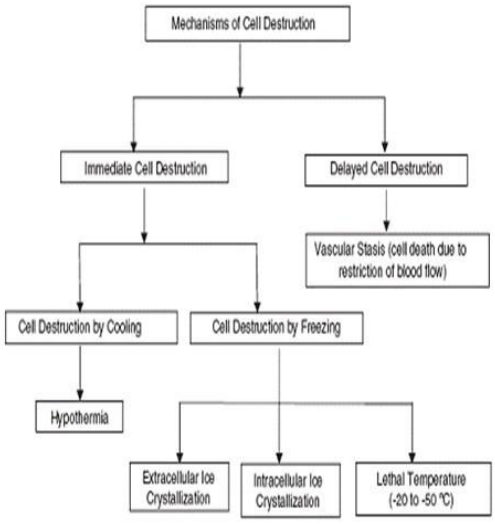
In early 1900's the most popular cryogenic agent was **solidified carbon dioxide** (-78.5 °C) which was introduced by Dr. William Pusey for clinical application. He treated warts, vascular nevi, lupus erythematous, lupus vulgaris, and epitheliums. And the results from these treatment made many physicians use the freezing techniques in dermatology [2]. In 1920's **liquid oxygen** (-182.9°C) was introduced for clinical application. It showed good results with warts, lichen planus, and other skin conditions. Even though liquid oxygen showed good result it was rarely used because it was combustible, which hazardous is [3].

In 1950 Dr. Ray Allington introduced **cryogen** into clinical practice. In this technique cotton swabs dipped into liquid nitrogen for treating variety of nonneoplastic skin diseases [5]. Modern cryosurgery was introduced by a physician, Irving Cooper, and an engineer, Arnold Lee. They built a cryosurgical probe that became the prototype from which all other liquid nitrogen cryosurgical probe was built. Between 1961 and 1970, many other cryosurgical apparatuses were developed using liquid nitrogen and other cryogenic agents, like nitrous oxide, carbon dioxide, argon, ethyl chloride, and fluorinated hydrocarbons. Douglas Torre, a

dermatologist, used Cooper's apparatus for treating skin diseases. He developed a nitrogen spray device that could also be used with cryoprobe tips of various shapes and sizes, converting the conduit line to a closed system in 1965. Over the recent years, cryotherapy has become a well-established treatment modality for a wide variety of benign and malignant skin lesions, with novel uses continually described [6].

1.2. MECHANISMS OF CELL DEATH

Cryosurgery destroys tumors by freezing and thawing them. The destructive effect of the cryosurgery on tumors is due to two major mechanisms, one is **immediate**, and the other one is **delayed**. The immediate mechanism has a destructive effect to freeze and thaw cells. The delayed mechanism performs the progressive failure of microcirculation. Ultimately, vascular stasis which is an important cause of destruction of tumor tissue becomes operative. In addition the eutectic crystallization and involvement of apoptosis are also possible mechanisms of freezing injury [7].



2. CLINICAL APPLICATION

By using **liquid nitrogen** various lesions can be treated. In order to destroy these lesions different freeze-thaw cycles are used, because of the histologic difference in them. Lesions like actinic keratosis, warts, and seborrheic keratosis, cryotherapy are the standard first-line therapy. Several internal like lung cancer, prostate cancer, liver cancer, cervical disorders can be treated using cryotherapy. Soft tissue conditions like plantar fasciitis (Jogger's heel) and fibroma (benign excrescence of connective tissue) can also be treated with cryotherapy.

2.1. CRYOTHERAPY IN CANCER TREATMENT

Cryotherapy used for treating both external and internal tumors. For external tumors, liquid nitrogen is applied directly to the cancer cells with the help of a cotton swab or spraying device. And for internal tumors, liquid nitrogen or argon gas is circulated through a hollow instrument called a cryoprobe, which is placed in contact with the tumor[10]. The doctor uses ultrasound or MRI to guide the cryoprobe and monitor the freezing of the cells. This will limit the damages of nearby healthy tissue. A ball of ice crystals forms around the probe that freezing nearby cells. Sometimes more than one probe is used to deliver the liquid nitrogen to various parts of the tumor. The probes may be put into the tumor during surgery or through the skin (percutaneously). After cryosurgery, the frozen tissue thaws and is either naturally absorbed by the body (for internal tumors), or it dissolves and forms a scab (for external tumors) [9].

2.2. CRYOTHERAPY IN DERMATOLOGY

Three main techniques of cryotherapy are used in dermatological application. In the first technique is mainly for warts and other benign skin growths. Here a cotton swab or other applicator dipped into a cup containing a "cryogen" such as liquid nitrogen and applies it directly to the skin growth to freeze it. At a temperature of –320°F (–196°C), liquid nitrogen is the coldest cryogen available. The goal is to freeze the skin growth as quickly as possible, and then let it thaw slowly to cause maximum destruction of the skin cells. A second application depends on the size of the growth. In another approach, a device is used to direct a small spray of liquid nitrogen or other

cryogen directly onto the skin growth. Freezing may last for five to 20 seconds, depending on the size of the lesion. A second freeze-thaw cycle may be required [13]. Sometimes, the physician inserts a small needle connected to a thermometer into the lesion to make certain the lesion is cooled to a temperature low enough to guarantee maximum destruction. In a third option, liquid nitrogen or another cryogen is circulated through a probe to cool it to low temperatures. The probe is then brought into direct contact with the skin lesion in order to freeze it. The freeze time can take two to three times longer than with the spray technique.

2.3. CRYOTHERAPY FOR CARDIAC ARRHYTHMIA

Cryotherapy or Cryoablation is a therapy that uses the removal of heat from tissue to treat cardiac arrhythmia. It restores normal electrical conduction by freezing the cardiac tissue or pathways that interfere with the normal distribution of the heart's electrical impulses [10]. Cryoablation is done in two ways for the treatment of arrhythmia:

(1) Catheter-based procedures: A catheter is a very thin tube that is inserted into a vein in the patient's leg and threaded to the heart where it delivers energy to treat the patient's arrhythmia [23].

2) Surgical operations: In surgical procedures, a flexible probe is used directly on an exposed heart to apply the energy that interrupts the arrhythmia. By cooling the tip of a cryoprobe to sub-zero temperatures, the cells in the heart responsible for conducting the arrhythmia are altered so that they no longer conduct electrical impulses [23].

2.4. IN PHYSIOTHERAPY

2.4.1. ICE PACK THERAPY

Cryotherapy is a treatment of cold temperatures to an injured area of the body. An ice pack is placed over the injured area and it will absorb the heat of a closed traumatic or edematous injury by using conduction to transfer thermal energy [11]. The physiologic effects of cold application are the immediate vasoconstriction with a decreased local metabolism and enzymatic activity, and decreased oxygen demand. Cold decreases muscle spindle fiber activity and slows nerve conduction velocity, because of this effect it is often used to decrease spasticity and muscle guarding. It is commonly used to reduce the pain of minor injuries, and decrease muscle soreness.

2.4.2. WHOLE BODY CRYOTHERAPY

Whole-body cryotherapy (WBC) has been frequently used to supplement the rehabilitation of patients with rheumatoid arthritis, for weight loss, multiple sclerosis [12]. In this treatment individuals are exposed to extremely cold dry air (below -100 °C) for two to four minutes. To achieve the subzero temperatures two methods are typically used, they are liquid nitrogen and refrigerated cold air. WBC is effective in relieving soreness, or muscle pain, through reduced muscle metabolism, skin microcirculation, receptor sensitivity and nerve conduction velocity [11].

2.5. OCULAR CRYOTHERAPY

Ocular cryotherapy is the therapeutic use of cold temperatures to treat disorders of the lids or eyes. Cryotherapy has been used in ophthalmology since the mid-1960s. With the exception of cataract extraction, ocular cryotherapy is generally used as a surface technique, with the probe being applied to the lids or eye without any incision into the tissue. Because of the absence of an incision, it is considered to be a less invasive type of procedure than incisional surgery [10].

3. TREATMENT MODALITIES

3.1. SPRAY TECHNIQUE

The spray cryotherapy technique is the most commonly used technique. This method is suitable for most benign and some superficial neoplastic lesions. Pulsing each spray to avoid an overexpansion of the treatment site prevents complications. The nozzle tip of the spray gun is held about 1 cm from the treatment site, and liquid nitrogen is sprayed on the lesion until an ice ball is formed. This process is repeated until an ice ball of the desired size is created. The time for which the

lesion is frozen is the freeze time [5]. This freeze-thaw cycle can be repeated, depending on the type of lesion being treated.

Fig1: Spray gun

3.2. DIPSTICK APPLICATOR METHOD

The dipstick applicator method is the original method used to apply liquid nitrogen to lesions. A cotton-tipped applicator or cotton swabs is dipped into liquid nitrogen from a polystyrene cup. The dipstick applicator is then firmly pressed against the lesion for the desired duration. This method is mainly used for benign lesions [14].

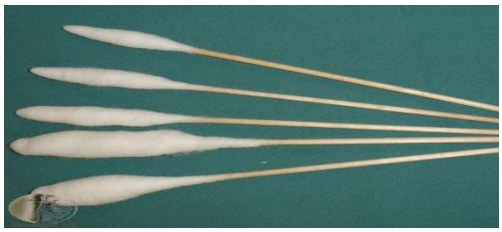


Fig2: Cotton swap

3.3. FORCEPS TECHNIQUE

Forceps or clamps can be used to freeze and to prevent collateral damage. A clamp is being used during the freezing treatment. Usually, 2 freeze applications of 15 seconds are required [13].

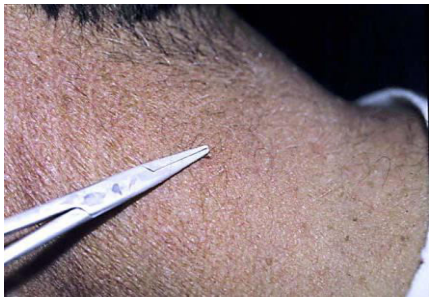


Fig3: Forceps

3.4. CRYOPROBE OR CRYOTHERAPY NEEDLES

3.4.1. LUNG CANCER

First general anesthetic or a drug is give before the procedure to make you drowsy. After that the doctor puts a flexible tube called a bronchoscope down to your throat and into the airway [9]. The doctor then inserts a probe called a cryoprobe down the bronchoscope. The probe freezes part of the tumour. The doctor then allows the area to thaw just enough for the cryoprobe to come away from the tissue. The doctor may repeat this process 2 or 3 times in that same area. They then move the cryoprobe along to freeze the next area. The process is repeated until the whole area of cancer is treated. They remove as much of the tissue as possible using forceps or the cryoprobe [16].

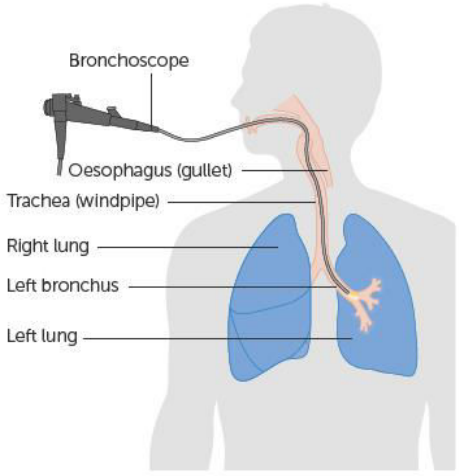


Fig 4: Inserting cryoprobe down the bronchoscope.

3.4.2. LIVER CANCER

First general anesthesia is given to the patient. In this technique one or more cryoprobe are placed into the tumor using ultrasound [19]. Here liquid nitrogen, at -190°C, is circulated in a closed system through the end of the probe creating an ice ball at the tip. The ice ball is then allowed to encompass with the tumor and approximately one-half-inch margin around it. The tumor is frozen and thawed twice, which takes up to 30 minutes [17].

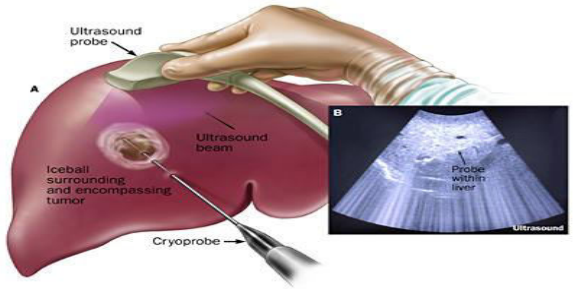


Fig5: A) Cryosurgery of liver cancer B) Ultrasound image showing the cryoprobe

3.4.3. PROSTATE CANCER

Before the treatment enema is done to clear out the lower bowel. In the treatment room the doctor insert a tube called a warming catheter into the tube in the body that takes urine from the bladder to the tip of the penis (the urethra). This helps in protecting the urethra from damage that occurs during the procedure. Then the surgeon puts special cryotherapy needles through the skin of the perineum (the area between the scrotum and the anus) [9]. With the help of ultrasound scan or X-rays doctor ensure that the needles are in the right place. A machine then circulates argon gas through the needles to freeze the tissue. A machine then circulates argon gas through the needles to freeze the tissue [18]. With the help of temperature needles the surgeon monitors the temperature of the other structures in the same area such as the bowel muscle (anal sphincter) and the back passage (rectum), in order to make sure that they are not damaged by cold.

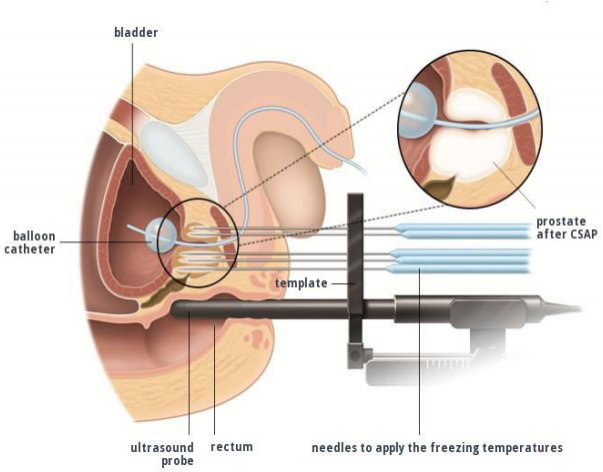


Fig. 6: Cryosurgical ablation of the prostate

3.4.4. KIDNEY CANCER

First local anesthetic or general anesthetic is given to the patient. The doctor uses X-ray or ultrasound guidance to find the tumour. They then make a cut in the skin over the kidney or use keyhole surgery. Keyhole surgery is done through smaller cuts and the surgeon uses a camera (laparoscope) to see inside the body to remove the cancer [9]. The surgeon first takes a small sample of tissue from the cancer. Then insert one or more cryotherapy needles through the skin into the kidney close to the cancer. They move the needle into position. When the needle with liquid nitrogen touches the cancer tissue it freezes and destroys the cancer cell [19].

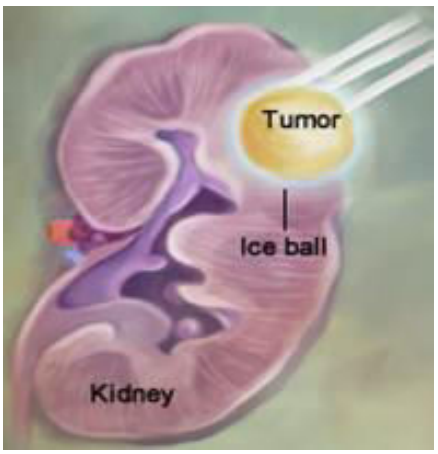


Fig 7: Ice ball formation

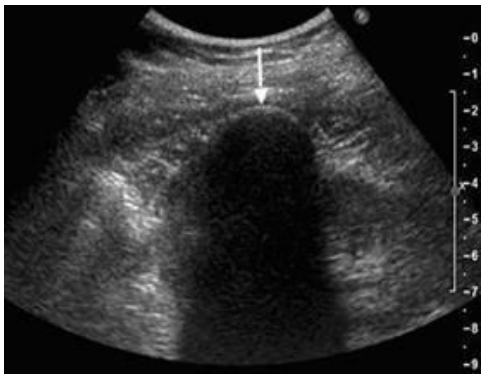


Fig 8: Grey-scale US image during the ablation

3.4.5. RETINAL TEAR AND DETACHMENT (OPHTHALMOLOGY)

In this procedure freezing the retina where a retinal tear has occurred. This keeps the retina attached in its proper place inside of the eye. The cryo probe is placed on the outside of the eye over the area of the tear [20]. The doctor uses a light mounted on his head and a lens held in his hand to check the position of the probe and make sure it is in the right place. The probe is turned on and a small area is frozen in a few seconds. Multiple areas may need to be frozen to seal the tear [21]. Cryotherapy is done on the front half of the retina where a laser cannot be used.

Fig 9:Ocular probe

3.5. CATHETER OR CRYOBALLOON

3.5.1. CARDIAC DISEASES

Cryoballoon ablation is a balloon-based technology that blocks the conduction of the arrhythmia in cardiac tissue by using coolant rather than heat. The catheter is inserted into a vein in the patient's leg and threaded to the heart where it delivers energy to treat the patient's arrhythmia. This freezing technology allows the catheter to stick to the tissue during ablation, allowing for greater catheter stability [10]. Cryoablation is a new and alternative method that uses freezing temperatures on targeted areas around the pulmonary veins.

Fig 10: Cryoballoon ablation

3.6. CRYOCAMBER

The body's response to cold air from WBC is merely due to the perceived threat that the body is freezing; when, in fact, only skin temperature is affected. WBC stimulates the sympathetic nervous system via alpha-adrenergic receptors, causing dramatic peripheral vasoconstriction. This induces adaptive changes correlating with effects of analgesia (pain relief), reduction of inflammation, and an increase in blood serum markers for tissue repair [12].

Fig11: Cryochamber

4. BENEFITS VS RISK

4.1. BENEFITS

- Recovery time for the cryosurgery of kidney or liver tumors may be less than for open surgical removal of the tumor [9].
- For percutaneous cryotherapy, the patient may stay overnight or be released several hours after the procedure.
- Cryotherapy causes less pain during and after the procedure compared to heat-based treatments such as radiofrequency ablation.
- It is less traumatic than open surgery since only a small incision is needed to pass the probe through the skin, which limits damage to healthy tissue.
- Cryotherapy is less costly and results in fewer side effects than open surgery .

4.2. RISK

- Bleeding may result from the puncture and the freezing of tissues.
- Complications like headache, pain, blister formation, hemorrhage, infection, excessive granulation tissue formation, scarring, and hypopigmentation can occur [8].
- If freezing occurs near the diaphragm, fluid can accumulate in the space around the lungs.
- Nerve damage may result. Completely frozen nerves can cause motor weakness or numbness in the area supplied by the nerves.
- Women should always inform their physician or x-ray technologist if there is any possibility that they are pregnant.

5. LIMITATION AND FUTURE OUTLOOK

Cryotherapy can be used many problems like dermatological problem, cardiac diseases, for physiotherapy and also as an alternative cancer treatment when surgical removal of a tumor may be difficult. But in the case of cancer its long-term effectiveness is still being examined. Cryotherapy is considered a localized therapy. It can only treat disease only at a single site. It cannot treat cancer that has spread to other parts of the body. Because physicians treat the tumors they see on radiologic images, microscopic cancer may be missed.

Although its use in the bone, kidney, liver and lung and especially in heart is promising, percutaneous cryotherapy research is ongoing to determine longer term clinical outcomes.

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Radiofrequency Ablation Therapies: Systems used, Clinical applications and Limitations.

B. E. Nikita Nownith, in the context of the course Instruments of image guided procedures by Prof. M. Friebe
Institute of Medical Engineering, Otto-von-Guericke-University, Magdeburg, Germany, Contact: nsalian41@gmail.com

Introduction

Background: With many advancements in minimally invasive, image guided ablation methods, radiofrequency ablation has become a high profile choice due to its safety and efficacy.

Approach: **Radiofrequency ablation** is a medical procedure, which heats and destroys diseased and dysfunctional tissue with high frequency alternating current.

Challenges: Electrode placement,
For accurate ablation the tissue temperature should be maintained in the range of 50°C to 100°C.

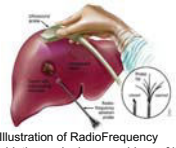
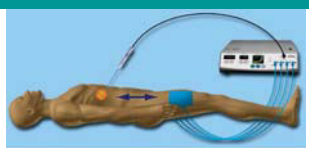


Illustration of RadioFrequency ablation under image guidance [1]

Mechanism of Radiofrequency ablation

The key strategy of radiofrequency ablation is to create a closed-loop system with RF generator, the needle electrode, the patient and passive electrodes(grounding pads) in series.
The RF signal generator provides the required energy to the needle like electrodes. Due to the high electric resistance of the tissue compared to the metal electrode, the energy at the tip of the electrode causes ionic agitation of the targeted tissue in turn leading to the heating up of targeted tissue. Effective ablation is achieved when the amount of heat produced is optimized and heat loss is minimized [2].



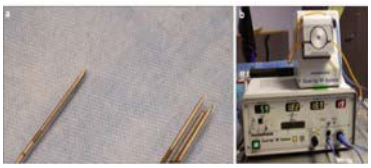
Representation of RF ablation procedure

Systems Used

Overview of the RFA systems used[3]

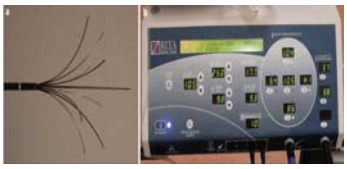
	Cool-Tip	1500X RF	RF 3000
Manufacturer	Radionics	AngioDynamics	Boston Scientific
Energy transmission	Monopolar	Monopolar	Monopolar
Frequency	480 kHz	460 kHz	480 kHz
Maximum power	200 W	250 W	200 W
Applicators	1	1	1
Active tip(for 3cm/5cm target ablation volumes	3/2.5 cm	3/5 cm	3/5 cm
Induced energy control mechanism	Impedance-controlled	Temperature-controlled	Impedance-controlled

Cool-tip RF ablation system



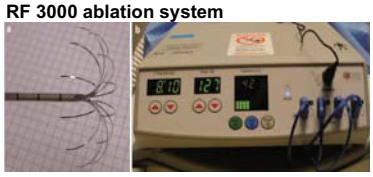
a: Cooltip RF ablation electrodes, b: Cool-tip Generator

1500RF ablation system



a: Starburst electrode, B: Model 1500RF Generator

RF 3000 ablation system



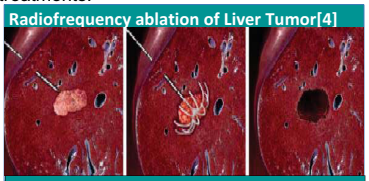
a: LeVeen Electrode, b: RF3000 Generator

Other Radiofrequeny ablation system includes CelonPOWER system which is the first bipolar and multipolar ablation system.

Clinical Applications

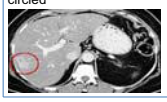
Radiofrequency ablation serves as a good option when open surgery is not possible due to medical risks or, if there are small tumors present in the organ. RF ablation has emerged as one of the front runner therapies that is used in the treatment of cancer, cardiac arrhythmias, in the treatment of varicose vein and in the chronic pain treatments.

Radiofrequency ablation of Liver Tumor[4]

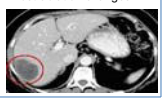


CT scan results before and after RF ablation

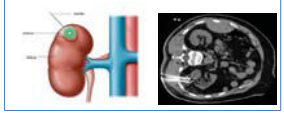
Pre-op CT scan: Tumor is circled



Three months post-RFA: Post-ablation changes



RFA of Kidney tumor



Needle electrodes are placed through the skin into the kidney tumor under image guidance

RFA for the treatment of Breast cancer

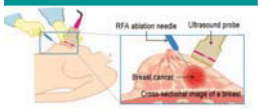
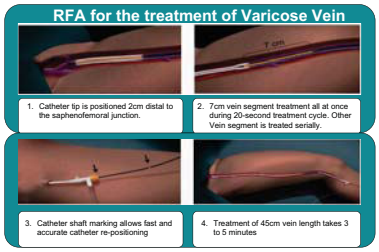


Illustration of radiofrequency ablation under ultrasound guidance

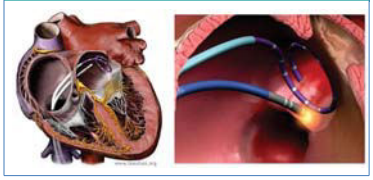
RFA for Chronic pain release

Radiofrequency ablation to treat nerves at spine for pain release

RFA for the treatment of Varicose Vein



RFA for the treatment of Cardiac Arrhythmias



Radiofrequency ablation of atrial fibrillation

Limitations

- Radiofrequency ablations are fundamentally limited by the heating mechanism.
- Multiple ablations are needed in order to achieve the required tumor margin.
- Heat sink effect.
- Image guiding difficulties.

Conclusion

- Safe and effective method.
- In contrast to surgery,RFA is less expensive and less invasive.
- Can be applied to non-surgical candidates.

Future Outlook

- High power generators
- Ground pad design
- Adjuvant Therapies
- Electrode tracking systems.

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Radiofrequency Ablation Therapies

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Abstract—Radiofrequency ablation is a commonly used ablation therapy and is well documented in the literature on minimally invasive therapies. Today, radiofrequency ablation therapies are being employed in different medical fields such as in the treatment of nerve related chronic pains, destruction of tumors present in different locations, and in elimination of cardiac arrhythmia. It has become a promising image-guided ablation therapy because of it efficacy, ease of use, safety and cost effectiveness. This review investigates the Radiofrequency ablation mechanism, the systems used, clinical applications and procedures involved, limitations and the research avenues.

Keywords—Radiofrequency Ablation, Catheter Ablation

1 Introduction

1.1 Background

Last decade has seen great advancements in minimally invasive, image guided ablation methods. Among them Radiofrequency ablation has emerged out as a high profile choice due to its efficacy and safety. Radiofrequency ablation has emerged as a high profile choice, due to its efficacy and safety. Radiofrequency ablation is a procedure performed under image guidance, used to heat and destroy a dysfunctional or diseased tissue using high frequency alternating current (350-500kHz). An alternating current is delivered via a needle electrode that causes localized ionic agitation and frictional heating of the tissue around the needle resulting in the ablation of the diseased tissue. It can be performed as a outpatient procedure and would require just conscious sedation or local anesthesia in some cases. In this review we analyze the history of RF ablation, the mechanism of RF ablations, the clinical applications, the limitations and the future scope.

1.2 History

There have been numerous techniques developed over time for tissue ablation. One of them is the radiofrequency ablation. The basic technique of radiofrequency ablation was described in the year 1891 by D'Arsonval [1], who demonstrated that when the RF waves passed through the tissue, they will cause an increase in the tissue temperature. With the introduction of the Bovie knife in the year 1928 by Cushing and Bovie [2], radio frequency for the medical applications saw its new future. Since 1940s, diathermy has been an effective method used in many rehabilitation medicine in order to relieve pain resulting from strains and stress. Organ [3] successfully demonstrated that, RF works by the principle of causing ionic agitation around the needle. In the year 1990 McGahan et al [4], modified the prior RF technique in order to create coagulation necrosis and could be applied percutaneously. McGahan et al [5] in 1992 demonstrated that needle placement for RF ablation could be monitored by ultrasound. Leveen in 1997 demonstrated a monopolar electrodes with prongs that could be deployed from the needle tip. In 1996 and 1997 a needle that could be cooled by chilled saline and could be pumped through the needle shaft was described by Goldberg et al and Lorentzen et al. The past 10 years have seen a rapid growth in radiofrequency ablation that could be done by percutaneous, laparoscopic and by open surgery in order to treat various tumors. There has been significant advancements with the design of powerful generators,

- *Radiofrequency Ablation therapies*

.

improved needle designs and more sophisticated programs for heat deposition in order to achieve lager volumes of coagulation necrosis.

2 Mechanism of Radiofrequency Ablation

2.1 Coagulation Necrosis

Coagulation necrosis denotes irreversible thermal damage to cells even if the ultimate manifestations of cell death do not fullfil the strict histological criteria of coagulative necrosis. Thermal damage that is caused by radiofrequency heating depends on both the duration of heating and the tissue temperature achieved. At various temperatures:

- At 42°C, cells will die but this will take a significant amount of time (approximately 60 min).
- Between 42°C and 45°C, cells are more susceptible to damage by other agents like chemotherapy and radiation.
- Over 46°C depending on the duration of heating irreversible damage occurs.
- Between 50°C and 55°C, Coagulation necrosis occur in 4 6 minutes.
- Between 50°C and 100°C there is near immediate coagulation of tissue, almost instantaneous protein denaturation, melting of lipid bilayers, irreversible damage to mitochondrial and cytosolic (key cellular) enzymes of the cells, DNA and RNA.
- From 100°C to 110°C, tissue vaporizes and carbonizes, all of which decrease energy transmission and impede ablation [6].

In order to achieve successful adequate ablation, the temperature of the tissue should be maintained in the ideal range (50°C - 100°C) and in order avoid carbonization around the tip of the electrode due to excessive heating. Hence the main aim of RFA therapy is to attain and maintain the temperature of 50°C - 100°C through the entire target volume for a period of 4-6 minutes.

2.2 Principles of RFA

Energy deposition into the tumors causes thermal injury and result in what we call as a tumoricidal effect. Radiofrequency ablation is primarily based on radiofrequency current about 480 kHz that passes through a lesion from the active electrode tip towards a dispersive electrode serving as a grounding pad.The grounding pad usually placed firmly on the thigh of the subject. The active electrode is usually in the form of a needle-like probe which is inserted into the tumor. The key strategy of RF ablation is to create a closed-loop circuit that includes the RF generator, the needle electrode, the patient (tissue) and the passive electrode (grounding pad) in series. The radiofrequency generator connects the two electrodes and an alternating field is created within the patient tissue. Due to the high electric resistance of the tissue when compared to the metal electrode, the energy at the tip of the probe leads to ionic agitation of the target tissues which in turn leads to conversion of friction into heat, since the tissue ions attempt to follow the change in direction of the alternating electric current. The active electrode has a very smaller cross-sectional area of few square millimetres when compared to the dispersive electrode. The passive electrode is much larger in area when compared to the active electrode. The Current that flows into the passive (dispersive) electrode is the same as the current that flows into the active electrode. But due to a far smaller cross-sectional area of the active electrode in comparison to the dispersive electrode, the current density in amperes per square meter is far greater. Due to the marked discrepancy between the surface area of the needle electrode and the dispersive electrode, the generated heat is tightly focused and concentrated around the needle electrode. Maximum surface area for dispersion of current from the needle electrode is ensured by the use of a large grounding pad. The grounding pad also minimizes the risk of burns by maximizing the dispersion of equal amounts of energy and heat at the grounding pad sites. The tissue that is in contact with the active electrode is resistively heated to elevated temperatures sufficient for tumor ablation [6].

The tissue is heated up because of the power dissipation in the tissue, which could be found from the following expression :

$$P = \rho V {I_d}^2 \quad (1)$$

where V is the tissue of the volume, I_d is the current density, P is the power in watts (W), ρ is the resistivity of the tissue in Ohm-metres $(\Omega - m)$,

Effective ablation could only be achieved if the amount of heat produced is optimized and heat loss is minimized. The production of heat is related to the intensity and the duration of the RF energy deposited, and the heat loss is mainly due to the blood flow in the nearby blood vessels. This is called the heat-sink effect.

When the tissues are heated to a temperature greater than 100°C and when charring of the tissues occur, the effectiveness of radiofrequency ablation is decreased. Extent of Ablation zone is a important element of effective ablation. The ablation zone needs to include arears beyond the tumor margin, as to ensure eradication of the tumoral extensions. This is called the tumor margin, and this varies depending on the organ being ablated.

3 Radiofrequency Ablation systems

Fig. 1 shows the block diagram of the ablation system. The most important section of the RF ablation system is the Radiofrequency signal generator. The RF signal generator provides the required energy to the needle like active electrode. The system consists of a closed circuit with a radiofrequency generator circuit, a power amplifier circuit, and the control circuit. In order to meet the power supply requirements of the system, A power supply circuit is included .The active electrode delivers the energy generated by the system is to the tissues. In order to complete the circuit, a dispersive electrode acts as a patient plate and provides a return path.

In order to reduce charring and to achieve larger and more effective abnormal tissue damage there has been substantial efforts made in recent times. As a result of all the efforts many new RF ablation devices with powerful generators (200W) have been produced. Some major commercially available RF Ablation systems are mentioned below:

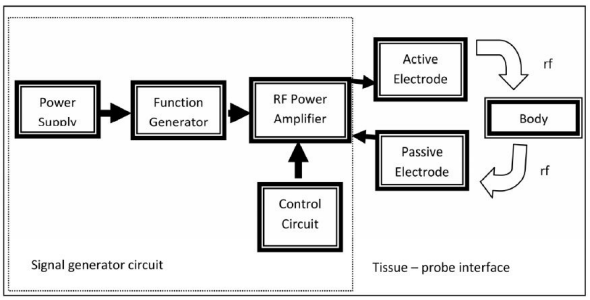

Fig. 1. Block diagram of a RF ablation system.

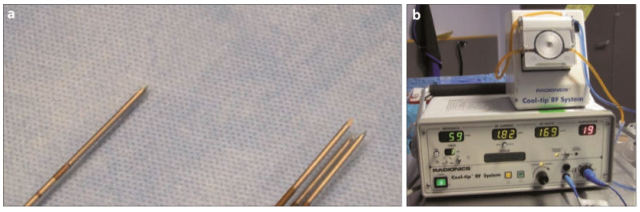

Fig. 2. Cool-tip RF ablation system.

1) Cool-tip™ system (Covidien)
Cool-tip™system (Fig. 2) is designed with a purpose to address a need for an alternative solution to surgery when treating the lesions. The system will monitor the impedance (electrical resistance) of the tissue during the ablation procedure and automatically adjust the power output in order to assure a consistent flow of current to the tissue [7].
   - Cool-tip™ RF ablation Electrodes
   Cool-tip™ system uses internally cooled electrodes in order to minimize charring and to maximize energy deposition and deeper tissue heating. Multiple probe systems (or cluster system) can achieve a greater coagulation necrosis than any individual electrode alone. The entire electrode could be seen with ultrasound or CT guidance.
   Figure shows the internally cooled needle-like electrodes (a) of the Cool-tip system. An electrode is electrically insulated along its shaft except for the final 13 cm exposed active tip. On the left is a single 17 G electrode with a 3 cm exposed tip; on the right is a cluster electrode

comprised of three 2.5 cm tipped single electrodes incorporated into one handle.

- Cool-tip™ Gernerator
  The generator provides nearly 2 amps of RF electrical current, and delivers a power of up to 200 watts. The numeric displays on the front control panel allows the user to observe the electrical impedance in the tissue, the probe temperature, the current and power as well as the elapsed time.

2) RF 3000® (Boston Scientific Corporation)
RF 3000® too tracks the issue impedance. Any increase in impedance of the tissue is taken as the clinical endpoint, correlating to a complete coagulation of tissue around the electrode [8].

- LeVeen Electrode (Boston Scientific Corporation)
  LaVeen Electrode is a array type electrode. It is Expandable, multi-tined electrode that allow the deposition of energy over a larger area and thus decreases the distance between tissue and the electrode. With the help of image guidance, the electrode is placed in the tumor and the non-insulated tines are deployed. The figure 6a shows a deployed electrode. The array diameters that are available are in a range of 2 to 5 cm.
- RF 3000® Generator
  RF 3000® Generator as shown in Fig. 3 (b) nearly 2 amps of current, and delivers a power of up to 200 watts which promotes efficient and rapid ablation of a larger volume of tissue. The level of the power delivered can be controlled by the user. The power level is set low to start and is steadily increased to promote a gradual heating of tumor volume. When heating is sufficient enough to coagulate the target tumor volume, the numeric display which is in the center of control panel (that reads 42 ohms) will show a marked increase in tissue impedance by an order of magnitude.

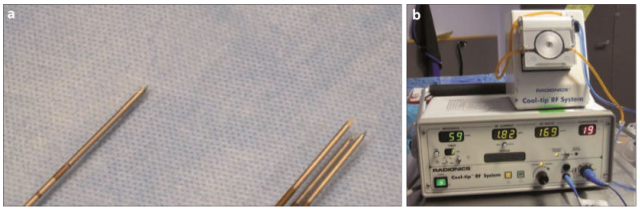

Fig. 3. RF 3000 Generator system.

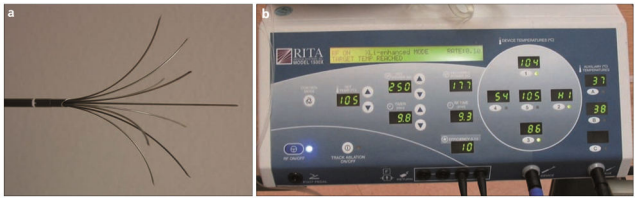

Fig. 4. Startburst system.

3) Startburst®System(Angiodynamics, formerly RITA Medicals)
This Radiofrequency ablation system provides real time tissue monitoring at the ablation margin [9]. The prerfused RF electrodes (Fig. 4) allows slow infusion of saline from the tines into the tissue around the electrodes allowing thorough heating.

- Startburst® electrode
  This is a array type electrode, which provides scalable , spherical ablation of 3 to 5 cms. The Alternating tines of the array have built in sensors allowing temperature detection in the tissue and providing a feedback to the generator.
- Model 1500X RF Generator
  The Model 1500X RF generator offers controllable ablations from time to time. It delivers 250 watts of power. In order to ensure controlled and predictable ablations the, 1500X provides automatic temperature control.

4 Clinical applications of Radiofrequency Ablation

4.1 Radiofrequency Ablation for Cancer treatment

Radiofrequency ablation is emerged as one among the many ablation therapies that is used for the treatment of many conditions. It serves as a good option minimally invasive tissue ablation when open surgery is not possible due to medical risks or, if there are small tumors present in the organ.

- Procedural Outline:
  As a pre-procedural evaluation, a MRI or a CT scan will be performed in order to determine the location of the tumor. An ultrasound (US) will be done in order to see if the tumor could be seen with ultrasound. Blood test tests will be conducted in order to determine the liver and kidney functions, blood count and tumor markers will be done.An electrocardiogram will be performed 6 months before. RFA can be performed with percutaneous, laparoscopic, or open-surgical approaches. The choice depends on the condition of the patient, tumor location, number, tumor size, growth pattern, and operator and local practice patterns. For laparoscopic or surgical RFA, the patient must not be at high risk for general anesthesia.In the laparoscopic approach, typically three or four small incisions are made. Ports are then inserted into these incisions, which enable the surgeon to easily guide the radiofrequency and ultrasound probes into the liver. The location of each incision depends upon the location of the tumor within the liver.
  The percutaneous approach requires that tumors not lie adjacent to the bowel or other organs which can be injured by thermal conduction. The percutaneous approach could be done using conscious sedation. If a guiding needle is used, the needle electrode is placed by a tandem technique. Once the RF probe is guided to the desired location the electrodes are deployed, and hence delivering the RF energy. Thus the heat causes the death of tumor cells.When the ablation volume does not achieve an adequate margin, overlapping ablations have to be performed (Fig. 5). Follow-up CT/ MRI scans are performed within hours and months following the radiofrequency ablation procedure in order to ensure that the tumor is completely destroyed.

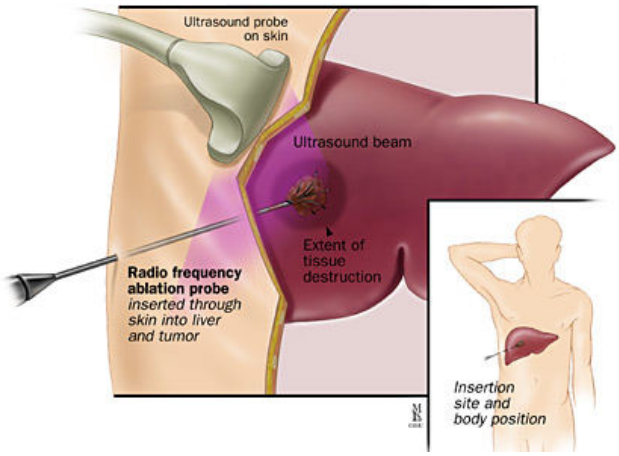

Fig. 5. Radiofrequency ablation procedure.

4.1.1 *Radiofrequency ablation for Liver Tumor*

According to sources Liver cancer ranks fifth among the frequently diagnosed cancers worldwide. Among primary liver cancer, hepatocellular carcinoma (HCC) accounts to 70% to 85% of the total liver cancer burden worldwide. The second most common site of metastases for solid tumors is the liver. The patients diagnosed with liver metastases, from colorectal carcinoma have a survival time of less than a year. The patients with primary and metastatic liver cancer are not suitable candidates for liver transplantation or surgical resection, and hence RFA provides local control with minimally invasive approach. Radiofrequency ablations are done keeping in mind the patients best interest. In patients with small tumors ($\leq$ 3cms), RF ablation was found to be superior to PEI with respect to local recurrence-free survival rates [10]. RF ablation procedure is performed under image guidance. A radiofrequency needle is inserted deep into the lesion and multiple electrodes are deployed. The generator is then activated in order to achieve high temperatures within the tumor. The duration of the treatment

varies from 6-15 minutes for the percutaneous approach.

4.1.2 Radiofrequency ablation for kidney tumor

Another clinical application of radiofrequency ablation has bee for the treatment of kidney tumors, Radical nephrectomy has been the conventional treatment approach for renal cell carcinoma in patients with a functional contralateral kidney. Radical nephrectomy being a invasive approach, RFA may offer a minimally invasive treatment alternative for small renal masses, RFA offers a minimally invasive treatment alternative for small renal masses. Reports demonstrate that renal RFA is most effective in tumors less than 3 cm in diameter [11].

For Radiofrequency ablation of kidney tumors, needle electrodes are placed through the skin into a kidney tumor with the help of image guidance. High-frequency electrical currents are passed through the electrode, creating heat that destroys the cancer cells. RFA is an effective treatment option for patients with one kidney or those who might face difficulty with surgery.

4.1.3 Radiofrequency ablation of lung tumors

Lung cancer has been a leading cause of cancer related deaths among men.Non-small-cell lung caner (NSCLC) accounts for the majority of the cases. Patient with NSCLC incapable to surgery, due to their medical condition or the location of the tumor. Hence RF ablation has been a promising approach for these patients.RF ablation can also be used in patients with metastatic lung disease for eradication of small tumors ($\leq$3cms) In stage I NSCLC following RFA, small case series report one-year survival of 67% to 97%, two-year survival of 35% to 74%, and five-year survival of 20% to 61% [12]. Radio frequency ablation is performed using computed tomography [CT]. Ablation is performed under sedation analgesia, local anesthesia of the needle track, or general anesthesia with doublelumen intubation, depending on the number, size, and location of tumors. reveals the scan details (Fig. 6) of a 72-year-old woman who underwent percutaneous RF ablation for a biopsy-proven NSCLC, who was not a surgical candidate due to severe chronic obstructive pulmonary disease. The mass (arrowhead) was 2.5×2 cm in size, pleural-based, and was located in the left upper lobe on CT.

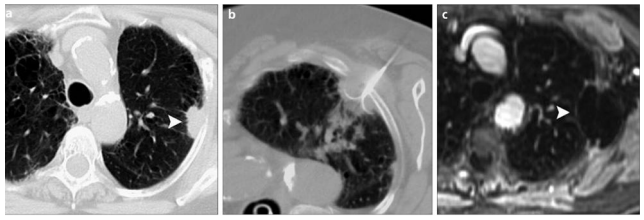

Fig. 6. Scan details of a 72-year-old woman who underwent percutaneous RF ablation for a biopsy-proven NSCLC.

- It was ablated using CT guidance and a 3 cm expandable, multi-tined RF ablation electrode (Boston Scientific Corporation)
- RF energy was applied according to the standard vendors protocol, starting from 40 watts and gradually increasing up to 150 watts over a total of 22 min.
- Follow-up MRI obtained the next day showed no residual tumor (arrowhead) in the ablation zone. There was no recurrence at 12 months follow-up (not shown here) [13].

4.1.4 Radiofrequency ablation for Bone Cancer

A common cause of morbidity in the cancer patients are painful bone metastases. The practical alternative in order to treat the painful bone metastases that do not respond to standard measures such as narcotics or radiation therapy is RF ablation. During RF ablation of osteoid osteoma or any other skeletal tumors, RF electrodes can be placed into the tumors with help of a bone biopsy system such as the Binopty (Radi Medical Systems). First, under CT guidance, a 14 G penetration set of the bone biopsy system is placed into a tumor and then the RF electrode is inserted through the penetration needle. The RF electrode should be selected to be long enough so that the penetration needle can be withdrawn by at least a few centimeters from the tip of the RF electrode, to prevent skin burn along the shaft of the needle [13].

4.2 Radiofrequency Catheter ablation

Radiofrequency catheter ablation (RFCA), is a procedure where the areas of the heart are electrically inactivated of ablated to resolve any abnormal rhythm arising from that area. This procedure has transformed the treatment for diffrent types of arrhythmias like the ventricular tachycardia, Arrial fibrillation. RFCA procedure prevents any abnormal electrical signals from leaving the damaged heart muscles and traveling to the rest of the heart. The procedure is usually carried out in the cath lab.Intravenous medications are given to help the patient relax. A vascular access is achieved through the the groin. A sheath is then inserted inserted into the blood vessel. The doctor then gently guides a catheter into the vessel through the sheath. A video screen will show the position of the catheter.The doctor then inserts several long, thin tubes with wires, called electrode catheters, through the sheath and feeds these tubes into the patients heart. In order locate the abnormal tissue causing arrhythmia, the doctor sends a small electrical impulse through the electrode catheter. This activates the abnormal tissue that is causing the arrhythmia. A mapping catheters records the hearts electrical signals to locate the abnormal sites. The doctor places the catheter at the exact site inside the heart where the abnormal cells are. Radiofrequency energy is sent to the tissue. This destroys heart muscle cells in a very small area (about 1/5 of an inch) that are responsible for the extra impulses that caused your rapid heartbeats (Fig. 7). Catheter ablation usually takes 2 to 4 hours. If the patient has more than one area of abnormal tissue, the procedure will take longer. The patient can usually go home the same day, or may have to stay overnight[17].

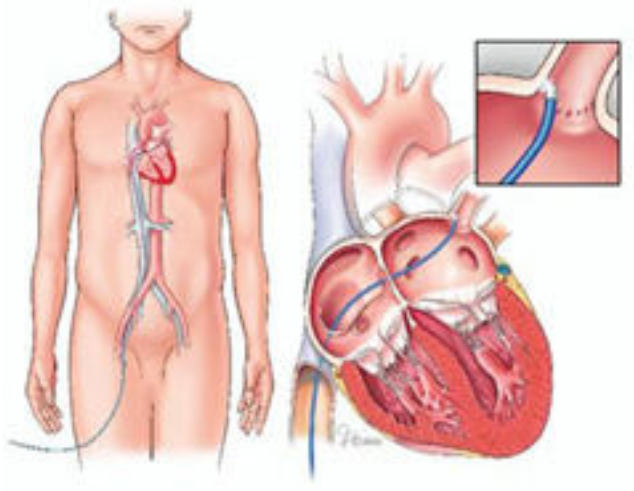

Fig. 7. Radiofrequency Catheter ablation.

4.3 Radiofrequency ablation for the treatment of varicose vein

Radiofrequency (RF) endovenous ablation is a minimally invasive treatment procedure for the venous reflux disease. Varicose vein are a medical condition, a more serious instance of the venous reflex diseases. Varicose veins are accompanied by symptoms such as burning sensations, throbbing, muscle cramps and fatigue, pain, blood clots and other health-imperilling conditions.

The VNUS closure procedure (Fig. 8) is a cutting edge technology that use endovenous RFA treatment alternative with less bruising and less pain when compared to the traditional laser treatment and the vein stripping treatments. By using the VNUS ClosureFAST catheter for the closure procedure, the physicians can close the diseased veins by inserting the catheter under image guidance into a diseased vein through a very small incision and threading the device through the vessel up to the groin area and then heating the vein wall using temperature-controlled RF energy in 20-second intervals to sequentially heat and ablate the vein in seven centimeter increments. After each segment is treated , the ClosureFAST catheter is then manually withdrawn and the process is repeated until the entire length of the vein had been ablated. Heating the veins will cause the collagen wall to shrink and thus results in vein closure .The body automatically will reroute blood flow through healthy veins, and the restoration of normal circulation relieves the distention of the surface veins. The ablated vein becomes scar tissue and is eventually absorbed by the body.

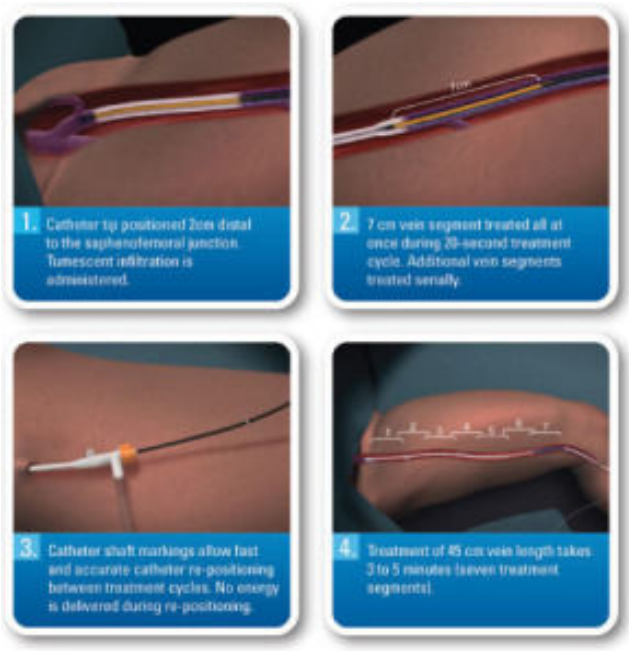

Fig. 8. Radiofrequency ablation for vericose vein treatment.

4.4 Other applications of Radiofrequency ablation

- Aesthetics dermatology RFA is used as one of the modalities for skin treatments. Based on the current research, fractioned radiofrequency could be used to ablate the skin surfaces [16].The ractional ablative radiofrequency devices like the Matrix RF (Syneron, Irvine, CA USA) and Fractora (Invasix, Irvine, CA USA)can be used to treat skin laxity, fine and course wrinkles, and ability to improve skin texture and tone. Radio frequency ablation could be used in the treatment of pancreatic cancer [19]. RFA is being investigated to treat uterine fibroids. A system that is developed by Halt Medical Inc. uses heat energy of the radio frequency waves in order to ablate the fibroid tissue. The device is inserted via a laparoscopic probe and guided inside the fibroid tissue using an ultrasound probe. Radiofrequency ablation has been a safe and effective treatment for Barrett's esophagus. This is carried out as a outpatient procedure and lasts from 15 to 30 minutes [22].
Radiofrequency ablation can also be used for the treatment of breast cancers [14].

4.5 Radiofrequency ablation for low back pain

Back pain is one among the most common complaints in a pain management clinic. One of the most common applications of radiofrequency ablation is the lumbar facet nerve ablation. The facet join provides mobility to the spine. Studies show that Lumbar facet arthropathy and pain contributes up to 30% of low back pain.Radiofrequency neurotomy involves shutting off a certain transmission of pain signals to the brain applying heat to certain nerve pathways.Diagnosis of Facet related pain is got by history, physical examinations, X-rays, CT scan and potential diagnostic injections. Before the treatment the doctor will confirm your diagnosis by making sure that the patient had at least 2 successful medial branch blocks [**?**]. The procedure (Fig. 9) is carried out under fluoroscopic guidance. Radiofrequency neurotomy is performed while the patient is awake but sedated. To begin, the area to be treated is numbed with a local anesthetic. Using image guidance, the doctor will insert a needle and electrode into the treatment location. In order to confirm correct placement,a very small electric current will be initiated which would cause a tingling sensation. A high-frequency electrical current is hen passed through the electrode, heating up and lesioning the sensory nerve. Once the procedure is complete, the needle and electrode are removed and the treated nervous tissue is no longer inflated. After the procedure the patient can go home after 1 to 3 hours. For the majority of patients multiple clinical studies show that radiofrequency neurotomy reduces pain severity and frequency for 1 to 2 years [15].

5 Benefits and Risks associated with Radiofrequency Ablation

Every treatment modality is accompanied by some benefits and and risks. Benefits of this method of treatment are as:

- Radiofrequency ablation is minimally invasive procedure, with rapid recovery speed

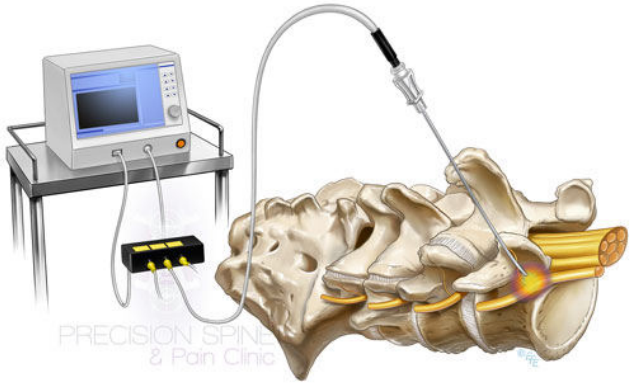

Fig. 9. Radiofrequency ablation for lumbar facet nerve ablation .

- It is less expensive than the other treatment options.
- It can be performed as a outpatient procedure.
- Can be a good choice for people who are not fit for surgery, due to medical conditions.
- In case of treatment of chronic pains there has been significantly lower complications and morbidity rates [21]
- Good efficacy, feasibility and safe technique.

The risks associate with this method of treatment are as:

- Frequently associated problem with radiofrequency ablation is brief or long lasting pain post after the procedure.
- Since radiofrequency ablation involves penetration through the skin, It can cause infections, which would require administration of intravenous antibiotics.
- Tumor seeding and back bleeding are also some risks associated with radiofrequency ablation.
- Skin burns may occur if the grounding pads are not place properly
- Some patients experience post ablation syndrome with a flu like symptom that can appear three to five five days after procedure.
- During the ablation procedure of tissues near the target tumor could be at a risk of being injured.
- One of the organ specific complication with radiofrequency ablation of the lung is pneumothorax, which occurs when air collects in the chest and causes the part of the lung to collapse

6 Limitations of radiofrequency ablations

The current procedures of radiofreqency ablation have their own clinical concerns. Following are some of the limitations of radiofrequency ablations. Radiofrequency ablations are fundamentally limited by the heating mechanism. The tissue temperatures during the ablation procedures should be maintained below 100°C in order to avoid charring.Radiofrequency ablation has many limitations in treating lung tumors. A normal aerated lung tissue is generally characterized by high impedance. This limits the current flow , decreasing the energy deposition during RF ablation. This results in potential treatment failure.

Despite of having large electrodes, multiple ablations are needed in order to achieve the required tumor margin. For instance, to ablate a 3-cm-diameter tumor with 1-cm margin, a minimum of 14 perfectly placed ablations is required to cover 5-cm sphere using a mathematical model. The size of the tumor that can be practically ablated by RFA is limited to 5cms. Attempting to ablate lager tumors increases the risks and decreases the success rate.

Radiofrequency ablations relies on image guidance to place the needles inside the tumors. Ultrasound, Computed tomography followed by MRI is generally used for image guidance. Due to hyperechogenity, ultrasound imaging can create problems for monitoring the ablation.CT definitely offers better image quality but also increases the radiation exposure to the patient and also the Operator.

Tumors that lie close to blood vessels can be effected by cooling effect of the blood flow leading to incomplete ablations [20].

7 Future Scope and Conclusion

Today Radiofrequency abaltion is a front runner technique used in many medical fields. In order to investigate and develop new techniques, many experimental models have been

employed. In the near future more concrete ablation procedure models needs to be designed in order to achieve accurate and complete ablation of the diseased tissues. More powerful generator need to developed in order to achieve consistent tissue ablation. Improving the image guidance during the ablation procedure would also lead to more accurate electrode placements. Raiofrequency ablation can give better results if its combined with other treatment therapies. With continued experience and ongoing research radiofrequency ablation can be expected to place a important role in many medical fields.

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"MRI-Guided Brachytherapy", Is this needed? System and Setup; Limitations and Problems;Possible Solutions

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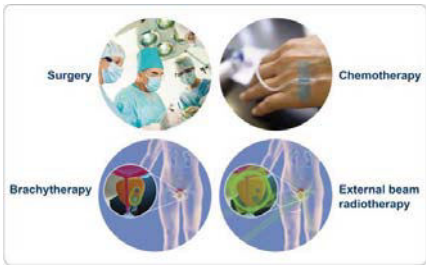
Introduction

Brachytherapy (sometimes referred to as curie-therapy or endocurie therapy) is a term used to describe the short distance treatment of cancer with radiation from small encapsulated radionuclide sources.

Dose rate	Numerical value of the dose rate at the dose specification point(s)
Low dose rate (LDR)	0.4–2 Gy/h
Medium dose rate (MDR)[b]	2–12 Gy/h
High dose rate (HDR)	>12 Gy/h

Brachytherapy treatments classified with respect to dose rate



Current methodologies for cancer treatment

State of the art + Motivation

- The last two decades have witnessed an increasing access to MRI and an increasing use of MRI for brachytherapy treatment planning.
- Brachytherapy demands a high level of accuracy and precision.
- Given that accuracy in brachytherapy is largely dependent on the quality of the images, the rationale for using MRI during brachytherapy catheter placement and treatment planning is strong.

Is this needed?

Accurate target and organ delineation performed according to standardized protocols is required.

Tumor shrinkage and changes in dimensions and topography of the normal organs should be considered

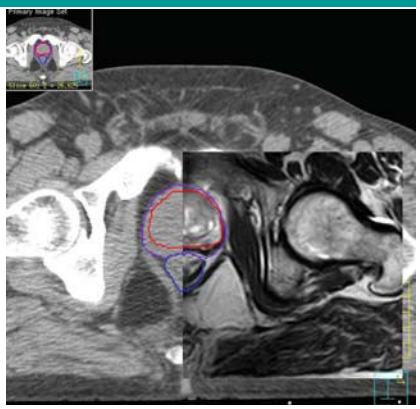
CT provides limited information about radiation changes

Accurate detection of tumor and parametrial infiltration on CT is challenging compared to MRI.

The use of MRI reduces uncertainties and improve quality.

Various Studies revealed that MRI-defined CTV is significantly smaller than the CT-defined.

Therefore, MRI remains the gold standard for delineation of target structures in image-guided brachytherapy.



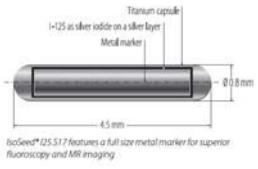
Axial CT- 3T MRI scan fusion. The red line is the MRI-delineated prostate contour, the purple line is the CT-delineated prostate contour and the blue line is the contour of the rectum delineated on CT-MRI fusion.

System and Setup, Limitations and Possible Solutions

MRI scanners with 3 T are increasingly utilized in the radiology community.
T2-weighted MRI sequences are considered the gold standard for IGBT

MRI-Guided Brachytherapy setup room. Entire needle placement procedure performed inside of scanner room.

microSelectron® Digital remote afterloader



Eckert & Ziegler BEBIG´s IsoSeed® I25.S17 for Brachytherapy

The Vienna Ring CT/MR Applicator

The MR Line Marker used for making the source path of gynecologic CT/MR applicators visible with MR-imaging.

LIMITATIONS

Many institutions do not have access to an MRI
MRI is not routinely implemented for EBRT treatment planning mainly due to two major limitations:
- intrinsic spatial image distortion
- missing electron density information

Brachytherapy sources have a complex geometry which induces reproducablity problems
MRI compatible applicators are fragile and expensive and generally not affordable by all centers.
Titanium produces heating effects when imaged with higher magnetic field scanners

POSSIBLE SOLUTIONS

Tissue attenuation coefficients have to be assigned manually or a homogeneous attenuation has to be assumed within all image regions.
Co-registration and fusion of MR and CT images, which allow achieving desirable imaging information.
Using low magnetic field scanners reduce heating effects of Titanium

Conclusion

Image guided brachytherapy (IGBT) has been mainly possible due to MRI, where it is possible to image the applicator with tumor volume and other normal tissues. MRI-guided brachytherapy involves advanced imaging, target concepts, and dose planning. The key issue for safe dissemination and implementation of high quality MRI-guided brachytherapy is establishment of qualified multidisciplinary teams and strategies for training and education.

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MRI-Guided Brachytherapy— Is this needed? System and Setup; Limitations and Problems;Possible Solutions

Dilan Paul Arimbilly Poulose

Abstract The application of MRI-guided brachytherapy has demonstrated significant growth during the last two decades. Clinical improvements in Cervix and Prostate cancer outcomes have been linked to the application of repeated MRI for identification of residual tumor volumes during radiotherapy. The aim of this report is to discuss about its significance among modern therapeutic techniques for treating cancer, the limitations which the system is having and possible solutions.

***Key words*—Brachytherapy, EBRT, LDR,HDR,MDR,ICRU,Organs At Risk (OAR),Dose Volume Histogram (DVH)**

I. Introduction

External Beam Radiation Therapy (EBRT) involves high-energy x-ray beams generated by a machine that are directed at the tumor from outside the body while Brachytherapy involves placing a radioactive material directly inside or next to the tumor. Brachytherapy (sometimes referred to as curie-therapy or endocurie therapy) is a term used to describe the short distance treatment of cancer with radiation from small, encapsulated radionuclide sources. This type of treatment is given by placing sources directly into or near the volume to be treated[1]. The first radium implant was performed in 1901 by Dr. M. Danlos and others at St.Louis Hospital in Paris. A few cases of lupus (a skin disease) were successfully treated.

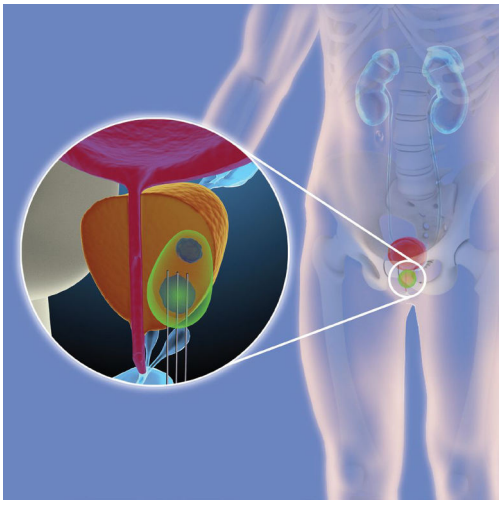

Fig 1 Brachytherapy in Prostate cancer
Source [8]

Brachytherapy may be either temporary or permanent: In temporary brachytherapy, a highly radioactive material is placed inside a catheter for a specific amount of time and then withdrawn. Temporary brachytherapy can be administered at a low-dose rate (LDR) or high-dose rate (HDR). Permanent brachytherapy, also called seed implantation, involves placing radioactive seeds or pellets in or near the tumor and leaving them there permanently. The needle or device is then removed, leaving the radioactive seeds behind. Seeds may also be implanted using a device that inserts them individually at regular intervals.

X-rays, ultrasound, MRI or CT scans may be used to assist the physician in positioning the seeds. Additional imaging tests may be done after the implantation to verify seed placement. After several months, the radioactivity level of the implants eventually diminishes to nothing. The inactive seeds then remain in the body, with no lasting effect on the patient.[19]

Dose rate	Numerical value of the dose rate at the dose specification point(s)
Low dose rate (LDR)	0.4–2 Gy/h
Medium dose rate (MDR)[b]	2–12 Gy/h
High dose rate (HDR)	>12 Gy/h

[a] The definitions here are according to the ICRU. In practice, HDR treatments are given with a substantially higher dose rate than that given by the lower limit of 12 Gy/h.
[b] MDR is not in common use. In those few cases in which it has been used, the treatment results have been rather poor compared with LDR or HDR treatments.

Table 1 Brachytherapy treatments classified with respect to dose rate[a]
Source [1]

Brachytherapy, designed and delivered with accurate anatomic reference, is well suited for dose escalation. By virtue of the "inverse square" law, brachytherapy results in a much steeper dose gradient, and hence can achieve an improved therapeutic

ratio compared with External Beam Radiation Therapy (EBRT)[4].

II. MRI-Guided brachytherapy

Magnetic resonance imaging (MRI) is an important imaging modality for management of oncologic disease. With its excellent soft-tissue contrast, MRI is used for staging, treatment planning, monitoring of treatment response and surveillance after treatment in many cancer. The application of MRI-guided brachytherapy has demonstrated significant growth during the last two decades. The ability of magnetic resonance imaging (MRI) to create exquisite images of the body's soft tissues – and the tumors that arise amid them – is helping physicians to precisely shape brachytherapy doses to tumors, while at the same time avoiding exposure to critical healthy organs and tissues.

For many years, x-ray imaging, computed tomography (CT), and ultrasound (US) have been the preferred imaging modalities for cervix and prostate brachytherapy treatment planning. However, the last two decades have witnessed an increasing access to MRI and an increasing use of MRI for brachytherapy treatment planning. The technique, however, demands a high level of accuracy and precision. Compared with other imaging modalities, for example, MRI provides far better visualization of the prostate and surrounding anatomy, making it the mode of choice for imaging the prostate gland[9]. Given that accuracy in brachytherapy is largely dependent on the quality of the images, the rationale for using MRI during brachytherapy catheter placement and treatment planning is strong. MRI offers a three-dimensional data set, arbitrary imaging planes, and unparalleled soft tissue contrast[4].

Collaborating MRI with Brachytherapy enables clinicians to adapt the dose to the unique anatomy of each patient, accounting for not only the position of organs at risk, but also tumor regression or movement, which may have occurred during preceding external beam radiotherapy and/or chemotherapy, and between Brachytherapy sessions themselves.

III. is this needed?

High-precision radiotherapy techniques offer the option of enhancement of the therapeutic ratio, because the dose to the target is escalated and the normal organs are spared. However, in order to increase conformity, accurate target and organ delineation performed according to standardized protocols is required. Additionally, inter-/intrafraction variation due to tumor shrinkage and changes in dimensions and topography of the normal organs has to be taken into account, thus representing the main challenge for successful application of Image Guided Brachytherapy(IGBT)[2]. To reduce contouring uncertainties and to identify inter-/intrafraction variation with high accuracy, a radiation oncologist has to apply image acquisition protocols adapted to the needs of image-guided therapy, to analyze sectional images with particular attention to tumor regression, regions of potential tumor spread, and lymph nodes regions[2].

CT is the standard imaging technique for most of the Radiation therapy techniques. CT provides information about the electron density of tissues that is required for the dose calculation algorithms of all the commercially available treatment planning systems. Modern CT scanners obtain 64 slices for each turn of the gantry and offer the possibility of image acquisition of the entire abdomen and pelvis in less than 1 min. However, there are some inherent limitations of CT for 3D delineation of relevant structures for IGBT. The uterus is displayed as a homogeneous organ located in the center of the true pelvis. Distinction between different patho-anatomical parts (corpus, cervix, tumor mass), relies on indirect information about the topography of the endometrial cavity and uterine artery. Parametrial ligaments and uterine arteries can be identified on CT with a wide variation of shapes and thicknesses. Accurate detection of tumor and parametrial infiltration on CT is challenging compared to MRI[2]. CT provides limited information about radiation changes and distinction between cervix and residual disease (within the parametria and the uterus).

The major advantage of using MRI for Prostate gland LDR and HDR treatment as compared to US and CT based approaches is to reduce uncertainties and improve quality. Currently,the addition of MRI has not resulted in significant changes to clinical practice and dose administration, however, dose differentiation and OAR avoidance (i.e. urinary sphincters and rectum) has the potential to measurably impact future clinical outcomes[9].

MRI appears to discriminate soft tissue and tumor in the pelvis and has the capability of imaging in multiple planes, as compared to CT. A comparison between MR and CT as imaging modalities used for IGBT, revealed no significant differences in volume sizes and Dose Volume Histogram (DVH) parameters for the organs at risk (OAR), but for target volumes, CT allows for OAR delineation, but CT-based target contouring shows systematically wider contours than with MRI[2]. This uncertainty limits the degree of dose optimization possible, in particular in large tumors with parametrial invasion. Therefore, MRI remains the gold standard for delineation of target structures in image-guided brachytherapy. Furthermore, MRI technology offers the unique possibility of integrating a wide range of biologic images to precise dosimetric maps within the gland and of studying the underlying molecular properties of images and the changes that occur during RT[4].

IV. system and setup

Modern brachytherapy exploits technological advantages such as high strength sealed radioactive sources, remotely controlled after-loading machines, sophisticated treatment planning systems and implants.

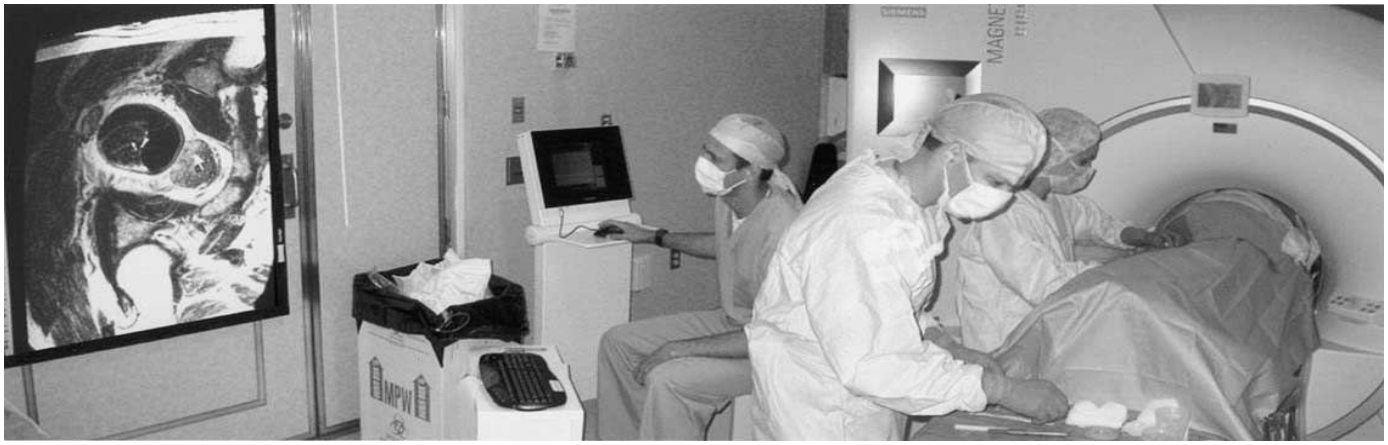

Fig 2: Magnetic resonance imaging (MRI) scanner room setup.
Source [4]

A. MRI Device

Low-field 0.2–0.5 T (Tesla)open MRI scanners offer improved patient accessibility and are suitable for claustrophobic patients. However, the image quality of low-field scanners is not equivalent to the image quality of those with standard magnetic field strength of 1.5 T and higher. Therefore, scanners with 3 T are increasingly utilized in the radiology community. With higher field strength, the signal-to-noise ratio is increasing and the voxel volume can be reduced. Image distortion is also increasing with increasing field strength[4]. Fig 2 shows MRI-Guided Brachytherapy setup room. Entire needle placement procedure performed inside of scanner room.

Higher magnetic fields, like 7 and 8 T have been installed only in a few research centers as they present some technical challenges, e.g., the safety limits can be exceeded due to higher gradient amplitudes and radio-frequency power deposition. Furthermore, they do not automatically produce better diagnostic images because of dielectric resonance effects[2].

Imaging to define tumor and normal structures must be performed with the patient in the treatment position, with all treatment conditions duplicated as closely as possible. For example, if the patient is to be treated supine with the knees slightly elevated then imaging should be performed with the patient in the same position. Markers for localizing tumor margins or normal tissues, if used, must be MR-compatible. Images must be obtained 5 cm superior to the most cephalad part of the brachytherapy sources to 2 cm inferior to the most caudad part of the brachytherapy sources. Imaging is to be performed for one or more brachytherapy insertions.

Intravenous contrast enhancement, with gadolinium chelates (0.1 mmole/kg), may be useful in characterizing and better depicting the extent of lesions as well as in assessing vascular anatomy. Gadolinium chelates can be used safely in patients with allergies to iodinated contrast media and/or renal impairment. Gadolinium is routinely used in the evaluation of endometrial and ovarian disease.

B. Brachytherapy Photon Sources

The choice of an appropriate photon emitting radionuclide for a specific brachytherapy treatment depends on several relevant physical and dosimetric characteristics, the most important of which are the:

- Photon energies and photon beam penetration into tissue and the shielding materials;
- Half-life;
- Half-value layer (HVL) in shielding materials such as lead;
- Specific activity;
- Source strength;
- Inverse square fall-off of dose with distance from the source (this is the dominant dosimetric effect, because of the very short treatment distances used in brachytherapy).

Over a dozen radioactive nuclides have a history of use as sealed sources in brachytherapy, but only six are commonly used today, while a few others are used under special circumstances.

The common sources are 60Co, 137Cs, 192Ir, 125I, 103Pd and 90Sr/90Y; the less common sources are 198Au, 106Ru and 252Cf. The use of 226Ra and 222Rn was discontinued because of safety concerns, but their long history of clinical use still influences modern brachytherapy concepts[1].

Some physical characteristics of common brachytherapy sources are listed in Table 2

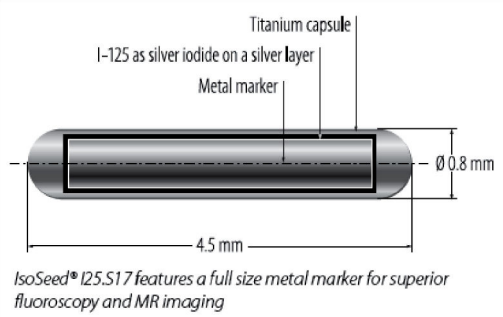

Fig 3 : Eckert & Ziegler BEBIG´s IsoSeed® I25.S17 for Brachytherapy

Source [12]

Brachytherapy photon sources are available in various forms (needles, tubes, seeds, wires, pellets) but are generally used as sealed sources. Usually they are doubly encapsulated in order to provide adequate shielding against the α and β radiation emitted from the source and to prevent leakage of the radioactive material

- Caesium-137 is available in several forms, such as needles, tubes and pellets.
- Iridium-192 is available in the form of wires, the radioactive core being an iridium–platinum alloy with an outer sheath of 0.1 mm thick platinum. Iridium-192 sources are also available as seeds, again doubly encapsulated with an outer sheath of stainless steel, and as strands of nylon ribbon. HDR remote after-loading units use specially designed 192Ir sources with typical activities of 370 GBq.
- Iodine-125, 103Pd and 198Au sources are only available as seeds. They are usually inserted into the tumor volume using special delivery 'guns'.
- Cobalt-60 brachytherapy sources are available as pellets with a typical activity of 18.5 GBq per pellet.

Isotope	Average[a] photon energy (MeV)	Half-life	HVL in lead (mm)	Γ_{AKR} [b, d] $\left(\frac{\mu Gy \cdot m^2}{GBq \cdot h}\right)$	Λ [c, d] $\left(\frac{cGy \cdot h^{-1}}{cGy \cdot cm^2 \cdot h^{-1}}\right)$
Co-60	1.25	5.26 a	11	309	1.11
Cs-137	0.66	30 a	6.5	77.3	1.11
Au-198	0.41	2.7 d	2.5	56.2	1.13
Ir-192	0.38	73.8 d	3	108	1.12
I-125	0.028	60 d	0.02	–	–
Pd-103	0.021	17 d	0.01	–	–

[a] These are only approximate values, depending on the source make and filtration.
[b] Γ_{AKR} is the air kerma rate constant.
[c] Λ is the dose rate constant.
[d] Using generic values of the air kerma rate constant or dose rate constant for a low energy photon source may lead to substantial errors in dose calculations. They are therefore not given here for ^{125}I and ^{103}Pd.

Table 2 Some characteristics of isotopes used in Brachytherapy
Source [1]

C. *MRI Compatible Applicators*

Different applicators are used for particular tumour sites according to specific demands and possibilities from a clinical and dosimetric point of view. In addition, for an applicator to be useful, it should be visual, reliable and reproducible with as little negative impact as possible on the image quality of the tumour and the organs at risk and with no negative effect on the geometrical accuracy of the image. These requirements vary with the image technology used and are met to different degrees by specific devices: for ultrasound by echogenic needle tips; for CT by applicators, which do not produce metallic artefacts; for MRI by non-metallic applicators and needles

For permanent implants, radioactive material (which is enclosed within small seeds or pellets) is placed directly in the site of the tumor using a specialized delivery device. For temporary implants, the delivery of radiation sources to the target tumor area is performed via specialized applicators such as catheters or needles that are directly inserted into either:

- A body cavity (e.g., uterus, vagina), body lumen (e.g., trachea, esophagus) or external surface (e.g., skin) – collectively referred to as contact brachytherapy
- The tumor (e.g., prostate, breast) – referred to as interstitial brachytherapy.

If MR is to be used, a non-ferromagnetic applicator must be used and should be tested in the MRI scanner prior to insertion into a patient to make sure that there is no interference with the magnetic field.

Fig 4 The Vienna Ring CT/MR Applicator
Source [17]

The Vienna Ring CT/MR Applicator in Fig 4 is enhanced with the addition of nine guide holes in the ring Tube. These guide holes allow placement of interstitial titanium needles using the ring Tube as a needle template, while maintaining the treatment channel of the ring Tube. The addition of interstitial needles makes it possible to achieve asymmetric alteration of the dose distribution. The needles are inserted perpendicular to the ring and in parallel to the tandem. The applicator's plastic and composite fiber materials minimize distortion on CT or MR imaging. The Round Point needle is designed to minimize tissue damage and for ease in implantation[17].

The mechanical properties of the applicators should be checked and verification should be made that the applicators and transfer tubes are of the correct length. Checks should be made to ensure that the product is functioning as described in the instructions for use. Any mechanical code, which is intended to force the connection of a specific applicator with a specific transfer tube, should be controlled. Applicators for a specific irradiation device are not to be used with other irradiation devices. If more than one type of afterloading machine is available in the institution all applicators have to be marked clearly as to which type of afterloading machine they belong. The correspondence of active source dwell positions with dummy source positions used for treatment planning has to be checked. This can be performed by comparing autoradiographic images of the source positions within the applicator with radiographic images of the dummy source within the same applicator. This can either be done on the same film or different films if the position of the films relative

to the applicator is known. This relation can be established by markings in the film. Verification should be made that the geometry of the applicator corresponds exactly with the geometry of the applicator in the treatment planning program

D. Remote Afterloading Systems

Brachytherapy concerns primarily the use of radioactive sealed sources placed directly into tissue either inside or very close to the target volume. Brachytherapy sources are usually inserted into catheters or applicators. One of the major exceptions to this is prostate seed brachytherapy, where sources are placed directly into the tissue of the prostate. When the radioactive brachytherapy source is positioned in the patient after the surgical procedures, i.e., after the insertion of the applicators, the technique is called "afterloading".[10]

Generally, the radiation sources are manually afterloaded into applicators or catheters that have been placed within the target volume. At the end of the treatment the sources are removed, again manually. These procedures result in some radiation exposure to the medical and support staff. Several computer driven remote afterloading systems have been developed to help minimize this radiation exposure.Remote afterloading devices are used in both interstitial and intracavitary clinical applications[1].

In addition to the advantage of increased radiation protection, afterloading techniques allow an improved dose distribution to the target volume because of greater precision in source positioning. Without radiation exposure to the staff it is possible to obtain an accurate idea of the placement of the sources within the body of the patient and to verify their proposed positions before the sources are introduced. Furthermore, many modern systems offer more flexibility in source positioning and dwell times, leading to a better dose distribution.

Fig 5 microSelectron® Digital remote afterloader

Source [11]

One of the latest Remote Afterloading platform developed by ELEKTA is shown in Fig 5. Cis Bio, now BEBIG (Germany), BUCHLER GMBH and Nucletron produce the most widespread remotely controlled low dose rate (LDR) and medium dose rate (MDR) afterloading systems commercially available. In contrast to the high dose rate (HDR) systems, low and medium dose rate systems show much more variability in their design. Many quality assurance features, however, are closely parallel for all types of systems.

E. Quality Assurance and Radiation Protection

All developments in technology, dosimetry, oncology and quality assurance aim mainly at reducing the risk of complications to the patient. As far as the staff involved are concerned (radiation oncologists, physicists, nursing staff and technicians), the three general principles of radiation protection should be followed: the justification of practice, the optimisation of protection, and adherence to individual dose limits (ICRP 1991)[10].

Safety system check procedures for MRI-Guided Brachytherapy :

- Source preparation : Preparation of sources is one of the phases that may result in a significant percentage of radiation exposure received by workers during brachytherapy procedures. Appropriate safety equipment should be available: mobile or fixed shields, devices for manipulation of sources, safes for storage of sealed sources.
- Source loading : Before the active sources are positioned, dummy sources should be used to check the source position within the inactive guides or applicators. Source strength and source position in the applicator should be identified. A check should be made to ensure that the correct sources occupy the correct positions within the applicators. A logbook of what type and strength of sources have been loaded in the patient, the room number and the date and time should be kept.
- During treatment : During a treatment with manually loaded applicators the patient emits radiation. Protection of personnel can be achieved by the use of mobile shielded screens. Check that long handle forceps, a lead transport container and a survey meter are present in the room and function properly.
- Removal of the sources
  - Verify that the time for removal is correct
  - Count all sources upon removal.
  - Check the inventory log and recount sources on return to the storage facility.
  - After removal, use a detector to monitor the patient, waste and linen to ensure that no sources are left in or near the patient

The position of sources placed within afterloading devices can be determined with autoradiographs. It is necessary to check that the unit will position the source with millimeter accuracy at predetermined programmed positions along treatment catheters. The use of appropriate radiographic markers and combination of a radiographic image with an

autoradiograph is a convenient method for checking source positioning

After implantation of sources in a patient, a radiation survey must be performed in areas within and around the patient's room. Radiation levels should be measured and recorded so as to assist in maintaining minimum exposure of hospital staff and visitors. The radiation levels in adjoining patients' rooms should be very low, such that no individual would receive more than 0.2 mSv in any one hour.

Prior to release of an implant patient from hospital, the patient and the room must be surveyed. For temporary implants a survey must be done upon removal of the sources so as to confirm removal of all sources. Patients with permanent implants may be discharged from the hospital if at the time of discharge the radiation level at 1 m is less than 0.5 mSv/h[10].

V. Limitations and possible solutions

With the introduction of interventional MRI techniques that require easy access to the patient and a concurrent use of instruments (made from non-ferromagnetic materials) inside the magnet bore during image acquisition, there has been a renewed interest also in low-field MRI systems (based on resistive or permanent magnets). MRI units designed for interventional procedures based on an open magnet design that combines with a medium-to-low field magnet could offer advantages over conventional whole-body MRI systems also for imaging applications in radiotherapy[14]. The open design concept allows for a patient to be imaged in the actual radiotherapy treatment position using individual immobilization devices. A low magnetic field is beneficial in interventional brachytherapy procedures, as susceptibility-induced artifacts from the applicators (MRI-compatible) increase at higher fields. The lower signal-to-noise and spatial resolution inherent to a low-field system compared to a high-field MR is, however, a significant drawback.

MRI enables improved soft tissue depiction and gives detailed information about pelvic topography and tumor regression during radiotherapy. It has to be noted though, that MRI is not routinely implemented for EBRT treatment planning mainly due to two major limitations: intrinsic spatial image distortion and missing electron density information This implies that if MRI scans are used for treatment planning, tissue attenuation coefficients have to be assigned manually or a homogeneous attenuation has to be assumed within all image regions. An alternate option is co-registration and fusion of MR and CT images, which allow achieving desirable imaging information and creating optimal conditions for precise dose calculation[2]. The problem of MR image distortions can be resolved by applying different image correction methods[14].Although MRI is superior to CT for imaging and identifying cervical cancer extension, many institutions do not have access to an MRI[5].

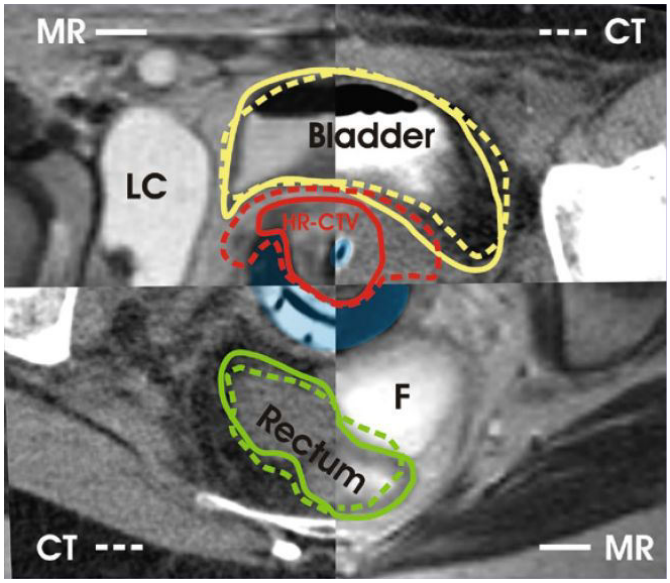

Fig 7 Image fusion between axial computed tomography (CT) and magnetic resonance (MR) scans at time of brachytherapy. Source [2]

See Fig 7 Bladder, rectum, and High Risk (HR) Clinical Target Volume (CTV) are contoured (CT – dotted line, MR – solid line). Organs at risk (OAR) contours deviate only slightly, whereas HR CTV is larger on CT, especially in lateral directions. Blue transparent color indicates tandem-ring applicator, which is depicted as a homogeneous black structure in magnetic resonance imaging (MRI). On the contrary, details of the applicator (source channel, holes for needles) are clearly visible on a CT scan (LC, lymphocyst after laparoscopic lymph node staging; F, free fluid in the pouch of Douglas)[2]

The detection of pathologic enlarged lymph nodes with sectional imaging is of major importance for IGBT. The precision of CT and MRI for the detection of lymph node metastasis is comparable. Since both imaging modalities rely on size criteria (short axis >1 cm) for the detection of pathologic lymph nodes, the sensitivity of these methods is rather low, ranging between 40% and 70%. Lymph node specific MRI contrast agents, e.g., ultrasmall particles of iron oxide (USPIO), show the potential of improving sensitivity for the prediction of lymph node metastasis. In the study of Rockall et al. the sensitivity increased from 29% using standard size criteria, to 93% using USPIO criteria based on a node-by-node approach, and from 27% to 100% based on a patient-by-patient approach[2].

One major issue in imaging assisted treatment planning in brachytherapy represents an important difference compared with external beam treatment planning. Irradiation in brachytherapy is performed through an applicator or a radioactive source brought into, or next, to the tumour, by which tumour topography and topography of organs at risk is often significantly changed. Therefore, in brachytherapy treatment planning, there is a separation between provisional image assisted treatment planning (without an applicator or with a dummy applicator) and definitive image assisted

treatment planning with the applicator in place.

The inability to obtain MRI scans with the conventional, stainless steel afterloading applicators has discouraged the implementation of MRI for gynecologic brachytherapy treatment planning to a large extent[20]. New applicators made from polymer material and titanium were introduced. These applicators are fragile and expensive and generally not affordable by all centers. In addition, titanium produces susceptibility artifacts and image distortion with MRI[5]. Moreover, it also produces heating effects when imaged with higher magnetic field (3 T). Such concepts have to be clearly understood and mandate further research in applicator development. Systematic investigation as a part of commissioning is required when new applicators are procured to be used with MRI/CT modalities. With conventional applicators, radiopaque dummies to represent source channel / positions were provided by the vendors; however, CT / MR compatible applicators lack dummies, adding to uncertainties during reconstruction of the applicator that may have consequences in dose distribution. Many methods like use of 6 F catheters filled with water, iodine, oil, etc., have been used to overcome these limitations.

MRI Guided brachytherapy in cervical cancer is evolving with promising results. It definitely needs an upgradation in the existing infrastructure or additional enhanced setup in terms of imaging, hardware and software, and training of staff. A treatment does not reach its goals if the source misses its aimed positions by a large margin; that is, if there are severe geographical misses in placing the sources relative to their intended positions. Owing to the steep dose gradient that characterizes brachytherapy, such geometrical misses may be seriously detrimental to the intended treatment. Thus there is a need for a quality control programme guaranteeing that the treatment is given in accordance with its purposes.

Brachytherapy sources have a complex geometry with very small dimensions. Those specificities induce problems of reproducibility in the manufacturing process. The consequence of this lack of reproducibility is a variation of the flux of the photonic emission from one seed to another. Consequently, it was observed that the spatial distribution of the absorbed dose to water is very dependent on the seed characteristics (geometry and components of the internal and wrapping materials).

The mechanical integrity of a source must be checked at regular intervals by visual inspection, leak testing and activity measurement. Applicators, because of their repeated clinical use, undergo severe handling, cleaning and sterilization. Visual inspection and radiographic evaluation of all applicators should be performed at some pre-established frequency. For gynaecological applicators it is necessary to check that the assembly is structurally sound, that all clamps, screws and retaining devices are functioning properly and that the source insert carriers seat correctly in the colpostats.

Brachytherapy is an important modality in the treatment of malignant disease; a modality that allows conformal treatment without heavy technological involvement. However, since it generally involves invasive procedures (interstitial brachytherapy), except for special instances in which intracavitary techniques may be employed, brachytherapy is relegated to second place behind external beam radiotherapy in the treatment of malignant disease. A typical radiation oncology department will treat about 80% of its patients with the various external beam techniques and about 10–20% of its patients with brachytherapy. The basic principles of brachytherapy have not changed much during the past 100 years of radiotherapy; however, the advent of remote afterloading brachytherapy has made brachytherapy much more efficient for the patient and safer for staff from the radiation protection point of view. In terms of physics human resource needs, a brachytherapy patient requires considerably more involvement than an average external beam patient[1].

Nearly every malignant disease in the human body has been treated with brachytherapy; however, gynaecological cancer treatments provide the greatest success and permanent prostate implants are becoming increasingly common. There are also various sites for which brachytherapy has proven a complete failure. The newest application of brachytherapy is intravascular (also referred to as endovascular) brachytherapy, used for the prevention of restenosis in arteries following coronary arterial angioplasty.

While assessing the treatment procedure itself, the complications of brachytherapy are measured using the "Radiation Therapy Oncology Group grading system (grade I: minor symptoms requiring no treatment; grade II: symptoms requiring simple out-patient management but not affecting lifestyle; grade III: distressing symptoms altering lifestyle and requiring minor surgical intervention or hospitalization; grade IV: major symptoms requiring major surgical intervention or prolonged hospitalization; grade V: mortality) [21]." Most of the negative effects of brachytherapy are in the short term. One study reported that only 8.8% of the patients experienced grade III or grade IV complications[21]. Most commonly, patients experience urinary tract infections due to the swelling of the prostate, pain, fatigue, and proctitis [22]. One of the major disadvantages of brachytherapy is the chance of damaging normal tissue with an escaped radioactive seed; however, with pre-planning, unexpected normal tissue damage is rare. Also, brachytherapy is not the best treatment option for higher-grade tumors because seeds only radiate within a small radius of the prostate and do not reach metastases outside of the prostate area [22].

VI. CONCLUSION

Image guided brachytherapy (IGBT) has been mainly possible due to MRI, where it is possible to image the applicator with tumor volume and other normal tissues. MR-based IGBT is practiced mainly in Europe and a few centers in the US. As compared to robust 2D outcome data, it is still evolving with initial clinical data showing promising results. Like any other advanced technique, viz. Intensity-modulated radiation therapy (IMRT), Image Guided Radiation Therapy (IGRT) , External Beam Radiation Therapy, IGBT too requires stringent quality assurance procedures to be adhered to; otherwise, it will lead to a geographical miss and even increased toxicities to patients.

Various publications from leading hospitals around the world have shown that use of this advanced technology allows health-care teams to treat even the most complex cervical cancers, expected to result in lower recurrence rates and higher survival. Intensive multicenter research is ongoing with the aim to provide more data to confirm these treatment benefits over traditional methods.

MRI-guided brachytherapy involves advanced imaging, target concepts, and dose planning. The key issue for safe dissemination and implementation of high quality MRI-guided brachytherapy is establishment of qualified multidisciplinary teams and strategies for training and education.

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HYPERTHERMIA-CLINICAL APPLICATIONS AND LIMITATIONS SYSTEMS USED AND LIMITATIONS WITH FUTURE OUTLOOK

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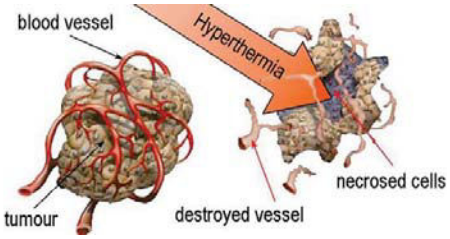
Introduction

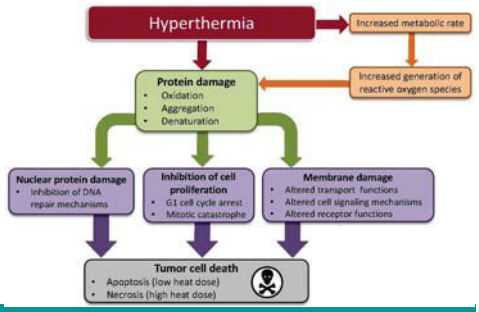
State of the art

- Hyperthermia is the condition of having higher body temperature than the normal.
- Considered as the fourth leg cancer treatment method.
- It is also called as thermo therapy or thermal therapy in which body is exposed to high temperatures (up to 113ºF).
- Researchers have found out that high temperature can damage and kill cancer cells without causing much negative effect on healthy tissues.

Idea:



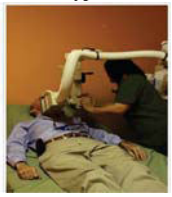
Procedure Flowchart



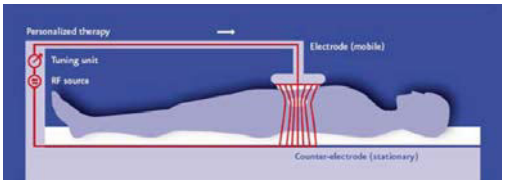
Hyperthermia Therapy And Its Clinical Applications

Hyperthermia is rarely used as a single cancer treatment modality and is usually combined with radiation therapy, chemotherapy or radio chemotherapy, and also with gene and immunotherapy. They focuses on treating different types of cancer, especially those with poor outcome. Several methods of hyperthermia techniques are currently employed and each of them is used depending on the tumor location. They are local, regional and whole body hyperthermia. . But, Hyperthermia is now considered as the oldest weapon against cancer. It alone could not give the best results and hence oncothermia was introduced.

Local Hyperthermia

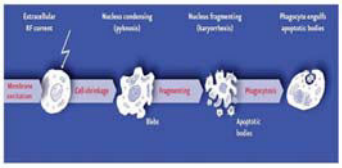


Regional Hyperthermia



Whole Body Hyperthermia

Oncothermia



- Clinical Hyperthermia has two separate domains, WBH and RHT.
- Noninvasive WBH (Whole Body Hyperthermia) can be controlled with an Aquatherm radiant heat device with temperatures up to 41.8 ° C.
- Noninvasive RHT (Regional Deep Hyperthermia Therapy) is done by using single microwave.
- Ultrasound applicators are used for superficial hyperthermia and arrays of multiple applicators for deep heating.

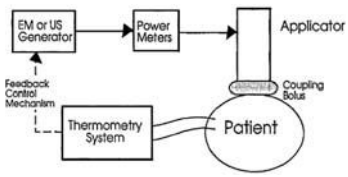
Types of hyperthermia	Type/site of tumour	Clinical applications	Types of energy/equipment
Local HT: – superficial – intracavital – intraluminal – interstitial	Superficial tumours Intracavital tumours Intraluminal tumours Intracranial tumours	Head & neck cancers Locally advanced or recurrent breast cancer Malignant gliomas Rectal cancer Oesophageal cancer Soft tissue sarcomas	Microwaves (MW) Radiofrequency (RF) Ultrasound (US) Hot sources: – Hot water perfusion – Resistive wire implants – Ferromagnetic implants – Nanoparticles
Regional/Part-body HT: – abdominal – pelvic – limbs	Deep seated tumours Locally advanced tumours	Cervical cancer Rectal cancer Bladder cancer Prostate cancer Soft tissue sarcoma Ovarian cancer Mesothelioma Peritoneal carcinomatosis	
Whole-body HT	Disseminated/metastatic diseases	Malignant melanoma Recurrent soft tissue sarcomas Ovarian cancer	Infrared radiators Hot water blankets Thermal chambers

Clinical Applications Of HT

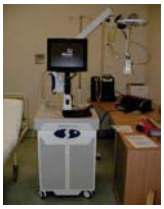
Systems Used And Its Limitations

- Operate by exposing target tissue to either electromagnetic (EM) fields or ultrasound (US) radiation.
- The EM or US power is supplied by a generator and delivered to the patient through an applicator.
- Temperature is monitored by thermometry system and feedback is sent to the generator.

System Design



BSD 500



Limitations

- Negative effects depends on the source and they are temporary.
- Cardiac problems
- Burns
- Increase in blood pressure and pulse
- Normal tissues are damaged.
- Perfusion techniques can cause swelling, blood clots etc.
- Whole body Hyperthermia can cause cardiac and vascular problems.

Conclusion & Future Outlook

After continuous research, higher level of preferential heat induction into tumor tissue and repeated hyperthermia at 42-43.5 degrees C for 45 minutes per session immediately following radiation therapy yields favorable therapeutic results. Tumor regression response rate of over 70% was achieved without concomitant increase of normal tissue complication. Therefore, the potentially significant impact on clinical cancer therapy, by moderate thermotherapy is evident. It is a promising way to improve cancer treatment, but presently it is an experimental technique. And researchers continue to look at how hyperthermia is best used along with other cancer treatments to improve outcomes.

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Hyperthermia — Clinical Applications and Limitations, Systems Used and Limitations With A Future Outlook

Arathi Sreenivas

***Abstract*—The idea of killing tumor cells using high temperature, called hyperthermia, has become a mile stone in the field of oncology. Even though this technique was known since last decade, it was only recently they have used this for cancer treatment. The main objective of this report is to convey, how hyperthermia disease has become a treatment methodology, its clinical applications, systems used and its limitations.**

***Index Terms*— Hyperthermia, Oncology, Hyperthermia therapy**

I. INTRODUCTION

Hyperthermia (condition of having higher body temperature than the normal) is considered as the fourth leg cancer treatment method. It is also called as thermo therapy or thermal therapy in which body is exposed to high temperatures (up to 113ºF)[12]. Researchers have found out that high temperature can damage and kill cancer cells without causing much negative effect on healthy tissues.

What is Hyperthermia? It is one of the unique ability of human body to regulate its temperature. When the body temperature increases it uses several strategies to control them. There might be a chance of misinterpreting hyperthermia as fever. But," hyperthermia" is entirely a different concept. It is the increase in body temperature due to failure in thermoregulation. As a result of this, body produces or absorbs more heat than it dissipates. At this situation elevated body temperature could not be controlled by sweating like mechanisms and hence immediate treatment has to be taken. If a person spends more time in high temperature without taking in enough water, the body's cooling processes may shut down leading to dehydration and even to death. The most common causes for this include heat stroke and adverse reactions to drugs. The early symptoms include acute temperature elevation caused by exposure to combination humidity and heat. The latter side effect is a relatively rare one which affects central nervous system. This is mainly due to some kind of drugs like selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants. Some types of general anesthesia may cause a rare complication called Malignant Hyperthermia [11].

The application of heat therapy for certain illnesses has started quite a long back. Ancient Greeks, Romans, and Egyptians initially used heat to treat breast masses. This is still a recommended treatment for breast bulge. Medical practitioners in ancient India used regional and whole body hyperthermia as treatments. The outbreak of oncological hyperthermia had been reported in late 18^{th} century. De Kizowitz (France) in 1779 described for the first time about the inhibition of tumor growth by high fever caused by malaria. In 1866, Busch (Germany) described the complete reduction of histologically confirmed face sarcoma after two erysipelas infections with subsequent 2 year disease free survival. Typically, the reports documented the rare regression of a soft tissue sarcoma after erysipelas (an acute streptococcus bacterial infection of the skin; a different presentation of an infection by "flesheating bacteria") was noted. Efforts to deliberately recreate this effect led to the development of Coley's toxin. A sustained high fever after induction of illness was considered critical to treatment success. This treatment is generally considered both less effective than modern treatments and, when it includes live

bacteria, inappropriately dangerous. Around the same period Westermark used localized hyperthermia to produce tumor regression in patients. Encouraging results were also reported by Warren when he treated patients with advanced cancer of various types with a combination of heat, induced with pyrogenic substance, and xray therapy. Out of 32 patients, 29 improved for 1 to 6 months. Later in the 1970s they began controlled clinical trials on deliberately induced hyperthermia [5, 12].

Although hyperthermia therapy was known from last century, it is only recently its mode of action and clinical application has been known to the scientific world. Presently, many clinical institutions have boarded upon hyperthermia programs because of its success results. It gave a clear idea about the anatomical sites that can be effectively heated, the physiological and biochemical conditions which make tumors responsive to this form of therapy. Hyperthermia with the combinations of radiotherapy and chemotherapy gave great results and so it is always used with other forms of cancer therapy, such as radiation therapy and chemotherapy. The main reason behind this is, hyperthermia could make some cancer cells more sensitive to radiation or harm other cancer cells that radiation cannot damage. It can also increase the effects of certain anticancer drugs. Numerous clinical trials have been studied based on these combinations. They focused mainly on the treatment of many types of cancer, like sarcoma, melanoma, and cancers of the head and neck, brain, lung, esophagus, breast, bladder, rectum, liver, appendix, cervix, and peritoneal lining (mesothelioma).

BSD500, BSD1000, BSD2000, Celsius42, EHY2000plus, EHY3010 ML, EHY1020IL, Sonotherm 1000, ThermoChem HT1000, 8 Medical Hyperthermia Pump, Beaumont Hyperthermia Pump are the normally used devices for performing hyperthermia therapy. Out of this, BSD2000 got recently approved in the year 2011. Far infrared rays are also used for the same. They are radiated directly to the body from a very close distance between the device and the body area being treated. The unique property of this technique is that, it travels in a straight line and penetrates the body to a depth of two to two and half inches and is an absolutely safe and natural treatment with no side effects [9].

Even though it has a wide range of benefits, it has also negative outcomes. Major drawback is that normal tissues are not damaged during hyperthermia if the temperature is below 111°F. But regional differences in tissue characteristics can cause higher temperatures in different area. This can result in burns, blisters, discomfort, or pain. Perfusion techniques can cause tissue swelling, blood clots, bleeding, and other damage to the normal tissues in the perfused area. However, most of these side effects are for very short period. Even though they are uncommon, whole-body hyperthermia can cause more serious effects such as cardiac and vascular disorders. Diarrhea, nausea, and vomiting are commonly observed after whole-body hyperthermia[9,12].

Including the temperature control, number of challenges has to be overcome, before considering hyperthermia as a standard treatment for cancer. However, there is more evidence to support that its use as primary treatment for cancer in different regions like Europe, including the Netherlands, Germany, and Austria. Different clinical trials are also being conducted to evaluate the effectiveness of hyperthermia. Trials based on the combination therapy technique as well as the improvising techniques are still under progress. In spite of the high interest in hyperthermia, it remains the case that our knowledge about its modes of action, either alone or in combination, and its clinical applications are still under developed.

II. Hyperthermia Therapy And Its Clinical Applications

Hyperthermia is rarely used as a single cancer treatment modality and is usually combined with radiation therapy, chemotherapy or radio chemotherapy, and also with gene and immunotherapy. All these treatment methodology mainly focuses on treating different types of cancer, especially those with poor outcome (melanoma, soft tissue sarcoma, head and neck cancers, and malignancies of the brain, lung, breast,

cervix, colon, bladder, oesophagus and liver). Some of them have already given the best results, but others have not. Hyperthermia when combine with radiotherapy in breast cancer, melanoma, glioblastoma, head and neck tumors and cervix cancer gives the best results. If HT is either delivered alone or in combination with other cancer treatment with temperature less than 44.0°C then it rarely affects the normal tissue. But as the thermal depositions increases it can gradually lead to blistering, burns, pain or necrosis. In case of perfusion techniques there may appear swelling of the heated tissue, ischaemia due to blood clots or bleeding. On the whole, thermal side effects are short-lived. Even though there is a strong rationale for using HT in some clinical situations, there is still a lack of strict indications in which cases HT should be delivered obligatorily[1-4].

A. *Types*

Several methods of hyperthermia techniques are currently employed and each of them is used depending on the tumor location. They are

- Local,
- Regional,
- Whole-body.

Local hyperthermia heats a very small area and is typically used for cancers near or on the skin or near natural openings in the body (e.g., the mouth).The heat may be created with microwave, radiofrequency, ultrasound energy or using magnetic hyperthermia. Depending on the location of the tumor, the heat may be applied to the surface of the body, inside normal body cavities, or deep in tissue through the use of needles or probes. One relatively common type is radiofrequency ablation of small tumors. This is very easy to achieve when the tumor is on a superficial part of the body, which is called superficial hyperthermia, or when needles or probes are inserted directly into the tumor, which is called interstitial hyperthermia. In order to internally heat the area, sterile probes like thin, heated wires, hollow tubes filled with warm water, implanted microwave antennae, and radiofrequency electrodes are used.

Local Hyperthermia treatment can be performed using MRI guidance also. In this technique first the tumor will be located and will be treated either externally or internally. Externally, the area of interest is heated from outside with high energy waves targeting the tumor. Internally, they can be performed by inserting probes or antennas onto the tumor. Several types of sterile probes may be used. Radiofrequency ablation (RFA) is a type of internal hyperthermia that uses high-frequency energy to heat and destroy cancer cells.

Figure 1: Local Hyperthermia

Source: [10]

Regional hyperthermia heats a larger part of the body, such as an entire organ or limb. The main objective is to weaken cancer cells so that they are more likely to be killed by radiation and chemotherapeutic medications. Sometimes this technique may rely on local hyperthermia or they might depend on blood perfusion. Perfusion is a method that is used for regional hyperthermia. In blood perfusion, the patient's blood is removed from the body, heated up, and returned to blood vessels that lead directly through the desired body part. Chemotherapy drugs are injected into the blood stream to get best results. Continuous hyper thermic peritoneal perfusion (CHPP) is a specialized technique which is used to treat difficult cancers within the peritoneal cavity (the abdomen), including primary peritoneal mesothelioma and stomach cancer. For this hot chemotherapy drugs are pumped directly into the peritoneal cavity to kill the cancer cells. Another method is the use of magnets, ultrasound, and devices

which use high energy. These objects are placed over the area to be treated.

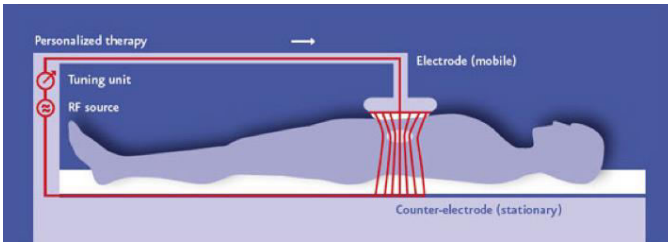

Figure 2: Regional Hyperthermia

Source: [11]

Whole body hyperthermia heats the entire body to temperatures of about 39 to 43 °C (102 to 109 °F). Usually it is used to treat metastatic cancer (cancer that spread to many parts of the body). Commonly used technique is infrared hyperthermia domes which include the whole body or the body apart from the head, putting the patient in a very hot room/chamber, or wrapping the patient in hot, wet blankets or a water tubing suit. Some other technique also include, submerging the patients in wax. Methods of pumping the blood outside of the body through heating elements have also been applied[10,12].

Figure 3: Whole body Hyperthermia

Source: [12]

B. Clinical Applications

Clinical Hyperthermia has two separate domains, WBH and RHT. Noninvasive WBH (Whole Body Hyperthermia) can be controlled with an Aquatherm radiant heat device with temperatures up to 41.8 °C. Currently, noninvasive RHT (Regional Deep Hyperthermia Therapy) is most preferred and it is done by using single microwave or ultrasound applicators for superficial hyperthermia and arrays of multiple applicators for deep heating. Preferential heating of different tumor regions is achieved by the lower convection of heat from relatively poorly vascularized areas of tumors compared to their surrounding tissues. During hyperthermia treatments the measurement of the actual temperature distribution in the tumor or immediately adjacent tissue is crucial to the clinical evaluation of the quality of RHT. So far, noninvasive methods for temperature measurements in deep-seated tissues are under investigation. From temperature measurements acquired as temperature versus time and temperature versus depth plots, time-averaged temperatures can be calculated at each site monitored.

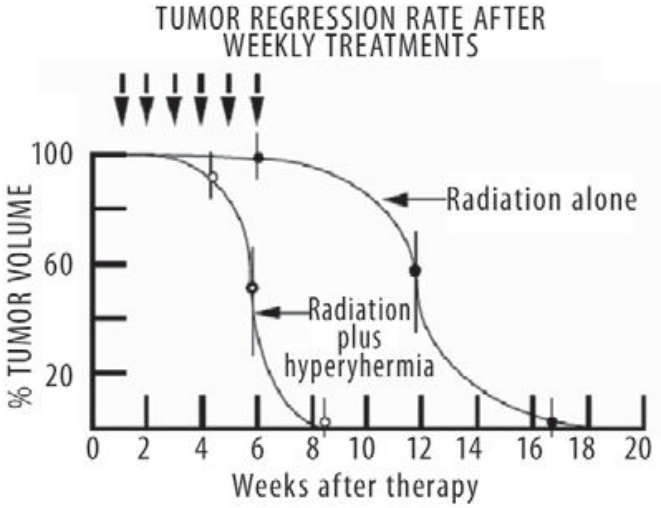

Figure 4: Hyperthermia added to radiation therapy and its influence on tumor regression in an example of malignant melanoma

Source: [1]

Stomach and pancreatic cancer was treated by the combination of clinical RHT and chemotherapy using 8MHz radio frequency device. The results showed that there was no tumor regrowth in patients. Patients suffering from soft tissue sacromas and bone tumors were given a combination of drug with RHT. Initial analysis reported that there were no clinical side effects as well as toxicity. Also, application of melaphon and WBH at 41.8ºC for 60 minutes gave the best results and it was considered as the basis for severe cancer treatment. The application of RHT with other drugs showed great results even for pediatric cancer [1-9].

Types of hyperthermia	Type/site of tumour	Clinical applications	Types of energy/equipment
Local HT: – superficial – intracavital – intraluminal – interstitial	Superficial tumours Intracavital tumours Intraluminal tumours Intracranial tumours	Head & neck cancers Locally advanced or recurrent breast cancer Malignant gliomas Rectal cancer Oesophageal cancer Soft tissue sarcomas	Microwaves (MW) Radiofrequency (RF) Ultrasound (US) **Hot sources:** – Hot water perfusion – Resistive wire implants – Ferromagnetic implants – Nanoparticles
Regional/Part-body HT: – abdominal – pelvic – limbs	Deep seated tumours Locally advanced tumours	Cervical cancer Rectal cancer Bladder cancer Prostate cancer Soft tissue sarcoma Ovarian cancer Mesothelioma Peritoneal carcinomatosis	
Whole-body HT	Disseminated/metastatic diseases	Malignant melanoma Recurrent soft tissue sarcomas Ovarian cancer	Infrared radiators Hot water blankets Thermal chambers

Figure 5: Examples of clinical applications and types of energy delivered to tumors

Source: [1]

Hyperthermia is now considered as the oldest weapon against cancer. It alone could not give the best results and hence oncothermia was introduced. It is the modulated deep electro-hyperthermia system and is a fast-developing supportive, complementary treatment method against different types of tumors. The basic principle of oncothermia is same as hyperthermia, but instead of absolute increase in temperature directs electric field energy which is absorbed by extracellular liquid and destroys the membrane of the cancer cells. Oncothermia's effect is synergic to radiotherapy and to numerous chemotherapies. Furthermore, it leads to an increased immunogenicity and effectively reduces the pain of the patient. Other than brain tumors, were conventional hyperthermia failed, it was able to find solutions for liver, pancreas carcinoma, and lung as well the bones[13-15].

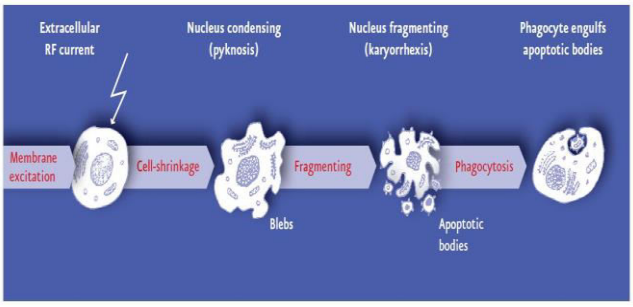

Figure 6: Process of Oncothermia

Source: [14]

III. SYSTEMS USED AND ITS LIMITATIONS

For clinical applications hyperthermia systems operate by exposing target tissue to either electromagnetic (EM) fields or ultrasound (US) radiation. The EM or US power is supplied by a generator and delivered to the patient through an applicator. For a generator to be suitable for clinical hyperthermia it must be capable of tolerating some impedance mismatch. If the manufacturer specifies the generator to be immune to any impedance mismatch, one should test this capability by connecting the output to an in-line power meter. Equipment which exhibits instabilities, especially if it has the tendency to grossly exceed the output power selected by the power control or if it cannot tolerate these tests without damage, should not be used for hyperthermia. In a clinical setting an occasional slippage of an applicator (electrode, induction coil, etc) is virtually unavoidable. An unstable generator which responds to the ensuing change in load impedance with a sudden increase in output power is not sufficiently stable for clinical hyperthermia. However, a generator which reduces the output power in response to an impedance mismatch, or which shuts itself off completely, is acceptable.

Applicators in use today consist of implantable or external electrodes, antennas, waveguides, and transducers. These devices may deposit energy to only a small volume of tissue

directly adjacent to the heating device, or they may be intended to deliver regional or whole-body hyperthermia. The external applicators usually used consist of coherent arrays of dipole antenna pairs positioned in a ring pattern around the patient. The antennas emit microwave or radiofrequency energy to be focused in a cancerously altered part of the body. With such equipment selected anatomical regions can be heated up to 41–42°C and this temperature is limited by power deposition in surrounding tissues [1,2].

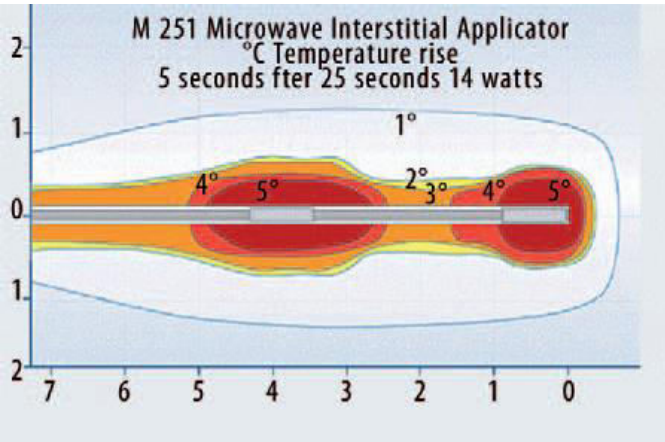

Figure 7: Interstitial applicators for MW hyperthermia used in BSD 500 systems. The distal 4.5 cm are used for heating the tissues

Source: [1]

The results of hyperthermia therapy depend on the tissue temperatures obtained during the therapy. It is important to have accurate information concerning the temperature throughout the treated region of the patient. Therefore the choice of a particular thermometry system should be made. In local hyperthermia where large temperature fluctuations are encountered, an extremely accurate thermometer may not be required. An overall error not exceeding 0.3°C is probably acceptable, but achieving this accuracy in a clinical environment may require that the thermometer agree with an institution's standard to within 0.1 or 0.2%. In whole body hyperthermia, on the other hand, where temperatures are only a few tenths of one degree below the lethal limit and homogeneity is excellent, instrument errors of more than +/- 0.05% may be unacceptable. Although non-invasive thermometry which could yield complete 3-dimensional temperature information would be most desirable. But such equipment's are presently unavailable in the market. Therefore clinicians depend on small implanted probes, and in some cases they move the probes within implanted catheters to obtain one-dimensional temperature profiles. To minimize the need for mechanical mapping, probes having multiple temperature sensors distributed along their length are used.

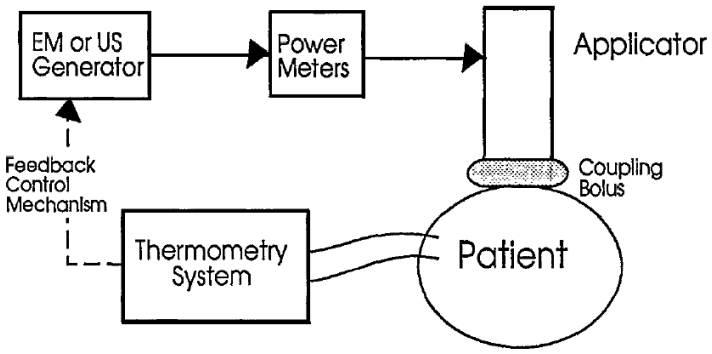

Figure 8: Block Diagrams of Hyperthermia Systems

Source: [2]

A. Hyperthermia Systems

BSD500, BSD1000, BSD2000, Celsius42, EHY2000plus, EHY3010 ML, EHY1020IL, Sonotherm 1000, ThermoChem HT1000, 8 Medical Hyperthermia Pump, Beaumont Hyperthermia Pump are the normally used devices for performing hyperthermia therapy. Out of this, BSD2000 got recently approved in the year 2011. Far infrared rays are also used for the same. Other than this, External Radio-Frequency devices, Hyperthermic perfusion, Frequency enhancers Apply heating to the target site with a catheter, Magnetic and ferroelectric particles and Magnetic Nanoparticles were also used. External Radio-Frequency devices are medical system with a radiating antenna and receiving elements to transmit microwave energy to the target site. Hyperthermic Perfusion is used as whole body perfusion for hepatitis C treatment. Frequency enhancers uses a method where injection of biocompatible fluids with high RF or microwave absorption in a particular frequency. In catheter method, medical device with antenna and a catheter is introduced into the body to provide electromagnetic energy. Magnetic and ferromagnetic method uses microcapsules incorporated with magnetic material for hyperthermia treatment.

Figure 9: An example of equipment for superficial and interstitial hyperthermia (BSD 500 hyperthermia system) operating on microwaves of 915MHz.

Source: [1]

The BSD2000 Hyperthermia System which was recently approved by FDA is intended to deliver focused therapeutic heating (hyperthermia) with temperatures greater than 40º Celsius by applying radiofrequency (RF) energy at the frequency range of 75 to 120 MHz. It delivers RF energy to a patient using a power source and an array of antennae that surround the patient's body. The energy delivered by the system can be electronically focused to produce a localized EM power field. This can be adjusted to target the 3dimensional shape, size, and location of the tumor, providing dynamic control of the heat delivered to the tumor region. This method of therapeutic heating utilizes the adjustment of frequency, phase, and amplitude from multiple power sources, along with an applicator selection and patient positioning, to optimize heating of the targeted body tissues. The BSD2000 Hyperthermia System is indicated for use in conjunction with radiation therapy for the treatment of cervical cancer patients who are ineligible for chemotherapy. The BSD2000 Hyperthermia System increases the response of tumor cells to radiation therapy [9].

B. Parameters To Be Considered

Thermo tolerance is an important phenomenon referred to as transient resistance to additional heat stress, thus making it impractical to apply two different HT sessions with an interval shorter than 48–72 hours, until the resistance decays to a negligible level. On the other hand, thermo tolerance does not really affect radio sensitization and can be avoided by exposure of the tumor to temperatures over 43°C. Higher temperature is difficult to attain in clinic. The higher the temperature and the longer time that heat is delivered to the tumor, the stronger the lethal effect and the less thermo tolerance is induced in it. Temperature elevated above the physiological level results in changes in blood flow, vascular permeability and tumor oxygenation. The final effect of the above is necrotic or apoptotic death of preheated cells or their sensitization to ionizing radiation or chemotherapy.

Thermal Dose appears to be the most useful dosimetric parameter. Researchers say that, heat when delivered at 43°C in cumulative intervals can give good results. Simplifying the above, the higher the minimum temperatures obtained in the tumor, the better the clinical outcome achieved. By definition, thermometry in tumors is invasive, and thus connected with particular complications. Some ongoing investigations are targeted at developing magnetic resonance imaging (MRI) as a tool of non-invasive thermometry [1].

C. Limitations

Most side effects of hyperthermia are generally minor, according to most sources. These include discomfort, local pain, and blisters, pain being the most pronounced side effect. Side effects such as an increase in blood pressure and pulse are expected and are only temporary. One source noted that cardiac problems are possible in some patients. In a very small number of cases however, first, second, or third degree burns have resulted. One source noted that an overdose of pyrogens (fever-inducing chemicals) can lead to "serious, even fatal reactions in humans" and that the use of perfusion could cause "frequent persistent peripheral neuropathies, abnormal…blood coagulation, some damage to liver and kidneys, and brain hemorrhaging and seizures" Major drawback is that normal tissues are not damaged during hyperthermia if the temperature is below 111°F. But regional

differences in tissue characteristics can cause higher temperatures in different area. This can result in burns, blisters, discomfort, or pain. Perfusion techniques can cause tissue swelling, blood clots, bleeding, and other damage to the normal tissues in the perfused area. However, most of these side effects are for very short period. Even though they are uncommon, whole-body hyperthermia can cause more serious effects such as cardiac and vascular disorders. Diarrhea, nausea, and vomiting are commonly observed after whole-body hyperthermia.

IV. CONCLUSION

One of the most dreadful diseases that have become a nightmare for the mankind is cancer. According to the American Cancer Society, in the year 2001, 1,268,000 people contracted cancer. Since 1990 around 15,000,000 have been diagnosed with cancer. One out of four Americans will die from cancer and cancer is the leading cause of death after heart disease. Researchers says, the reason of cancer could be because of an uncontrollable spread of abnormal cells and can be triggered by various risk factors like an unhealthy lifestyle, exposure to radiation and chemicals, hormones, and genes. As per the studies, hyperthermia in conjunction with other treatments gave the best results. After more than 600 hyperthermia sessions, it has been found that local hyperthermia with microwave alone or in combination with ionizing radiation can be used, with excellent normal tissue tolerance, provided local tissue temperatures are carefully monitored and controlled. Also, significantly higher level of preferential heat induction into tumor tissue is possible as compared to surrounding normal tissues and repeated hyperthermia at 42-43.5 degrees C for 45 minutes per session immediately following radiation therapy yields favorable therapeutic results. Tumor regression response rate of over 70% was achieved without concomitant increase of normal tissue complication. Therefore, the potentially significant impact on clinical cancer therapy, whether of curative or palliative intent, by moderate thermotherapy is evident.

V. FUTURE OUTLOOK

Hyperthermia in the field of oncology has a bright future, provided, the two major technological challenges, the ability to achieve a uniform temperature in a tumor, and the ability to precisely monitor the temperatures of both the tumor and the surrounding has to be solved. It is a promising way to improve cancer treatment, but presently it is an experimental technique. Many clinical trials of hyperthermia are being done to better understand and improve this technique. For instance, the use of nanoparticles and the induction heating of magnetic materials that are implanted into tumors are some new types of hyperthermia that are under study. And researchers continue to look at how hyperthermia is best used along with other cancer treatments to improve outcomes.

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"Image guided sentinel lymph node biopsies- Clinical setup, systems used and future potential"

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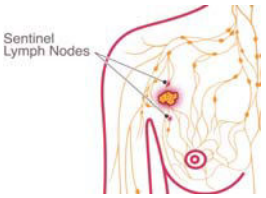
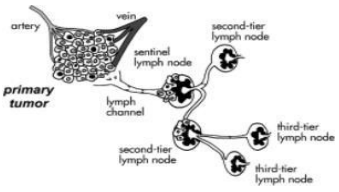
Introduction

Statistics: In 2015, nearly 1.5 million new cases of cancer were diagnosed in the USA; among that 36% would die from breast and prostate cancer



Sentinel lymph node close to the tumor [Source- National Breast Cancer.org]

Problem:	Identifying, determining and removing the presence of cancer cells in the axillary lymph nodes
Solution:	Biopsy procedure guided by Imaging modality procedures have become essential tool in oncologic diagnosis and treatment planning.
Challenges:	Tracing, targeting and marking the exact location, false negative results, Differentiation from Healthy Tissues[3]



Schematic conceptualization of sentinel lymph *Mariani G et al.,*

Sentinel Lymph Node Biopsy

Sentinel Lymph Node Mapping

Claim:
Real Time Interventional Biopsy

Motivation :
Recommendations on image guidance procedure

Advantage:
Minimally Invasive Protocol

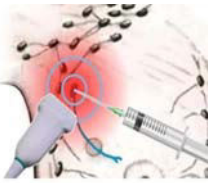
Clinical Setup

Defining requirements[6]

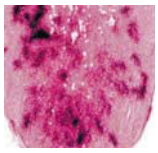
Characteristics	Description
Intraoperative	Use in the operating Room
Real-Time	24 p fps image acquisition and display
High specificity	Low false negatives
High sensitivity	Detection sensitivity
High resolution	Interrogation of the tumor boundary
Wearable	Ergonomic, hands-free movement
User friendly	Requires minimal training and no specialized operators

Clinical Workflow

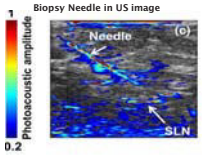
Injecting the Tracer


Photoacoustic Tomography –Ultrasound (PAT-US) imaging pinpoints the SLN[1]

Low magnification histo autoradiograph


Auto Radiography of sentinel node removed about 20 h after injection of 99mTc-HSA Nano colloid[2]

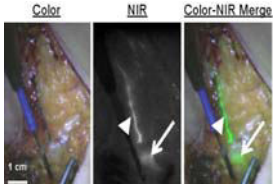
Biopsy Needle in US image



In vivo images of the SLN and the needle acquired using PAT-US[1]

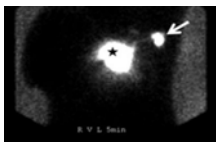
Modalities

Lymphoscintigraphy NIR fluorescence

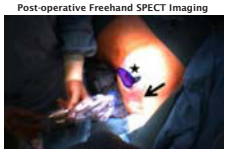


The lymphatic vessel (arrowhead) draining to the sentinel node (arrow) located deeper into the tissue[3]

Free hand SPECT

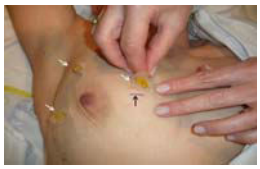

Free hand SPECT of Patient with SLN arrows in the axilla- a preoperative scintigram[4]

Post-operative Freehand SPECT Imaging

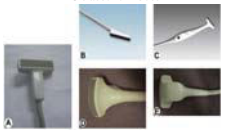

Postoperative Free hand SPECT image with no remaining activity stars injection site[4]

Materials

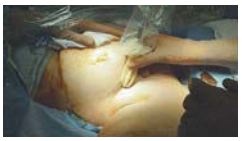
Ultrasound-MRI


Vitamin E soft gel capsules (white arrows) used for US-MRI co-registration placed over lineal skin marks (black arrow)[5]

Ultrasound Probes


Intraoperative ultrasound probes: (a) T probe; (b) 'I' shaped array; (c) an end-firing array; (d) a curved array, particularly useful for hepatic scanning and (e) the back of the curved array is shaped to take the sonographer's fingers[6]

Handheld Gamma Camera

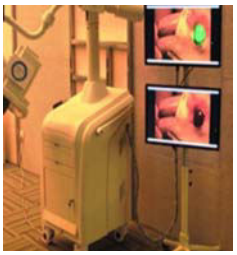

Handheld Gamma Camera used to identify the SLN Charles R Scoggins et al.,

Functional Models

Portable intraoperative FMI systems

a) Novadaq SPY™ system, b) ArtemisTM [7]

Surgical navigation system GXMI Navigator


Surgical navigation system GXMI Navigator- Institute of Automation, Chinese Academy of Sciences [7]

Future Outlook

Current efforts to miniaturize the technology, hopes that imaging method could become an enabling platform for diverse biopsy diagnosis

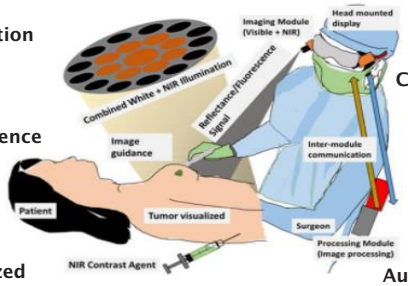
Using a hybrid interventional imaging system for non-surgical accurate visualization in a low cost environment would be the next decade's breakthrough.

Miniaturization

Clinical Evidence

Fusion of Technology

Computerized



Google System overview [8]

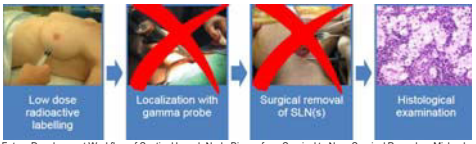
Clinical Trail

Robotics

Automation

Problems with Current Setup

Takes longer learning process for adopting the new clinical protocol. Resolution of the Imaging modality and accuracy of the needle pathway with amount of tissue sample are factors to be considered.



Future Development Workflow of Sentinel Lymph Node Biopsy from Surgical to Non- Surgical Procedure Michael Friebe et al.,

Conclusion

As continued improvements in systemic therapy and radiation, management of the axilla strives to be less invasive by means of advancing the image guiding setup there are significant probabilities for evolutionary systems with appropriate clinical evidence. During when the sentinel node is negative, sentinel node biopsy alone with no further axillary dissection is an appropriate, safe, and effective diagnosis for with clinically negative lymph nodes bringing an effective revolution in the clinical practice.

References

[1] Garcia-Uribe A, Erpelding TN, Krumholz A, et al. Dual-Modality Photoacoustic and Ultrasound Imaging System for Noninvasive Sentinel Lymph Node Detection in Patients with Breast Cancer. Scientific Reports
[2] Mariani G, Moresco L, Viale G, et al. Radioguided Sentinel Lymph Node Biopsy in Breast Cancer Surgery*. J Nucl Med 2001; 42: 1198–1215.
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[4] Bluemel C, Schnelzer A, Okur A, et al. Freehand SPECT for image-guided sentinel lymph node biopsy in breast cancer. European journal of nuclear medicine and molecular imaging 2013; 40: 1656–1661.
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[6] Amso NN, Shayeb AG. Intraoperative imaging. Best practice & research. Clinical obstetrics & gynaecology 2013; 27: 323–338
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+ IMAGE GUIDED THERAPIES

Image guided sentinel lymph node biopsies

Clinical setup, systems used and future potential

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Abstract: Cancer remains a major public health and a huge economic burden. A sentinel lymph node is the first draining lymph node to which cancer cells are most likely to spread from a primary tumor. Before a decade, regional nodal basins were assessed by complete lymph node dissections depending on the location of the primary tumor to detach the sentinel lymph node. If the sentinel lymph node are not cancerous, then the cancer would not spread to any other regions of the body. This mapping approach was inaccurate with false negative results that many patients did not have lymph node metastases but underwent extensive surgery that lead to high morbidity. To elude the false diagnosis and achieve accurate results; image guidance assisted procedures are being significantly refined and combined with the biopsy system for effective isolation of the SLN in the recent years. The paper reviews the currently used and upcoming modalities of image guided procedures for sentinel lymph node biopsies.

Keywords: Image guidance, sentinel lymph node, biopsy, diagnosis

Abbreviations: SLN- Sentinel Lymph Node, SLNB- Sentinel Lymph Node Biopsy, US- Ultrasound

1. Introduction

In 2015, an estimated 1,658,370 new cases of cancer were diagnosed in the United States and it is estimated that 589,430 people would die from the disease while breast cancer and prostate cancer are the most common cancers in 2015. The number of people with cancer diagnosis reached nearly 14.5 million in 2014 and is expected to rise to almost 19 million by 2024 [1].

Currently, medical imaging procedures have become an essential tool in oncologic diagnosis, treatment planning and are used during surgical interventions as well. The need for accurate visualization of tumors during surgery has spurred the claim of image guidance in the operating room. Consequently to ensure efficacious identification of cancerous tissue in the first attempt of diagnosis by means of biopsy. Biopsy is a procedure used to remove tissue or cells via special biopsy needles. The tissue specimen is pathologically evaluated to confirm the presence of malignant tumor cells [2]. Sentinel Lymph node biopsy is the standard of care for identifying, determining and removing the presence of cancer in the axillary lymph nodes as shown in the Fig.1 with tumor presence near the SLN [3]. Lymph nodes are small round organs connected to one another by lymph vessels throughout the body located at neck, underarms, chest, abdomen, and groin. “A clear fluid called lymph flows through lymph vessels and lymph nodes” [4]. Lymph nodes contain B lymphocytes, T lymphocytes, and other types of immune cells. These cells

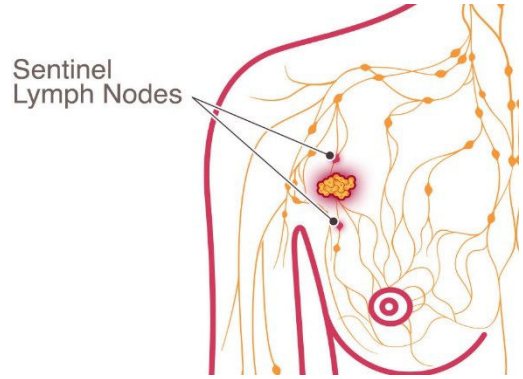

Fig.1. Sentinel lymph nodes close to the tumor [5].

monitor lymph for the presence of foreign substances. Samples of these cells are utilized to determine whether the cancer cells have developed the ability to spread to other parts of the body. Many types of cancer spread through the lymphatic system. One of the earliest sites of spread for these cancer cells are nearby lymph nodes [4] called sentinel lymph nodes, the cancer cells spread from the tumorous cells to regions of the body (see Fig.2). Depending on the location of the tumor there can be more than one sentinel lymph node.

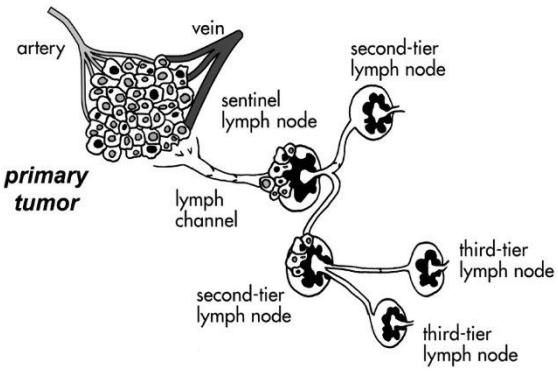

Fig.2. Schematic conceptualization of sentinel lymph node [6].

2. Clinical Setup

From a clinical point of view, lymph node status remains one of the most important prognostic factor in cancer [7]. A negative SLNB result suggests that cancer has not developed the ability to spread to nearby lymph nodes whereas a positive SLNB result indicates that cancer is present in the SLN and may be present in other nearby lymph nodes [4]. Thereby a surgeon can develop a treatment algorithm as a protocol to determine the extent of the disease within the patient's body.

2.1. Methods

The clinical workflow for image guided Sentinel Lymph Node Biopsy is as follows:

Injecting Tracer- The surgeon injects (Fig.3) radioactive material (e.g. Tc-99m), a blue dye or both as a tracer into the tissue next to tumor (Fig.4). Dye and radioactive tracer gather in the SLN and serve as an optical or radioactive marker [4].

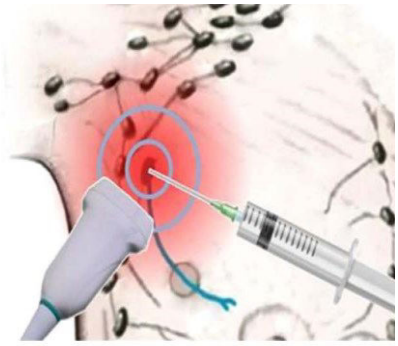

Fig.3. Injecting Blue Dye as a tracer in Photoacoustic Tomography–Ultrasound (PAT-US) imaging pinpoints the SLN [8].

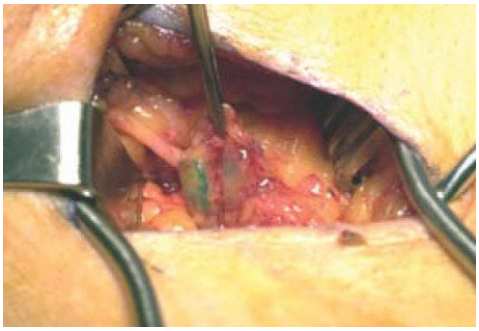

Fig.4. Isosulfan blue dye (1 %) was injected into the skin. The blue dye travels into the lymphatic channels and is followed to the sentinel lymph node [9]

Identification- The surgeon uses gamma probe to identify the SLN or looks for lymph nodes that are stained with the blue dye (see Fig.3 above).

Pathological Assessment - To identify if the biopsied cells are is another significant stride in SLN mapping the pathologist receives a single lymph node, or just a few nodes. Immuno Histochemistry (IHC) involves the use of tumor specific antibodies to detect micro metastases confirms the presence of tumor cells [9]. Accurate examination of the clinically negative axilla relies on the anatomical location, morphology, size and flow characteristics in the nodes. Black grains and white dots (Fig.5) show the retention of radioactive agent in the sinusoid. [7].

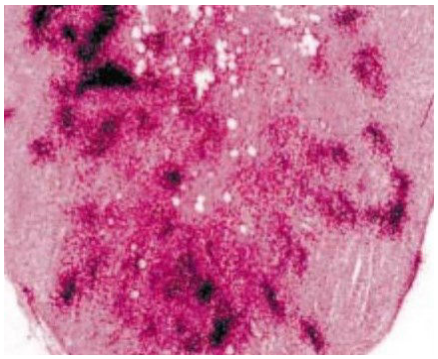

Fig.5. Auto Radiography Low magnification histo autoradiograph of sentinel node removed about 20 h after injection of Tc-99m Human Serum Albumin (HAS) Nano colloid [6].

3. Systems and Tools

Choosing any of the following imaging modality as guidance system depends on the surgeon's skill, experience in operating the instrument and actual need in handling them parallel with the biopsy procedure.

- Ultrasound (US)
- Photoacoustic Tomography-Ultrasound (PAT-US)
- Fluorescence Imaging (FI)
- Positron Emission Tomography (PET)
- Single-photon emission computed tomography (SPECT)
- Magnetic Resonance Technology

3.1. Ultrasound (US)

guided lymph node biopsy identifies patients with extensive axillary nodal disease burden with 100% specificity [7]. Intraoperative ultrasonography reported; reduced level of false negative sentinel lymph node procedure [10]. The commonly used Ultrasound probes are shown in the Fig.6. Fine needle sampling Micro biopsies [10] using Ultrasound guidance is shown in Fig.7.

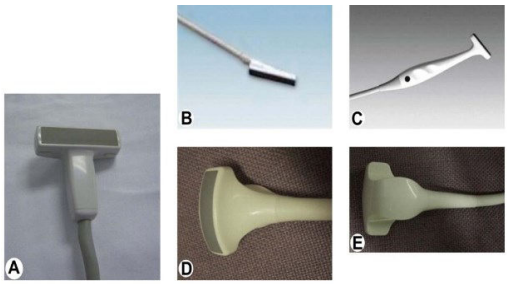

Fig.6. Intraoperative ultrasound probes: (a) T probe; (b) 'I' shaped array; (c) an end-firing array; (d) a curved array, particularly useful for hepatic scanning and (e) the back of the curved array is shaped to take the sonographer's fingers[11]

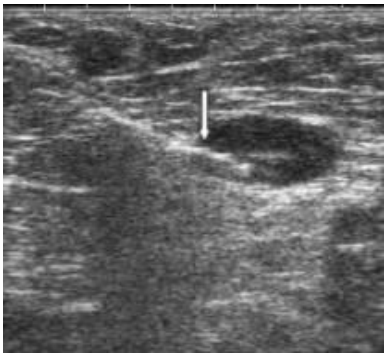

Fig.7. Targeted sampling from the cortex – Navigation of the Micro Biopsy Needle in the US image(arrow) [10]

3.1. Photo Acoustic Tomography - Ultrasound (PAT-US)

Photoacoustic imaging is an emerging hybrid imaging technology that uses short laser pulses to irradiate chromophores in tissue, inducing localized thermo-elastic expansion that is detectable by wide-band ultrasonic transducers. The photoacoustic signals are measured by an ultrasonic transducer placed outside the body. Due to the scattering and absorbing nature of biological tissue, optical fluency decays rapidly with the increase in depth. The Light reaches deep enabling the surgeon to detect the SLN [8]. A handheld photoacoustic probe system was recently developed for image-guided needle biopsy of sentinel lymph nodes for use in the operating room (Kim et al., 2010).

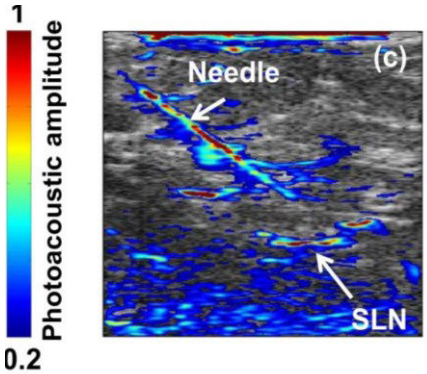

Fig.8. In vivo PAT image of the SLN and needle. (c) Registered PAT-US image of the SLN and needle [8].

3.3 Fluorescence Imaging (OMI) is a promising technique that provides a high degree of sensitivity and specificity in tumor margin detection (Fig.9) is a Near Infra-Red (NIR) Fluorescence based imaging. Fig.10 is the system overview in monitor used for the interventional procedure in detecting the sentinel lymph node and navigating the biopsy needle.

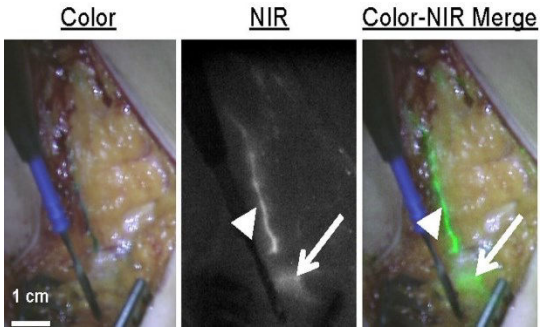

Fig.9. The lymphatic vessel (arrowhead) draining to the sentinel node (arrow) located deeper into the tissue, is clearly identified by NIR fluorescence [12].

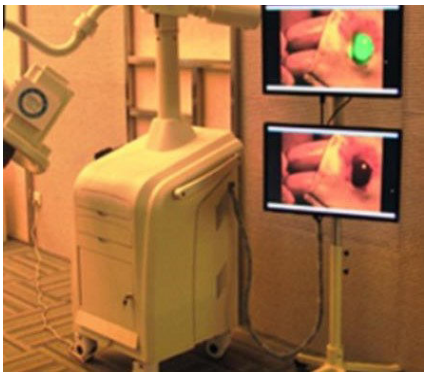

Fig.10. Surgical navigation system GXMI Navigator from the Institute of Automation, Chinese Academy of Sciences [13].

3.4 Lymphoscintigraphy localizes the radiolabeled SLN and visually directs the surgeon to the proper nodes and basin for biopsy. In other ways, Tc-99m Nano colloid are divided into 4 aliquots tuberculin syringe and are intradermally injected in the periareolar region. Patients were imaged using a hand held gamma camera (Fig.11) with a low-energy, high-resolution, parallel-hole collimator [14].

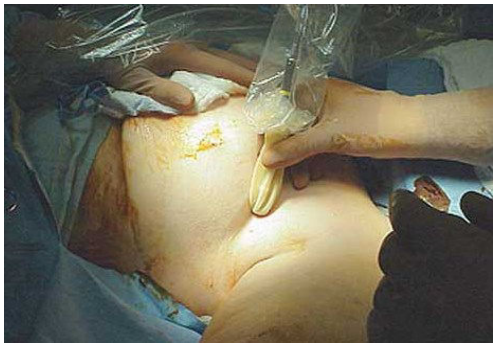

Fig.11. Handheld Gamma Camera used to identify the SLN [15].

3.4 Free Hand SPECT

Infra-Red optical tracking system is used to fix the relative position and the orientation of the patient in relation to the gamma probe; for synchronizing with the gamma probe in order to reconstruct the 3-D along with preoperative scintigraphy as shown in Fig.12 with the sctinigram image and in Fig.13 the surgeon is holding a Free Hand SPECT in imaging the spot of SLN. [16]

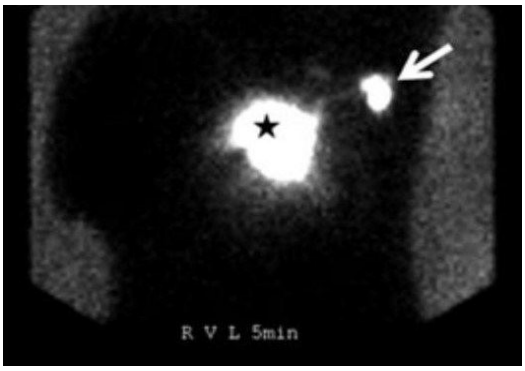

Figure 12: Free hand SPECT of Patient with SLN arrows in the axilla- a preoperative scintigram [15]

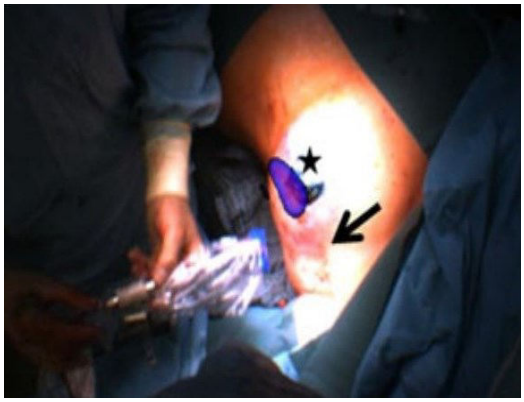

Fig.13. Postoperative Free hand SPECT image with no remaining activity; injection site is marked with Black star [16]

The declipse SPECT, a mobile system for freehand SPECT imaging stages tumor density enabling registration free overlay of the SPECT image (Fig.14) in the ultrasound plane for interventional needle guidance in real-time. This system reduced 20-30 min surgical procedure into a 10 min interventional practice (Fig.15) [17].

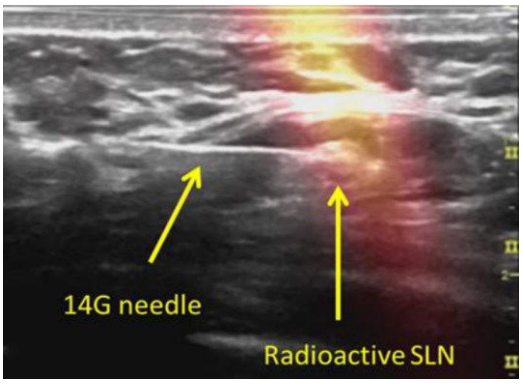

Fig.14. US image, the SPECT augmented SLN can be clearly differentiated and enable a needle biopsy [17].

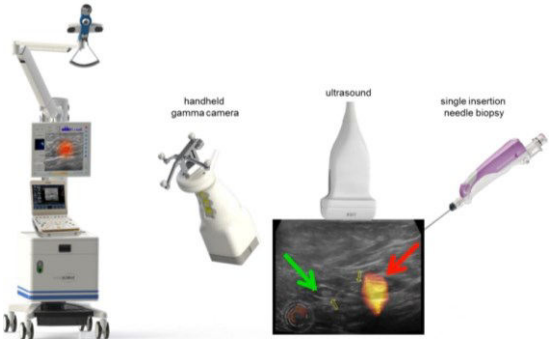

Fig.15. declipse SPECT, SurgicEye GmbH, Germany containing a mobile SPECT imaging system, a navigated ultrasound probe and a biopsy needle [17].

3.5 Magnetic Technique

[18] provides a color change brown or black in lymph nodes and allowing SLN identification using a handheld probe as shown in the Fig.16. The most commonly used magnetic tracer consists of a sterile aqueous suspension of 60-nm superparamagnetic carboxydextran-coated iron oxide particles which have a diameter similar to standard radioisotope tracer particle. The particles gather in the Lymph Node which gives the contrast to the surrounding tissue. Preparation of the patient before supine breast MRI is shown in the Fig.17. Breast magnetic resonance imaging (MRI) generates images by recording the signals generated after

radiofrequency excitation of magnetic particles in tissues exposed to a strong magnetic field. It typically involves use of an intravenous contrast agent, gadolinium diethylenetriamine penta-acetic acid (DPTA), which can locate tumors by highlighting areas containing dense vessel networks [19].

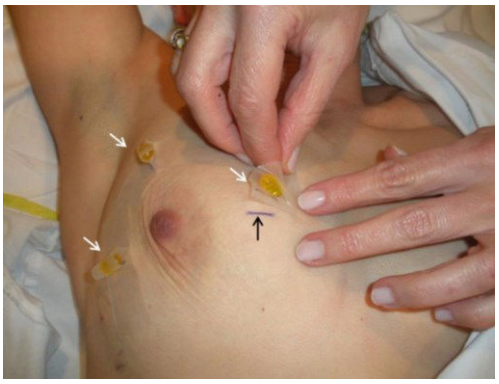

Fig.16. Vitamin E soft gel capsules (white arrows) used for US-MRI co-registration placed over lineal skin marks (black arrow) on the patient's right breast.

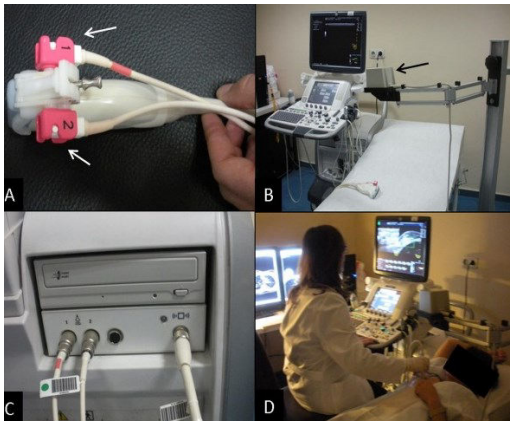

Fig.17. US and RtMR-US system. (a) Electromagnetic sensors on the tip of the probe (white arrows). (b) Electromagnetic transmitter (black arrow). (c) Connection unit between electromagnetic transmitter, sensors and the navigation system. (d) Rt MR-US exam after co-registration.[20]

4. Advantages

During SLNB [4] reduced unnecessary dissection metastatic capacity can be taken place. The following facts are the foremost reasons for choosing Image Guided Sentinel Lymph Node Biopsies which are like:

a. Highly Targeted
b. Quick Recovery
c. Short Procedure Duration
d. Minimally Invasive Protocol
e. Reduced Radiation Exposure
f. Molecular Level Differentiation
g. Spare healthy Lymph Node
h. Real time Intervention and Biopsy

5. Limitations

There are chances to get false-negative results because multiple lymph nodes are removed at the same time [4]. Human eyes cannot see deeper than the tissue surface, while human touch which may not be able to distinguish small tumor nodes from the surrounding tissue. Preoperative interventional imaging modalities are currently limited to use in the operating room because of their large hardware footprint, slow image reconstruction, lack of resolution, use of ionizing radiation, prohibitive cost, and specialized operator requirement.

In case of assistance with a fluoroscopy guidance need for high concentration contrast agents to compensate the poor detection sensitivity, inability to detect microscopic lesions, and difficulty in miniaturizing are major problems. Relatively low sensitivity and limited spatial and temporal resolutions in few image guidance methods limits in vivo application.

In Ultra-sonographic signs of metastatic disease sometimes signals overlaps with those of benign reactive changes, limiting the ability of Ultrasound to accurately stage the axilla. Therefore, US cannot differentiate SLNs from

downstream lymph. In optical based imaging systems sensors try to mitigate its effect via various vertical trenches between photodiodes, the optical crosstalk is not completely eradicated.

The effect causes light to reflect and refract multiple times within the imaging system, such that light to be absorbed by one photo-detector will be absorbed by neighboring photo-detectors [21].

6. Recommendations

Fluorescence molecular imaging (FMI) has been established as a powerful tool for guiding precise intraoperative positioning; help surgeons distinguish between normal and malignant tissues labeled through the injection of a fluorescent detection agent [13]. Apparently, the imaging methods are expected to be real-time with higher sensitivity and specificity [21].

The lymphoscintigraphy and gamma probe guided SLNB is safe, simple and highly reliable with minimal morbidity or complications in patients. By coupling imaging with optional therapy, it is anticipated that the procedure will also guide treatment planning and monitor treatment response; this could improve patient outcomes, reduce hospital revisits, and enhance the quality of life [21] and less Lymphedema, or tissue swelling.

The tabled characteristics and its features below are most essential recommended factors for any ideal imaging system.

Characteristic	Description
Intraoperative	*Use in the operating room*
Real-time	*24 p fps image acquisition and display*
High specificity	*Low false negatives*
High sensitivity	*Detection sensitivity*
High resolution	*Interrogation of the tumor boundary*
Wearable	*Ergonomic, hands-free movement*
User friendly	*Requires minimal training and no specialized operators*

Table 1. Characteristics of Real time image guidance[21].

7. Future Potential

Through the development of intraoperative image-guided agents and imaging systems in Sentinel Lymph Node Biopsies , fluorescence molecular imaging technology and other imaging methods extends into the clinic; surgeons needs to empower them to improve patient outcomes[13]. With current efforts to miniaturize the technology, it is hoped that this imaging method could become an enabling platform for diverse surgical procedures. [21] The imaging modalities with a google hybrid (see Fig.18) system for accurate visualization and faster intervention miniaturizing the entire technology in a low cost environment attaining the ambience of faster and rapid diagnosis as well as therapy would be the next decade's breakthrough.

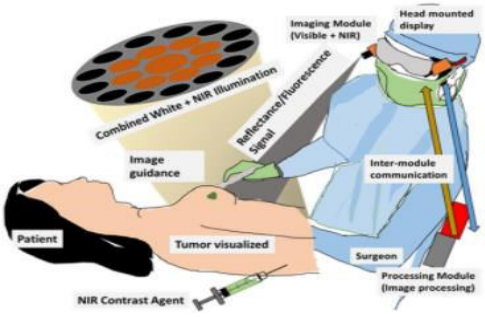

Fig.18. Google System overview[21]

8. Summary

Tumor metastasis usually occurs through the lymphatic system [13]. Tumor cells are defined as small clusters. Image guided Sentinel lymph node mapping and biopsy is a relatively new technique for staging and treating patients with melanoma or breast cancer. With tremendous benefits and minimal risk, SLNB has become so widely adopted that elective lymph node dissections are practically antiquated [9]. Visualization of tumor draining SLNs at distant depths using Ultrasound, NIR, MR, CT-SPECT and PET provides helpful guidance for SLN mapping and tumor metastasis diagnosis thereby revealing its potential clinical utility [22]. Real-time image guidance is highly desirable in the [21] boundary of the tumor adequate surgeon education has been identified as an crucial factor in handling the patient during the intervention and procedure [23]. Freehand SPECT-US can identify SLNs but its sensitivity is limited by sampling error and insufficient aspirated material for cytology. Larger studies and clinical evaluation are required to assess any individual image guiding system to gain additional biopsy value [24].

9. Conclusion

In certain patients with early cancer and small volume loco regional disease, complete axillary dissection has shown to offer no survival benefit and has largely been abandoned. As continued improvements in systemic therapy and radiation lead to pathologic response, management of the axilla strives to be less invasive even in the setting of later stage cancer; by means of advancing the image guiding setup there are significant probabilities for evolutionary systems with appropriate clinical evidence. Some randomized prospective trials are now investigating the utility of SLNB altogether [7]. It's concluded that when the sentinel node is negative, sentinel node biopsy alone with no further axillary dissection is an appropriate, safe, and effective diagnosis for with clinically negative lymph nodes [25] bringing an effective revolution in the clinical practice.

Acknowledgements

Thanks to Prof.Dr.Michael Friebe for offering the course on Instruments for Image Guided Procedures, M.sc Alexander Van Oepen for assisting me in structuring the paper and to other researchers in INKA chair for providing an opportunity to make a detailed literature review and write this paper.

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"Material properties for use in high field MRI" , Absolute no go's, limitations, possible solutions.

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Introduction

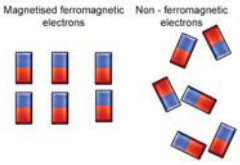
MRI Procedure

MRI human body scan

- Magnetic Resonance Imaging is one of the most potential methods of non-invasive diagnosis.
- Patients with metallic and other implants like pacemakers have some limitations when allowed to undergo MRI procedure.

Main issues:
In MRI, Implants affected by
- Magnetically induce displacement force.
- Radio frequency heating.

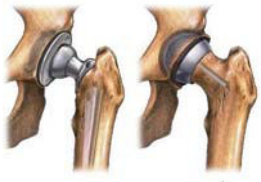
Idea:
Materials of Implants should be
- Non- Ferro magnetic or weak Ferro magnetic.
- Low conducive or non-conductive.



Materials

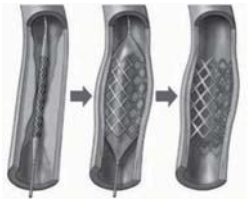
- A medical implant is a medical device manufactured to replace biological structure and support damage biological structure.
- The materials build to these structure are divided into three classes. They are
  1)Metals.
  2)Ceramics.
  3)Polymers.

Examples of Medical Implants



Metals

Ceramics

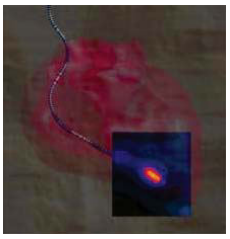


Polymers

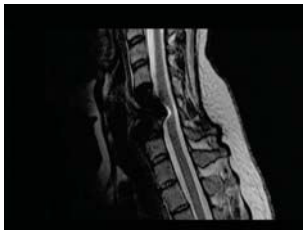
Issues of implants in high field MRI

In MRI procedure, Implants and diagnosis image are affected by following terms.
- Magnetic field interactions.
- RF heating
- Artifacts.
- Induced currents

Magnetic field interactions



RF heating

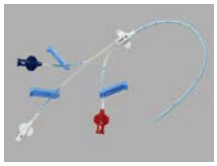


Artifacts

Possible solutions

- To overcome these issues, Materials of implants should have some additional properties
  1)Non Ferro magnetic or weak Ferro magnetic.
  2)Low conductive or non conductive.
- We have to choose the material should have these properties from each classes

Metals – Titanium/Titanium alloy



Polymers - 3 Lumen CVP Catheter

Absolute no go's

Conclusion

This provides an overview about the properties of materials used in implants and what kinds of properties are necessary for implants when a patient undergo MRI procedure. To ensure safety for individual and patients, MRI healthcare professionals should follow the guidelines whereby an MRI procedure should only be performed in a patient with a medical product that has been previously tested and demonstrated to be safe.

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Material properties for use in high field MRI

Absolute no go‟s, limitations, possible solutions

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1. Introduction

Magnetic Resonance Imaging is one of the most potential methods of Non-invasive diagnosis. It makes big evolution in medical industry. MRI is often safe to every individual. But patients with metallic implants like cardiac pacemaker have some limitations when allowed to undergo MRI procedure. Because the main issues of affecting the implants in the MR environment involve magnetically induce displacement force, torque and radiofrequency heating [2]. To avoid/reduce these issues materials of implants should have some properties such as non-magnetic or non-ferromagnetic or weak ferromagnetic and low conductivity or non-conductive.

2. Medical Implants Materials and Its Properties

A medical implant is a medical device manufactured to replace biological structure and support damaged biological structure. The materials build to these structures are divided into three classes [1]. They are,

1. Metals.
2. Ceramics.
3. Polymers

2.1. Metals and its Properties

The use of bio metals for a whole range of medical implants is justified by their superior mechanical properties compared to polymers and ceramic. Material composition of these bio metals makes an important role in medical diagnosis procedure.

The properties of bio metals are mentioned in the table (1). The design and selection of biomaterials depends on its specific medical application. In order to serve safely and appropriately for a long period of time without rejection, a metallic implant should possess the following essential characteristics [5].

- Excellent biocompatibility.
- High corrosion resistance.
- Suitable mechanical properties.
- High wear resistance.

2.2. Ceramics and its Properties

Bio ceramics is the class of ceramics used for repair and replacement of diseased and damaged parts of the musculoskeletal systems. Bio ceramics are bio compatible and range in biocompatibility from the ceramic oxides, which are inert in the body. Hardness and resistance to abrasion also makes them useful for bones and teeth replacement. The properties of ceramic materials are mentioned in table (2). Ceramics are refractory polycrystalline compounds [9]

- Usually Inorganic
- Highly inert
- Hard and brittle
- High compressive strength
- Good electric and thermal insulator

Attribute	Stainless Steel (316L)	Cobalt-Chromium	Titanium	Titanium Alloy
Strength	Medium (300/500 MPa)	High (600/1140 MPa)	High (880/950 MPa)	High (500/1400 MPa)
Stiffness	High (200 GPa)	High (200 GPa)	Moderate (90 GPa)	Very low (~25 GPa)
Fatigue	Good in load control	Good in load control	Good in load control	Good in strain control
Corrosion	Good – Cr_2O_3 (500 mv)	Good – $Cr2O_3$ (500 mv)	Excellent - TiO_2 (800 mv)	Excellent - TiO2 (800 mv)
Other	MRI artifacts	L-605 is radiopaque	Can be radiopaque	Shape memory

Table (1): Properties of Metal Implants

Materials	Young"s Modulus(GPa)	Compressive Strength(MPa)	Bond Strength(GPa)	hardness	Density(g/cm^3)
Inert Al_2O_3	380	4000	300-400	2000-3000(HV)	>3.9
ZrO_2(PS)	150-200	2000	200-500	1000-3000(HV)	=6.0
Graphite	20-25	138	NA	NA	1.5-1.9
(LTI)Pyrolitic carbon	17-28	900	270-500	NA	1.7-2.2
Vitreous Carbon	24-31	172	70-207	150-200(DPH)	1.4-1.6
Bio glass	=75	1000	50	NA	2.5
Bone	3-30	130-180	60-160	NA	NA

Table (2): Properties of Bio ceramic Materials

2.3. Polymers and its Properties

Polymers are long chain giant organic molecules are assembled from many smaller molecules called monomers. Polymers consist of many repeating monomer units in long chains. Two classes of polymers used in medicine such as homopolymers and copolymers include PMMA, polyethylene, polypropylene etc. Polymers used in orthopedic, dental implants, heart & heart component, facial prosthesis, knee joins, blood vessels, heart pacemaker and catheter systems. Polymers are classified as two sets based upon the physical property related to heating [1] [3]. They are,

- Thermoplastics.
- Thermosets.

Characteristics of these polymers are,

- Low density
- Low efficient of friction
- Good corrosion resistance.
- Excellent surface finish can be obtained.
- Poor tensile strength
- Low mechanical properties.
- Poor temperature resistance.

The physical properties of a polymer, such as its strength and flexibility depend on:

- Chain length – in general, the longer chains the stronger polymer.
- Cross-linking – if polymer chains are linked together extensively by covalent bonds, the polymer is harder and more difficult to melt.
- Side groups – polar side groups gives stronger attraction between polymer chains, making the polymer stronger.
- Branching – straight, un branched chains can pack together more closely than highly branched chains, giving polymers that are more crystalline and therefore stronger.

Dacron, Teflon and polyurethane are the most useful bio materials in making of heart valve replacements and blood vessels.

3. Issues of Metallic Implants in High field MRI

MRI may be contraindicated for a given patient because of risks associated with dislodgement of metallic (or) ferromagnetic device, excessive heating, induction of currents, changes in operational aspects of device and damage to the function of device [2] etc. Now we will discuss about the issues faced by the patients when they are undergo to MRI procedure.

3.1. Magnetic Field Interactions

In MRI procedure, translational force (or) torque may cause movement of ferromagnetic implant. This results comfortless sensation for the patient, an injury, sometimes it may cause fatality. Therefore, we must consider translational force and torque before the patients with metallic implants are allowed to MRI procedure.

3.2. Heating

The metallic implants, devices that have variety of sizes, shapes and metallic compositions like conductive/non-conductive materials. The temperature increases produce in association with the

MRI. In general, only minor temperature changes occur in association with MRI and relatively small objects or devices like aneurysm clips, prosthetic heart valves. However, MRI related heating is problematic for implants that have elongated shape. Those that form conduction loop of a certain diameters. This conducting loop may damage the healthy tissues around the device. There are many factors are causes for temperature increase in implants. Those are,

- Specific type of material in implant.
- Radiofrequency wavelength.
- Electrical characteristics of implants.
- Type of transmit RF coil.

3.3. Induced Currents

The induced currents are made from conductive materials such as cardiac pacemakers, neurostimulation systems when patients are undergoing to MRI procedure. This will injure the patients, damage devices and changes the operational aspects.

3.4. Artifacts

Artifacts are caused by disruption of local magnetic field produced by metallic implants. This may cause signal and image distortion. These artifacts in MR imaging depends on magnetic susceptibility, size & shape of a metallic implants.

4. Issues of Other Implants and Tools used in High field MRI

Usually, a range of polymers used for the construction of catheters. However, these polymers are non-ferromagnetic materials. For example, the thermo dilution Swan-Ganz catheter and other similar cardiovascular catheters have non-ferromagnetic materials that include conductive wires. A report indicated that portion of Swan-Ganz catheter that was outside the patient melted during an MR imaging. It was postulated that the high-frequency electromagnetic fields generated by the MR system caused eddy current-induced heating of either the wires within the thermo dilution catheter or the radiopaque material used in the construction of the catheter. This incident suggests that patients with this catheter or similar device that has conductive wires or other component parts could be potentially injured during high field MR procedure.

As seen in above, ceramics used for dental implants. These types of implants and devices incorporate with the magnets as a means of activating the implants. In high field MR procedure, there is a high likelihood of perturbing the function; demagnetizing or displacing of these implants may be occurred [6].

5. Possible Solutions

There are lot of problems occurred when we allowed the patients with implants, surgical tools undergo the MRI procedure. So, the materials of implants should have some additional properties to overcome these problems in High field MRI. The safety of a patient is a primary concern of MR professionals. Let‟s see one by one what kinds of properties needs for the material when subjected into high field MRI.

5.1 Metals

In high field MRI procedure, metallic implants are exerts magnetic field interactions and heating on it by translational force (or) torque and RF pulse from MRI. Also it makes artifacts in MR imaging. To overcome these problems, we have to use non-magnetic or weak magnetic and non-conductive or low conductive materials [2].

Now a day, four types of materials used to design and manufacture the implants. Those are stainless steel (316L), Co-Cr alloys, Titanium and Titanium alloys.

Here, stainless steel (316L) is non-magnetic and it has good strength. But corrosion resistance is low compared to other materials. Even stainless steels used as a temporary implant in medicine. Also it causes artifacts in MR imaging.

Co-Cr alloys have high mechanical strength and it is magnetic. So, translational force exerts on these kinds of materials. Also chromium becomes allergic to patients when its corrosion period.

Pure titanium and titanium alloys are the best choice of materials for metallic implants [7]. These materials have good mechanical strength, high corrosion resistant and excellent biocompatibility. Also these are non-magnetic and low-conductivity. So these materials should not affect by magnetic field interactions and RF heating. These materials labeled as MR-safe.

5.2. Ceramics

Usually ceramic implants used in dental and some orthopedic replacements. Ceramic implants are incorporate with the magnets in certain dental implants as a means of activating the implants [10]. In a high field MRI procedure, unrestrained external objects accelerate rapidly toward the main coil, exhibiting a „missile effect", and internal objects, implants and foreign bodies can undergo displacement.

So, before entering to the MRI procedure magnets should be removed from the concerned area by dentist [4].

5.3 Polymers & Tools

A total of fifteen different cardiovascular catheters and accessories were selected for evaluation because they represent a wide-variety of the styles and types of devices that are commonly-used in the critical care setting (i.e., the basic structures of these devices are comparable to those made by other manufacturers). Of these devices, the 3-Lumen CVP Catheter, CVP-PVC Catheter(used for central venous pressure monitoring, administration of fluids, and venous blood sampling; polyurethane and polyvinyl chloride, respectively), Thermoset-Iced, and Thermoset-Room (used as accessories for determination of cardiac output using the thermo dilution method; plastic),and Safe set with in line reservoir (used for in-line blood sampling; plastic) were determined to have no metallic components (Personal communications, Ann McGibbon,Abbott Laboratories, 1997). Thus, these devices were deemed safe for patients undergoing MR procedure and were not included in the overall ex vivo tests for MR safety.

6. Limitations

Some patients with metallic implants are allowed to high field MRI procedure like Neurostimulation system, spinal card stimulator and spinal fusion stimulator with limitations. Here, these devices are allowed to 1.5Tesla MRI procedure only. If static magnetic field strength becomes high, the operational aspects of the device should be changed or reset. Sometimes it causes damage to the device. Some implants have specific property or option to ensure safety from magnetic field interactions. We can switch it when patient subjected into MR procedure. So, each and every medical implants and devices has limitations. MR healthcare professionals are advised to contact the manufacturer to ensure that the latest safety information is obtained and carefully followed in order to ensure patient safety relative to the use of an MRprocedure

Safety relative to the use of an MR procedure.

7. Absolute No Go's

Patients with metallic implants that have high ferromagnetic and conductive property should not allow to MRI procedure. For example, patients with cardiac pacemakers, ICD‟s are generally not allowed in MRI environment. Cardiac pacemakers and ICD‟s suggested to present potential problems to patients undergoing to MRI procedure [8]. Those are,

- Movement of pulse generator or lead.
- Temporary or permanent modification of the function of device.
- Inappropriate sensing, triggering and activation of device
- Excessive heating of the leads and induced currents in the leads.

Other metallic implants also feel the same problems. But ICD and pacemaker are crucial implant devices for patients with heart conditions and serve to maintain quality of life and substantially reduce morbidity. If any problems occurred in these, it will affect the function of heart.

Acti patch is an electromagnetic frequency therapy device, used to reduce the pains in nerves. Patient with this device is not allowed to High field MRI procedure. It will be damaged and causes excessive heat undergo to MRI procedure.

Other passive implants like aneurysm clips, hemostatic vascular clips and penile implants cause severe injuries to patient undergo MRI procedure. Electronically activated implants also not allowed (e.g.: external hearing aids, capsule endoscopy device)

8. Conclusion

This chapter provides an overview about the properties of materials used in implants and what kinds of properties are necessary for implants when a patient undergo MRI procedure. To ensure safety for individual and patients, MRI healthcare professionals should follow the guidelines whereby an MRI procedure should only be performed in a patient with a medical product that has been previously tested and demonstrated to be safe. The MR conditional labeling given to medical product must be carefully followed to prevent patient injuries or other problems.

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Interventional and IGS Tumor Therapies in the Throat:
Systems Used and Limitations with a Future Outlook

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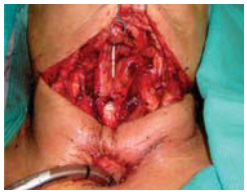
I. Introduction

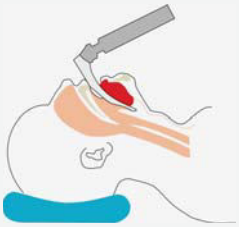


Total laryngectomy as an example for open surgery [1]

Problem:	Open surgery in region of the throat are for many people associated with a sustainable constrains in everyday life, such as loss of voice.
Solution:	Use of transoral and transnasal approaches for local suppression of cancer have several advantages, like a better preservation of functionality of the organs
Challenges:	The narrow space inside the throat and the small, sensible structures require that an easy handling of imaging and surgery instruments must be guaranteed.
Aim of this poster:	This poster presents the image guided surgery systems which are in use and their limitations.

II. Possibilities for Intraoperative Imaging

A. Direct Laryngoscopy



Insertion of a curved laryngoscope blade [Shutterstock]

- Direct line of sight
- Common used approach
+ Cost-effective
+ Robust
– Uncomfortable position
– General anaesthesia necessary
– Dental damaging possible

B. Indirect Laryngoscopy

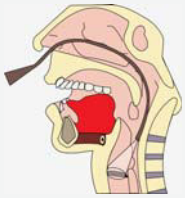
- Images are acquired by lens or fibre optical systems
+ Anaesthesia not necessary

Transoral Rigid Endoscopy

Transoral rigid endoscopy [2]

+ Better image quality than flexible endoscopy
+ Easier to manage
– Gag reflex
– Intervention is cumbersome with rigid endoscopy

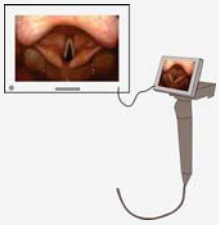
Transnasal Flexible Endoscopy



Transnasal flexible endoscopy [2]

+ Deeper view than rigid endoscopy
+ Can be equipped with working channel
+ More tolerated by patients
– Relative complicated pathway

C. Video Laryngoscopy



Videoendoscopic system

- Attaching CCD technologies
+ Better view on operational environment
+ Beneficial for documentation and teaching purposes
– Expensive

III. Microlaryngeal Surgery Techniques

A. Cold-Cutting Techniques

Non-Powered Cold-Cutting Instruments

Jako Microlaryngeal Alligator Forceps [Medtronic]

- Instruments are customized to the throat
+ Precise surgical incision
– No effective bleeding control

Microdebrider

Microdebrider with curved rotatable blade [Medtronic]

- Sucks and cut tissue
+ Suction of blood
+ No danger of airway fires
+ Suction and cutting in one device
– Rigid
– Mistakenly cutting of tissue possible

B. Hyperthermal Techniques

Laser Surgery

CO_2 Laser System CL20 for ENT surgery [Medicallaser]

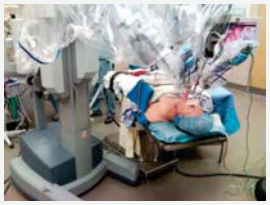
- CO_2 laser most used
+ Hemostasis
+ Very precise
– Laser reflections can be dangerous
– Overheating damage healthy tissue
– Transmission of CO_2 laser via fiberoptic is difficult
- PDL, KTP and Thulium lasers are better suited for fiberoptical transmission

Coblation (RFA)

Coblation electrode [Smith and Nephew]

- Heating by RF current
+ Less temperatures than laser surgery
– Rigid
– Large geometry

C. Transoral Robotic Surgery (TORS)

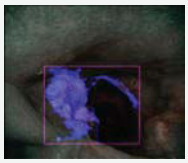


Da Vinci system as an example for TORS [3]

- Da Vinci System most used
+ Very precise movement
+ 3D imaging
– Not designed for throat
– Expensive

IV. Future Outlook

Flex Robotic System [Medrobotics]



Segmentation of the region-of-interest where malignant tissue is suspected [6]

- Flexible robotic systems makes manoeuvring in the narrow throat easier [5]
- Real time segmentation of tumors simplifies to distinguish between healthy and non-healthy tissue [6]
- CO_2 laser delivery via fiberoptic allows to use it in deeper regions of the throat
- Improving of surgeon workflow can be achieved by implementation of cutting, suction and endoscopic tools in one instrument or by development of special support systems

V. Conclusion

Movements of instruments in the throat are the biggest challenge for the surgeon. The use of flexible endoscopes and cutting tools can lead to an improvement of the work flow. The possibility of hemostasis and the high accuracy of laser surgery led that this is the most used approach for an intervention. The development of highly flexible robots and multifunctional instruments are priorities for further research.

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Interventional and Image Guided Surgery Tumor Therapies in the Throat

Systems Used and Limitations with a Future Outlook

by B. Sc. Thomas Gerlach, 17. December 2015

Abstract

Laryngectomy and pharyngectomy are for many people associated with a serious, invasive procedure with sustainable constraints in everyday life, such as loss of voice. The use of transoral and transnasal approaches for local suppression of cancer can ensure better preserving of organs and take the patient's anxiety of throat surgery.
For intraoperative visualization, the laryngoscopy is established as an excellent tool for the visualization of the throat. Although the direct laryngoscopy is a widely used procedure, however, a general anesthetic is required. The use of transnasal fiberoptic approaches requires only local anesthesia and would allow cheap and quick operation. Video sensors and the projection of images on screens could make the intervention for the surgeon more pleasant and clearly.
To combat the tumor, cold cutting techniques and hyperthermal approaches can be used. The cutting tools of micro laryngeal surgery are specially adapted to the operating environment. They facilitate a precise surgical incision, but an effective bleeding control is not possible.
Hyperthermal approaches, especially CO_2 laser, allows hemostasis of blood vessels and a very precise incision. However, scattered laser beams causes burns of healthy tissue. The approach of coblation possesses the advantages of laser surgery and there are fewer risks of burns, but the rigid structure of the instrument restricts the mobility in the throat.
For a precise and better control of the tool robot and manipulation units may be used. Most robotic system, however, are for applications of the abdomen designed and not for the narrow structures in the throat.

1 Introduction

Throat cancer often describes cancer in the region of larynx and pharynx. The American Cancer Society estimated that approximately 29,000 new cases of cancer in the pharynx and larynx will be diagnosed in the United States in 2015 [1]. Smoking, excessive drinking of alcohol, an unhealthy diet and infections with the human papillomavirus (HPV) can increase the risk of suffering from throat cancer [2]. There are several approaches for treating throat cancer, for example surgical approach, Radiation Therapy (RT) or chemoradiation therapy. But especially conventional RT and chemotherapy are often associated with severe late toxicities [3, 4].
The complex anatomy and the tight working space in the area of the throat represent a challenge for the surgeon. Nevertheless a precise operation must be guaranteed. On the one hand a complete removal of the tumor must be ensured, otherwise the tumor will grow up again. On the other hand complications can lead to loss of voice and inability to swallow.
Image Guided Interventions (IGI) and

Surgery (IGS) are developed which assist the surgeon during the complicated procedures. Transoral and transnasal approaches promise to treat cancer in the larynx and pharynx without the incision in the neck. Therefore optical and fibreoptical methods are used for visualization of the operational environment. Further advantages of intraoperative imaging are an increased accuracy during the intervention and a facilitation to respond to complications.
Interventions inside the throat requires instruments and systems which guaranties precise and accurate removing of the tumor. The usage of Transoral Laser Microsurgery (TLM) and Transoral Robotic Surgery (TORS) can fulfill the set claims of cancer removing as well as preserving the functionality of the organs.
An overview of possible IGI and IGS systems used in tumor therapies is discussed in this paper. Furthermore, a particular attention will lie on the limitations of the used methods. Finally will be improvements given of the systems for a future outlook.

2 Possibilities for Intraoperative Imaging

Imaging allows diagnosis of diseases, achieves an overview over the operating environment and helps to guide instruments during an intervention. To implement this, MRI and CT can be used [5]. But both systems are relatively expensive and they are sensitive to distortions. Especially on concerning with CT, someone should be aware that the thyroid glands are particularly sensitive to ionizing radiation.
The proximity to the mouth and nose area permit transoral and transnasal approaches to visualize the pharynx and larynx. These are mainly based on endoscopic and fiberoptical devices. One method to visualize the vocal folds and glottis is the laryngoscopy. Although laryngoscopy is a very old technique, it is still a very common method used for visualization in the throat. Reasons for that are a simplicity of the procedure, a high spatial resolution of the obtained images and the best temporal resolution. The laryngoscopy can be distinguished between indirect and direct laryngoscopy.

2.1 Indirect Laryngoscopy

Using indirect laryngoscopy a direct line-of-sight is not necessary for visualizing the larynx [6, pp. 955-962]. The images are acquired by reflection or using lens systems and enables that the patient head is in a comfortable neutral position. For indirect mirror laryngoscopy the doctor insert a mirror through the mouth of the patient [7]. With an external light source he is then able to visualize the vocal cords and glottis. In order to prevent fogging of the mirror it is possible to heat up the mirror. The drawback of this very cheap and simple method is the restricted field of view and movement possibilities inside the throat.
Another method for indirect laryngoscopy uses Rod-Lens Telescopes (RLT) [6]. Those systems consists of relatively long rod lenses but small air spaces [8]. Compared to conventional glass lens endoscope, RLT has a greater light transmission, better image resolution, wider field of view and image magnification [9]. Using RLT it is possible to connect the telescope with a light source [6]. Compared to mirror laryngoscopy, RLT allows a better adjustment of the viewing direction thereby it provides an "all-round vision" [10].
Using microlaryngeal instruments for tumor dissection in combination with mirror or RLT systems is cumbersome because of the limited mobility. Another disadvantage of the mirror and rod-lens laryngoscopy is that by touching the pharyngeal wall or tongues base, a gag reflex can occur which could lead to severe accidents during the intervention.
For avoiding such problems it is possible to

use fiberoptic transnasal endoscopy (see figure 1) [6]. Thereby a flexible endoscope is passed through the nasal cavity and enables a more deeper view of the larynx than mirror and RLT laryngoscopy. The flexible endoscope can be equipped with a working channel which allows the insertion of small forceps or laser waveguides for surgery [11, p. 166].
Because of the relative complicated pathway through the nose, transoral endoscopy are easier to manage for the endoscopologist than transnasal endoscopy [12]. Large diameter of the fiberscope can also damage some blood vessel inside the nose [12]. But studies show that transnasal approaches are more comfortable and tolerated by the patients than transoral approaches [13].
Bending of glass fibers for light transport causes loss of light. This leads to a worse image magnification and a higher rate of image distortions compared to rigid endoscopy [14, p. 145].

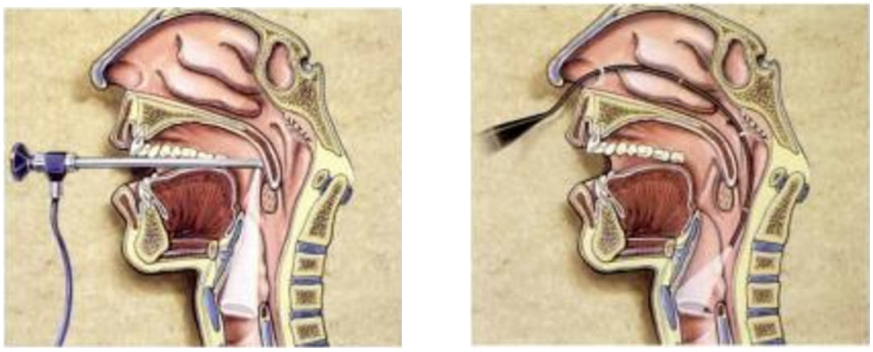
2.2 Direct Laryngoscopy

Direct laryngoscopy is based on a direct line of sight from the eye of the surgeon to the patients trachea and enables a visualization of laryngeal and pharyngeal soft tissue structures [15]. During the examination, the patient lies on a table and the head is typically raised in the so called "sniffing position" [15]. This position allows that the pharyngeal and laryngeal axes aligns with the oral axis. With the alignment of the axes and a displacement of the tongue with a laryngoscope blade, its possible to achieve a direct line of sight to the glottis [6, 16].
The blade is hereby used on the one side as a retractor and on the other side as an illuminator [17]. There exist different kinds of laryngoscope blades. The most common used blades are the curved Macintosh and the straight Miller blade (see figure 2) [15]. Other blades are for example the McCoy, Winsonsin, Belescope or the Siker blade [15]. The straight blades are more narrow and they have a rounded tip to lift the epiglottis [18]. Whereas, the curved blades have a broad flange for moving the tongue [18]. The tip of the curved blades are designed to fit into the vallecula [18]. The curved blade is often favored for a better tongue control and an easier intubation [15]. Whereas, the straight blade has a smaller displacement volume and is more suited for patients with smaller displacement space like children [15].
It is uncommon that during the operation the surgeon carries the laryngoscope in one hand and in the other hand the cutting device. For that special laryngoscope holders are used, which are fixed either over or directly on the patient's chest [19, p. 397].
Direct laryngoscopy offers guiding of instruments under direct visualization [18]. Furthermore, direct laryngoscopy is more cost effective than other imaging modalities [17]. This system is more robust and does not depend on fragile fiberoptic [17].
But there are also some drawbacks when using direct laryngoscopy. An alignment of the pharyngeal and laryngeal axes are necessary for successful laryngoscopy. If it is not possible to lay down the patient in the sniffing position, for example because of a trauma or the patient have a high misalignment of the axis since birth, it will be very difficult to see the glottic opening [18]. An improperly usage of the laryngoscope can lead to dental and mucosal damages [18]. As described for indirect rigid laryngoscopy, a too deeply placing of the laryngoscope into the mouth can lead to a gag reflex.
This for the patient unpleasant procedure and to avoid movements or gag reflexes by the patient during the procedure make a general anesthesia necessary [20]. The anesthesia requires an endotrachial tube, which allows a gas exchange of oxygen and carbon dioxide in the lungs [20]. During the intervention the tube can get in the way [20].

2.3 Video Laryngoscopy

Distances from the glottis to the laryngoscopist decreases the field of view [15]. At-

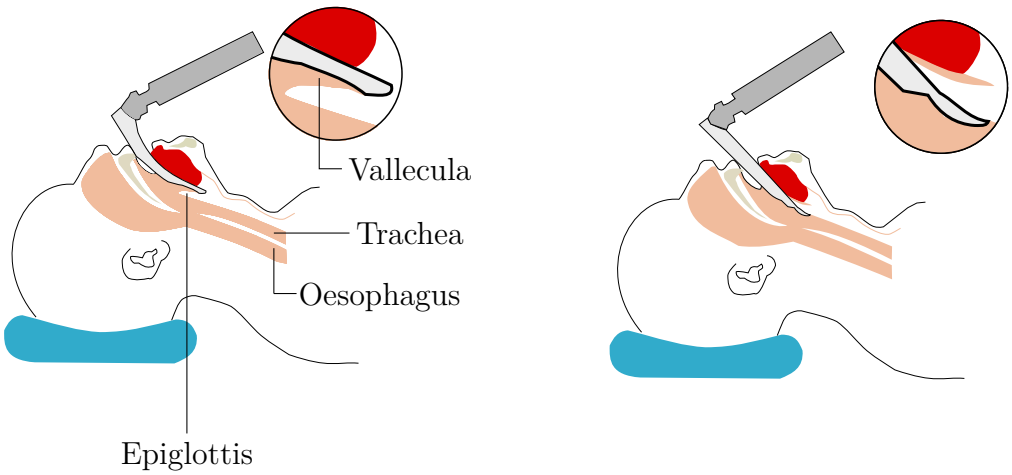
taching a small video chip on the tip of the laryngoscope could promise a better and a more pleasant view on the glottis compared to a direct line-of-sight or optical approaches [15].
The teaching of insertion the different laryngoscopes is very cumbersome and is based on an error-and-trial approach. The usage of an external monitor for viewing can improve the learning curve for trainees significantly [15]. Also the possibility of saving the images can be beneficial for documentation and teaching purposes [15]. But for high resolution images are expensive camera systems necessary which increases the financial expenses of the procedure.



(a) Transoral rod lens laryngoscope

(b) Transnasal fiberoptical laryngoscope

Figure 1: Different kinds of indirect laryngoscopy [6]



(a) Curved laryngoscope

(b) Straight laryngoscope

Figure 2: Comparison of the insertion of curved laryngoscope and straight laryngoscope [21]

3 Surgical Techniques for Removing Throat Cancer

3.1 Cold Cutting Approaches

3.1.1 Open Surgery and Closed Microlaryngeal Surgery

Open surgery for laryngeal and pharyngeal cancer is done when neither radiotherapy, chemoradiotherapy or other approaches are possible to treat the cancer. Those procedures are highly invasive and mostly the functionality of swallowing and breathing are impaired [14].
One possible intervention in the region of the larynx is the so-called laryngectomy. Depending on cancer stage, it is possible to divide the laryngectomy into total laryngectomy and partial laryngectomy. Total laryngectomy is done in cases when the cancer is in an advanced stage. Thereby, an U-shaped incision in the anterior neck is made for direct visualization and the larynx is completely removed [22, p. 478]. After removing of the larynx, the patient loses the ability of speaking so that he have to learn other methods for communication [14, p. 541]. The separation of the airway from the oral and nasal cavity also requires the placement of a tracheotomy tube, through which the patient is able to breath [14]. Partial laryngectomy promises a better preservation of the functionality of the organs. Thereby, only a part of the larynx will be removed. But still complications are common during or after the procedure which make it necessary to develop non-open surgery approaches [14].
The usage of microlaryngeal instruments while guidance with laryngoscopy through oral or nasal openings promise a better preservation of the functionality of internal organs. The instruments used must be long and thin so that the insertion into the throat and the guidance via laryngoscopy is possible. And the tips of the tool must also be very small for handling the tiny laryngeal or pharyngeal structures [20]. Those systems can acquire a precise surgical incision, but an effective bleeding control is not possible [23].

3.1.2 Microdebrider

A Microdebrider (MD) consists of three parts: a blade, a hand piece and a control console [24]. The blade is a hollow metal tube, which can be used only once in an intervention and is coupled to a suction system [24]. The hand piece drives the blade with an electrically powered motor [24]. And the console controls the speed and the direction of the blade via a foot pedal [24]. The MD sucks tissue into the hollow tube, which cuts the tissue [25]. This allows a simultaneously removing of tissue and blood for improving a better view of the surgeon. The usage of a non-thermal approach includes that airway fires are completely avoided and the risk of severe damages are reduced [24]. Furthermore there will be no smoke, which can mist the imaging instruments and impair the operational view. The implementation of a suction and a cutting device in one gadget offers higher freedoms during the intervention compared to traditional methods [25]. In traditional methods, the surgeon needs three instruments for intervention in the airway: an optical visualization instrument, a cutting system and a suction device [25]. By using MD only two instruments are necessary. In the one hand the surgeon holds a MD and in the other hand a visualization instrument [25]. So the surgeon is not bounded on the repetitive switching between the instruments, which could disturb the intervention and concurrently time can be saved.
But the usage of MD have some drawbacks. Typically such a MD has a diameter of 4 mm and is very rigid. So its not amenable to flexible endoscopy and therefore, rigid endoscopy or a direct laryngoscopy have to be used [26]. There is also the possibility of a mistaken cutting of healthy tissue. So the surgeon should use the powered instrumentation with caution. Otherwise he could injury for example the vocal folds and impairing the functionality of the organ [27, 28].

3.2 Hyperthermal Approaches

3.2.1 Transoral Laser Surgery

Beginning with introducing the first approach of CO_2 laser in laryngology in the early 1970s, TLS has become an effective alternative to cold-cutting techniques, open laryngectomy and radiation therapy in today's medicine [22].There exist a broad variety of lasers in medicine like the pulsed dye laser (PDL) and the potassium titanyl phosphate laser (KTP). Compared to most other laser types, the CO_2 laser can be more focused and consequently allows a minimal damage of the surrounding tissues [29]. This property and the fact that surgeons are more familiar with the CO_2 laser, makes the CO_2 laser to the most used laser in the throat for destroying squamous cell cancer [30].
It is necessary to achieve in combination with a microscope a straight line between the beam and the cancer cells for a successful intervention [29]. Also it is possible to use a micro-manipulator mirror system for CO_2 laser delivery [14, p. 632]. But these would need direct laryngoscopy approaches which require a general anesthesia.
A fiberoptical approach requires only a local anesthesia and enables an office-based intervention [29]. But classical fiberoptical approaches are not used for transmission of CO_2 laser [29]. Under specific circumstances, there is a possibility that a very high focused CO_2 laser beam can lead to especially high power densities inside the fibers [31, p. 220]. This could cause severe damages to the optical fiber which lead to severe accidents during the intervention [31]. But developments are made with special hollow fiber guides, which make a CO_2 laser transmission possible [32].
Typically laser types like PDL, KTP and thulium lasers offers a better possibility for fiberoptical transmission of the laser beam. Furthermore, PDL and KTP grant better hemostatic effects than the CO_2 laser [29].
Coupling the CO_2 laser to an operating microscope increase the accuracy of the surgical intervention [30, p. 43]. Because the laser light of the CO_2 laser is not visible, often a helium-neon laser is also mounted on the microscope [30].
Using laser surgery for throat surgery have several kinds of advantages, compared to cold-cutting surgery. TLS offers minimal damages to the surrounding tissue and allows an intraoperative hemostasis [29]. The need of only burning the tissue away decreases also the amount of tissue manipulations, which should be done with cold cuttings techniques [29]. Surveys also confirm that TLS have less short and long term side effects than cold-cutting techniques and there is a high chance that the swallowing and voice function can be preserved [33, 34]. Patients treated with TLS experience shorter hospital stays and the wounds recover faster [29]. In long term, the shorter hospitals stays of the patients lead to the fact that TLS is more cost-effective than cold cutting techniques [29].
The main advantage of hyperthermal approaches is the possibility of closing blood vessels by hemostasis.
Using laser in surgery requires some precautions. Reflections of the laser can injure the retina which makes eye protection for staff and patient necessary [30]. Another aspect which should be considered when using an endotracheal ventilation system, that this system could take fire or ignite when it is touched by the laser beam [22, p. 339]. An expensive tube which is specific designed for laser protection must be used [22]. Also could a jet ventilation system used, by this oxygen are blown under high pressure into the lungs [20]. This would obviate the tube [20].
The laser beam creates high temperatures. So the surgeon should operate with caution, otherwise he could increase scarring and damage healthy tissue [29].

3.2.2 Radiofrequency Ablation

Radiofrequency ablation (RFA) is a hyperthermal approach for destroying tumor cells

inside the body. Thereby, the surgeon places electrodes directly into the tumor. The electrode is connected to a radio frequency generator, which offers an alternating current (AC). Thereby heat is developed by means of Joule heating and dielectric losses. The electrode can be guided with tomographic imaging modalities like CT and MRI or by endoscopic approaches [35, 36]. In general RFA incorporates the advantages of CO_2 laser surgery like bleeding-control. But a non-necessity of expensive laser intubation tubes, makes RFA approaches more cost effective than laser surgery [23].
One problem of most hyperthermal dissections are that the temperatures acquired are often too high and an unwanted heating of healthy tissue can appear. Coblation (acronym for controlled ablation) is a special RFA approach which uses a plasma for energy transport [37]. The plasma is created in a high density energy field within an electric conductive fluid by a special delivery system [37]
Lower temperature developments during the coblation leads to a lower thermal penetration and so damages to the healthy tissue can be spared [37].
Optical fiber for flexible laser surgery can have a diameter of 0.6 mm [38]. In contrast the rigid coblation electrode has a diameter of 3.5 mm [38]. So there must be a higher effort made to navigate coblation electrodes in the narrow operational environment [38].

3.3 Transoral Robotic Surgery

Endoscopic surgery minimizes damages to the healthy tissue compared to open surgery [39]. But also endoscopic surgery has disadvantages like a lack of steerable instruments and a missing three dimensional view [39]. Transoral robotic surgery systems (TORS) allow to improve surgery in the region of the throat. The most common TORS system used is the da Vinci® system [39]. Those systems consists of a 3D imaging modality and independently steerable robot arms, which are controlled by the surgeon [39]. The greatest advantage of TORS is the increased degrees of freedom (DoF) [39]. These increased DoF of the da Vinci system simulate the movements which could be also done during an open surgery by the surgeons arm. The narrow spaces in the throat limit the use of da Vinci system [39].

Normally the da Vinci system was designed for abdominal and thoracic interventions, where the robot arms have much place. Surgeons claims it is only possible to insert one robotic arm within the laryngoscope [39]. Hockstein reported a feasibility for inserting three robotic arms using additionally a mouth gag [39]. But the requirement of movement space of the instruments can lead to overcrowding and inhibit the procedure. While the technology of the da Vinci system enables promising opportunities for improvement of the surgery, many scientists doubt a wide-spread use of these systems. Because the high cost factor dominates the small benefit factor [39].

4 Future Outlook

Complete removal of the cancer cells is a prerequisite for a non-regrowing tumor. However, for the surgeon, it is often difficult to distinguish between healthy and cancerous tissue. A computer generated segmentation can allow better distinction. Segmentation can be carried out by spectroscopy or by use of medical imaging, such as PET/MRI [40, 41]. The transfer of these segmented data in an augmented reality application could show the surgeon the boundaries between healthy and diseased tissue, thus improving a selective incision.
The patient discomfort during direct laryn-

goscopy, with the potential risks and problems of general anesthesia should be avoided when possible. One should here focus more on the transnasal fiber optical approaches, with no need for general anesthesia. A transnasal approach allows only working channels of small diameter and thus introduce only tools with small diameter. Transoral approaches would allow larger diameters of the working channel. Wherein a triggering of the gag reflex must be avoided.
The intervention should be designed as comfortable and uncomplicated as possible for the surgeon. Video endoscopy could bring significantly improvements. The surgeon can achieve a better operational environment over large external monitors and he can work in a more comfortable position.
The requisite of having to use different tools at the same time as cutting tools, endoscope and suction tools, may disturb the course of the intervention. Innovative ideas such as the implementation of a cutting system and a suction system in one tool or by creating special support systems can guarantee a much smoother intervention [42].
When precision cutting or handling multiple instruments is necessary, robotic systems can assist the surgeon. The challenge, however, is that these systems must be designed to the environmental conditions of the throat in order to ensure mobility. Highly flexible robots could overcome the impaired mobility of the da Vinci system [43].
Laser surgery is and remains an important component of the treatment of cancer in the throat area. Although lasers as PDL and KTP already suitable for fiberoptical transmission, efforts are made to transmit CO_2 laser via fiberoptic approaches due to the better surgical specification of the CO_2 laser. This would make intubation obsolete and costs for expensive laser-protected tubes could be saved. The risk of burn persist anyway. Concerning security, coblation could be an alternative to laser surgery. This has the bleeding control advantages of CO2 laser surgery, but the hazards of burns in this method are much lower.

5 Summary

The variety of different surgical interventions in combination with intraoperative imaging modality allows the surgeon to establish for different requirements of the procedure an optimal solution. Direct laryngoscopy is very uncomfortable for the patient and requires general anesthesia. Alternatives for this are rigid and flexible endoscopy. A transnasal endoscopic approach is thereby better tolerated by the patient and allows better in-office procedures.
The use of microlaryngeal cutting tools especially designed for the throat, facilitate a cheap and precise removing of tissue. Bleeding during surgery prevent the vision and require suction systems by which the blood could be removed. A microdebrider (MD) combines cutter and suction system in one gadget. This allows that the intervention can run more fluently and a repetitive change between cutter and suction system does not interrupt the intervention. However, a limited mobility limits possible applications in the throat.
Laser surgery is the most widely-used method for the removal of cancer in the throat area. The difficulty of transport CO_2 laser through fiber optical classical approaches, needs a direct laryngoscopy and thus a ventilation system. This requires strict and costly security measures to avoid collateral damage. The use of robotic systems is currently limited by the low mobility in the throat area.

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Liver Tumor Therapy with Y90:
Systems used, clinical results and limitations with a future outlook

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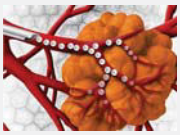
I. Introduction

Background: The use of external beam radiation to the entire liver as a treatment for liver malignancies is restricted due to the high amount of healthy tissue which is affected

Approach: Y90 Radioembolization as a minimal invasive catheter-based treatment option for liver tumors in which ionizing radiation is directly delivered to the tumor by microspheres placed into the hepatic artery

Challenges: An accurate placement of the microspheres is limited due to the lack of image guidance of the microspheres



Y90 microspheres are placed into the hepatic artery [1].

II. Treatment Procedure

A. Preoperative

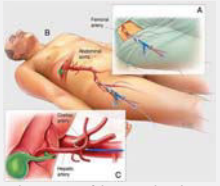
A Technetium-99 macroaggregated albumin scan is performed to determine the amount of extrahepatic shunting that could occur during Y90 radioembolization treatment. This is extremely important for dosimetry planning and the assessment of the microsphere's after the injection [2].

Technetium-99 macroaggregated albumin scan of the lungs to determine the amount of lung shunting [2].

Further preoperative procedures include an angiogram, a liver scan, dosimetry planning and the determination of the performance status.

B. Intraoperative

Y90 microspheres are selectively injected by percutaneous access to the femoral artery and are guided to the hepatic artery by fluoroscopy.



Schematic view of the microspheres' injection [3].

C. Postoperative

- Postoperative SPECT scan
- Evaluation of treatment success 30 days after injection.
- Possible further Y90 therapy after 4-6 weeks

III. Y90 Microspheres

	TheraSphere®	SIR-Spheres®
Material	glass	resin-based
Microsphere Size	20-30 µm	20-60 µm
Activity per Sphere	2500 Bq	50 Bq
Dosimetry Calculations	Partitioning model	BSA model
Costs	13,000 $	14,000 $

Dosimetry Calculations

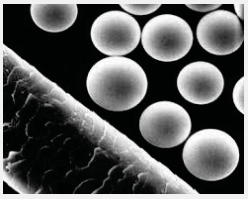
Partitioning Model

$$A = \frac{D \times M}{50}$$

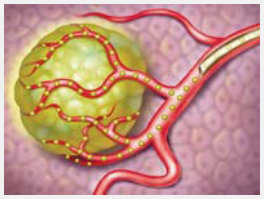
A = Activity needed to acquire desired dose [Bq]
D = Desired dose [Gy]
M = Liver mass
BSA = Body Surface Area

BSA Model

$$A = (BSA - 0.2) + \frac{\%tumor}{100}$$



Microscopic view of Yttrium-90 microspheres beside a strand of hair [4].



Schematic view of the intra-arterial injection of the microspheres and their delivery to the tumorous tissue [5].

Yttrium-90 (Y90) is used as the radioactive substance to deliver ionizing radiation to the tumorous tissue. Two different types of microspheres are in use which differ in their material (glass or resin-based) and in dosimetry calculations [2].

IV. Clinical Results

Tumor Response after Y90 Therapy [6]

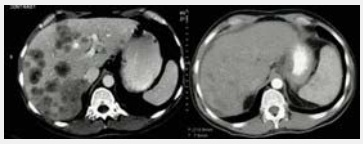
	Median	Range
Complete Response	0	0-6
Partial Response	31	0-73
Stable Disease	40.5	17-76
Progressive Disease	17.5	6-50

Side-effects caused by Y90 Therapy

	Median	Range
Acute Toxicity	0	0-6
Delayed Toxicity	31	0-73

Acute toxicity symptoms that emerged include fatigue, abdominal pain, vomiting and gastritis. The most common delayed complications have been liver dysfunction including liver failure, gall bladder complications and gastritis [6].

Chemotherapy in combination with Y90 Radioembolization



Left: CT scan of colorectal liver metastases before the treatment with chemotherapy in addition to Y90 radioembolization. Right: CT scan of the liver 6 month after chemotherapy combined with Y90 radioembolization [3].

- Y90 radioembolization is a possible alternative to TACE (Transarterial Chemoembolization) with similar survival outcome.
- Patients with portal vein thrombosis can be treated using Y90 radioembolization which is not possible in combination with TACE
- Response rates and mean survival time is higher in patients when Y90 therapy was used as an addition to chemotherapy in comparison to chemotherapy alone

V. Limitations

- Y90 radioembolization is limited to palliative treatment
- Imaging of the microspheres is not possible, therefore an accurate placement is difficult
- Clinical results have limited interpretation possibilities because they are deemed to be statistically non-significant due to the low number of patients

VI. Conclusion

- Y90 radioembolization is considered to be safe and efficient
- No significant differences in survival outcome between TACE and Y90 therapy
- Promising results of Y90 therapy in addition to chemotherapy
- Difficult detection of microspheres

VII. Future Outlook

- Image guidance and detection of the microspheres are a main goal in future research
- Extension of clinical studies to enable statistical significance
- Improvement of the determination of prognostic factors for the behavior of the disease after Y90 therapy

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Liver tumor therapy with Y90 - Systems used, clinical results and limitations with a future outlook

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December 17, 2015

Abstract

This work introduces Y90 radioembolization as a treatment option for unresectable liver malignancies. Microspheres which have Yttrium-90 as an integral constituent are placed intraarterial. Therefore ionizing radiation can be directly delivered to the tumor.
Systems used: Two different systems of microspheres are in use, TheraSpheres® and SIR-Spheres®, which differ in material, activity provided and dosimetry calculations.
Clinical results: Y90 radioembolization is concluded to be safe and efficient. Both types of microspheres are described to be equally feasible for the treatment procedure. No significant treatment differences were observed between Y90 radioembolization and other intraarterial treatment options like transarterial chemoembolization. Studies are often limited by small groups of patients.
Limitations: The image guidance of the intraarterial placement is restricted because Y90 microspheres cannot be imaged intraoperatively. Pre- and postoperative evaluation was used to enable a better placement.
Future outlook: Imaging of the placement procedure can be done using different materials for microspheres. Clincial studies should be extended for a better comparison between treatment options and statistical significance.

Abbreviations:
Y90 - Yttrium-90, **HCC** - Hepatocellular Carcinoma, **TACE** - Transarterial Chemoembolization, **RFA** - Radiofrequency Ablation, **SIRT** - Selective Internal Radiation Therapy, **CDCLM** - Colorectal Liver Metastases, **TC-99 MAA** - Technetium-99 Macroaggregated Albumin

1. Introduction

Hepatocelluar carcinoma (HCC) is, with over one million new cases worldwide per year, the most common primary liver cancer. The tumor stage and the level of liver impairment determine the possible treatment options. While a surgical resection of the entire tumor is ideal and provides the best chance for curing the patient, only about 20% percent of the patients are candidates for surgery. This is due to the fact that the disease is often diagnosed at an advanced stage [1].

In addition to primary liver cancer, other cancer types can metastasize into the liver. Colon and rectal cancer, which is the fourth most common cancer in the United States and Europe, is responsible for the majority of hepatic metastases [2], [3].

Given the high rates of unresectable liver malignancies the interest in, and importance of, alternative treament techniques advances. Standard techniques to treat unresectable liver malignancies during the last years include ablation and embolization techniques containing transarterial chemoembolization (TACE) for tumors at an intermediate stage and radiofrequency ablation (RFA) for tumors at an early stage. The focus in this paper is set on the novel technique called Selective Internal Radiation Therapy (SIRT) which uses Y90 microspheres for radioembolization.

Goal The goal of this work is to give an overview of radioembolization therapy using Y90 microspheres. The main focus will be set on the systems that are in use and their clinical results. Different types of microspheres are described and their limitations are discussed.

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2. Y90 Radioembolization

Yttrium-90 (Y90) radioembolization is a minimal invasive catheter-based treatment option for liver tumors. Using the Y90 therapy ionizing radiation is directly delivered to the tumorous tissue by microspheres placed into the hepatic artery. The treatment combines the advantages of internal radiation therapy and the embolic effect of Y90 microspheres. The importance of the Y90 therapy arises from the limited treatment options available for unresectable hepatic malignacies [4].

2.1. Background

The use of external beam radiaton to the entire liver to treat hepatic malignacies is restricted. The radiation dose tolerated for patients with nonaffected liver function is limited to 30 Gy. This is below the dose requiered to damage the tumor sufficiently, which is suggested to be around 95 Gy [4], [5].

The minimal invasive catheter-based placement of Y90 microspheres into the hepatic artery allows for specific internal radiation in direct proximity of the tumor. Yttrium-90 is a pure β-emitter and has a mean tissue penetration of 2.5 mm. Therefore, Y90 microspheres can deliver radiation doses of 50 to 150 Gy directly to the tumor, given that the majority of the radiation spares healthy liver tissue and only affects the malignant tumor region [6].

The basic principle behind the intra-arterial placement of micropheres arises from anatomic and physiological aspects of the liver tissue. The blood supply of the liver tissue is delivered by the portal vein and the hepatic artery. The technology takes advantage of the fact that healthy liver tissue derives over 70 % of its blood supply from the portal vein, whereas the tumorous tissure obtains the majority of its blood supply from the hepatic artery (90 %). Plac-

ing the microspheres inside the hepatic artery minimizes harmful effects on the normal liver parenchyma, but delivers them directly to tumor [4], [6].

2.2. Treatment Procedure

Y90 radioembolization does not only consist of the injection of microspheres itself, but includes necessary preoperative and postoperative procedures. Here the different parts of the treament are described seperately in order to give an overview of the Y90 radioembolization therapy. The pre-and postoperative treatment will gain its importance when the limitations of the technique are discussed at the end of this documentation.

Preoperative

After a patient is diagnosed with unresectable liver cancer the doctors must decide on an appropriate further treatment. If Y90 radioembolization is chosen as a possible opportunity, different preoperative procedures have to be performed to estimate the risks of the treatment and to evaluate any possible contraindications. Before a possible treatment with Y90 microspheres the following steps must be performed:

A) Performance Status
A physical examination is conducted to determine the performance status of the patient. This includes clinical laboratory tests to evaluate the liver function and to determine known tumor markers. Studies have shown that patients with a poor performance status have a high risk of liver failure during the treatment. The medical doctors have do decide on an individual basis if the performance status is a contraindication for Y90 radioembolization. Each patient requires special consideration weighting further favorable further factors. Patients with a poor performance status may be also suitable for Y90 therapy. In general it can be said that patients with a severely damaged liver function or a disseminated extra-hepatic malignant disease are not suitable for the therapy with Y90 microspheres [4].

B) Angiogram
An angiogram is required to determine the status of the blood supply to the liver for each patient individually and to verify the approriate placement of the catheter during the treatment. [1], [4].

C) Liver Scan
A MRI scan or a CT scan of the liver is necessary to estimate the mass of the liver. This is essential to calculate the dosage required for the desired effect on the malignant tissue [7], [8].

D) Dosimetry Planning
Applying internal radiation therapy into the human body always requires complex dosimetry planning to reach the desired target dose.

E) Technetium-99 macroaggregated albumin scan
A Technetium-99 macroaggregated albumin (Tc-99 MAA) scan is performed to determine the amount of extrahepatic shunting that could occur during Y90 radioembolization treamtment. Shunting sometimes occurs in patients when part of the hepatic arterial blood supply bypasses the capillary bed and flows directly into the venous system. In these patients a fraction of injeted microspheres would not be embolized in the hepatic artery but would be deposited into the lungs. To analyze the risk Technetium-99 macroaggregated albumin (MMA) is injected through a hepatic artery catheter and a scintigraphy scan of the thorax and the abdomen is done. This is used to determine the fraction of injected radioactive material that is delivered to the target tissue and the fraction which is shunted into the lungs (see equation 1) or is

delivered via blood flow to the upper gastrointestinal tract. Y90 radioembolization is contraindicated if the fraction of lung shunting is over 20 % and if the backflow to the gastrointestinal tract can not be corrected using catheterization methods (balloon catheterization or coiling) [4], [5], [9].

$$\text{Lung Shunt}(\%) = \frac{\text{Tc-99 lung}}{\text{Tc-99 lung + TC-99 liver}} * 100 \quad (1)$$

Intraoperative

After weighting all risks, excluding the contraindications and performing the additional preoperative tests, the actual injection of the microspheres can be performed. The Y90 microspheres are selectively injected by percutaneous access to the femoral artery and are guided to the hepatic artery by fluoroscopy. The intra-arterial catheter-based placement of the micropsheres can be done in a local (segmental), regional (right or left hepatic artery) or whole-liver (proper hepatic artery) treatment. The catheter must be placed such that it does not occlude the vessels in which it is placed. The exact position for the placement of the microspheres has to be evaluated using the preoperative techniques and depends on the tumor size and position. It is not possible to depict the excact placement of the microspheres intraoperatively. During the precise placement of the microspheres the patient's are sedated and the injection time runs between 2 and 4 hours [1], [5], [10].

Postoperative

Directly subsequent to the delivery of the microspheres a SPECT scan is performed to evaluate the placement and position of the microspheres. It is useful to compare this scan with the results of the Technetium-99 macroaggregated albumin scan to determine the difference between the scans and the actual distribution of the microspheres. This gives special advantages for the planning of a possible retreatment. Usually patients are discharged from the hospital on the day of treatment, there is no medical constraint for radiation safety in combination with the Y90 microspheres.
If no unexpected side-effects occur a follow-up exam is necessary to evaluate the success and the effects of the injection. This is usually done after 30 days using imaging methods and laboratory tests to determine the degree of tumor shrinkage. Further postoperative observation occurs at three-month intervals. A second and third treatment with Y90 microspheres is recommended after 4-6 weeks, if a positive result was achieved during the first session [1], [11].

3. Y90 Microspheres

All systems used for the Y90 radioembolization have Yttrium 90 as the radioactive substance to deliver ionizing radiation to the tumorous tissue.

Yttrium 90 The pysical properties of Yttrium-90 make it well suited for the medical treament of liver malignancies. It is a pure β-emitter and decays to Zirconium-90 with a half life of 64.1 hours. It has a mean tissue penetration of 2.5 mm and a maximum penetration of 1 cm. Yttrium-90 is the product of the β^--decay of Strontium-90. The maximum energy released is 2.27 MeV with a mean of 0.93 MeV. Although Yttrium-90 is a β-emitter secondary radiation in the form of gamma-radiation as an effect of Bremsstrahlung can occur [6], [12].

Since the 1960s Yttrium-90 has been used to treat hepatocellular carcinoma in patients. Initially metallic particles of Yttrium-90 oxide (Y-90_2O_3) were injected intraarterially into the human body. In 1987 the first animal studies with glass microspheres were tested.

Yttrium-90 incorporated in glass matrices solved the problem of leaching, which occured during the implementation with metallic particles. Nowadays Y90 can be delivered to hepatic malignancies as either an integral constituent of glass microspheres or as a resin-based microsphere. Therefore two commercially available systems are approved, in the following the different systems are explained and described [10].

3.1. TheraSphere®

TheraSphere® microspheres (MDS Nordion, Canada) are insoluble glass microspheres which have Yttrium-90 as an integral constituent of the glass. Figure 1 shows a microscopic view of TheraSphere® microspheres.

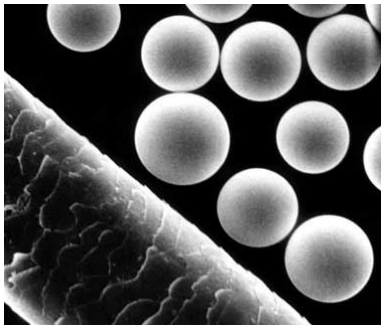

Figure 1: Microscopic view of yttrium-90 microspheres beside a strand of hair. [1]

Each sphere has a diameter between 20 and 30 μm and contains approximately 2500 Bequerel (Bq). TheraSphere® microspheres are supplied in a vial of 0.6 ml sterile, pyrogen-free water and are shielded with an 12-mm-thick acrylic shield. One milligram of TheraSphere® contains 22,000 to 73,000 microspheres. TheraSphere® microspheres are available in six different activity sizes at callibration (3, 5, 7, 10, 15 and 20 GBq). To obtain the different activity sizes the number of micropheres in one vial varies from 1.2 to 8 million. This is not sufficient to cause a significant blockage in the main hepatic artery, therefore the effect of complete embolization does not occur. The cost of TheraSphere® in the US market is 13,000 US$. This prie does not include treatment administration and follow-up treatment. [1], [4], [13].

Dosimetry

For treatments using substances which produce ionizing radiation it is of high importance to calculate the radioactivity required to deliver the desired dose to the malignant tissue individually for each patient. Dosimetry planning for Y90 radioembolization using TheraSphere® follows the so called partition model. The injected doses are based on the desired dose to the target mass. The recommended dose to treat liver malignancies is between 80 and 150 (mostly 120) Gy. Equation 2 describes the calculation of the activity A needed to aquire the desired dose.

$$A = \frac{D * M}{50} \tag{2}$$

D is the desired dose in Gy and M the estimated mass of the liver which is determined using imaging methods such as MRI or CT scans. It is common to estimate the liver volume using a CT scan and then convert it to the mass using the conversion factor 1.03 kg/ml. To determine the exact radiation dose delivered to the liver after the injection, the lung shunt fraction (F) has to be taken into consideration [4], [7], [8]:

$$\text{Dose (Gy)} = \frac{50\ \text{[Injected Activity (GBq)][1-F]}}{\text{Liver Mass}} \tag{3}$$

TheraSphere® is indicated for the radiation treament in patients suffering from unresectable liver malignancies [9].

3.2. SIR-Spheres®

SIR-Spheres® (Sirtex Medical Limited, Lane Cove, Australia) represent another type of microspheres used for Y90 radioembolization.

They consist of biodegradable resin-based microspheres containing Yttrium-90 with an average size of 35 μm (range 20-60 μm). SIR-Spheres® only come with the dose size of 3GBq and are provided in a vial of 5 ml sterile water. Each vial contains 40 to 80 million microspheres and is calibrated to deliver 3 GBq of Y90 on the day of usage. The corresponding activity per microsphere is approximately 50 Bq. Given the lower dose rate available when using SIR-Spheres® in comparison to TheraSphere® a higher amount of micropheres must be delivered to the patient to obtain the desired target dose. This, in addition to the larger diameter of the resin-based micropheres often leads to a saturation of the vascular bed with micropheres. Using SIR-Spheres® an embolic status can be reached which can block the blood supply in the hepatic artery. Therefore the fluoroscopic guidance is especially important for the treatment using SIR-Spheres® because the injection has to be stopped as soon as the embolic status is reached [1], [4], [12].

Dosimetry

The dosimetry calculation for SIR-Spheres® varies from TheraSphere® radiation treament. Two different methods based on the activity and not on the target radiation dose can be used to perform the dosimetry planning for SIR-Spheres® [4], [9], [12], [14]:

A. Empirical model

This method is based on a broad estimate of tumor infiltration and the recommended dose for the treament is obtained from table 1 [4]:

Table 1: Dosimetry calculations using the emprical model

Tumor Infiltration	Recommended Dose [GBq]
>50%	3
25-50%	2.5
<25%	2

B. Body Surface Area Model

This method uses the body surface area (BSA) as an estimation for the liver volume in combination with the tumor infiltration of the liver. It provides a more objective calculation of the required activity and is therefore the prefered model to use. The required dose calculation follows equation 4 [14]:

$$\text{Activity (GBq)} = (\text{BSA} - 0.2) + (\%\ \text{tumor}\ /100) \quad (4)$$

For both models the recommended dose has to be modified if significant lung shunting occurs or a partial liver treament is planned for a local or regional tumor treatment. Therefore, specific recommended multiplication factors are available in package-inserts of SIR-Spheres® [14].

Table 2 provides a final summarizing comparison of the differences between the two microsphere systems used:

Table 2: Comparison of Y90 radioembolization systems

	TheraSpheres®	**SIR-Spheres®**
Material	glass	resin-based
Microsphere size	20-30 μm	20-60 μm
Activity per sphere	2500 Bq	50 Bq
Dosimetry calculations	partition model	BSA model
Costs	13,000 US$	14,000 US$

After the development of the micropsheres TheraSpheres® was indicated for the treatment against HCC and SIR-Spheres® for the treatment against colorectal liver metastases [9]. Nowadays both types of microspheres can be used as a treatment option against both types of liver malignancies.

4. Clinical Results

Different clinical studies concerning the efficiacy and safety of Y90 radioembolization treatment have been done in the past. Analysis and evaluation of these studies have been proven to be difficult due to different types

Table 3: Summary of resonse of patients with CRCLM undergoing Y90 therapy

		Median	Range
Mean number of previous chemotherapies		3	2-5.1
Previous therapy	hepatic resection [%]	20	0-92
	ablation [%]	10	0-22
	other therapy [%]	13.5	5-36
Response	complete response [%]	0	0-6
	partial response [%]	31	0-73
	stable disease [%]	40.5	17-76
	progressive disease [%]	17.5	6-50

of microspheres used, low number of patients and heterogeneous evaluation criteria. Nevertheless the following section attempts to sum up clinical results of Y90 radioembolization for hepatic malignancies. The efficiacy and safety of radioembolization in general and in comparison to other treatmeent options is evaluated.

Y90 Radioembolization for unresectable hepatic malignancies

Saxena et al. (2014) [15] compared and evaluated the results of 20 different studies including 979 patients who where treated for unresectable colorectal liver metastases with either glass or resin-based microspheres. Their results are summarized in table 3.

Most of the patients who were chosen for Y90 radioembolization had undergone several lines of chemotherapy before the treatment with microspheres was started. There is also a not negligible number of patients who were previously treated with hepatic resection, ablation or other therapies including transarterial treamtements such as TACE. Transarterial chemoembolization has been used in the previous years as the standard treatment for unresectable hepatic malignancies which were insensitive to chemotherapy. Y90 radioembolization was usually chosen when resection or ablation were not possible and transarterial chemoembolization did not lead to the desired effect. This group of patients naturally has a relatively poor prognosis.

A complete response of the tumor to Y90 radioembolization was very rarely seen. About a third of the patients have shown a partial response and on average 40.5 % had a stable disease after treatment. Only 17.5 % had a progressive disease after the injection of microspheres. The response rates concerning Y90 radioembolization are comparable with those from TACE treatment. There has been no significant difference mentioned between results of treatment with microspheres based on glass or resin.

Table 4 shows that about a half of the patients developed symptons related to the acute toxicity caused by the microspheres. Values here varied between 11 % up to 100 % in the different studies [1]. Symptoms that emerged were fatigue, abdominal pain, vomitting and gastritis. The majority were transient and could be solved without any active intervention. These complications are related to the therapy and are summarized as the post-radioembolization syndrom. The incidencee of patients developing delayed toxicity complications was low (5 %). The most common delayed complications have been liver dysfunction including liver failure, gall bladder complications and gastritis.

[1]The discrepancy between the different studies was high. Some mentioned fatigue and abdominal pain as complications. Others did not see those symptoms as complications

Table 4: Side effects caused by Y90 radioembolization

		Median	Range
Acute toxicity %		40.5	11-100
Type of acute toxicity	fatigue [%]	38.5	0-100
	abdominal pain [%]	16	0-48
	nausea/vomitting [%]	19	5-56
	gastritis [%]	2	0-13
Delayed toxicity %		5	4-10

In general the rate of complications after a Y90 therapy was not increased in comparison to complications occuring after radiofrequeny ablations or transarterial chemoembolization. The authors of the study concluded that Y90 therapy is a safe and effective treatment against colorectal hepatic metastases [15].

Although the study by Saxena et al. (2014) only covered colorectal liver metastases, the results can be generally transferred to the treatment of hepatocellular carcinoma. Salem et al. (2010) [16] observed the treatment against HCC with TheraSphere® in 291 patients. Portal vein thrombosis was not considered as an exclusion factor. Response rates and side-effects that occured were comparable to the study of Saxena et al. (2014) but the main goal of the study was to determine the interaction between specific tumor factors and the survival outcome. They concluded that an advanced disease lead to lower response rates and a reduced time-to-response. Multifocal tumor distribution was found to be associated with a poor prognosis, whereas, portal vein thrombosis and extrahepatic metastases had no significant influence. The authors concluded that the relatively small group of patients often limits the significance of the studies. Further studies are necessary to define specific prognostic factors and to make a comparison of the influences of those factors between other locoregional therapies (radiofrequency ablation and TACE) [16].

Y90 radioembolization vs. TACE

Both Y90 radioembolization and Transarterial Chemoembolization (TACE) are transarterial treatment options for liver malignancies. During the last years TACE has become the standard treament for unresectable hepatic malignancies (at an intermediate tumor stage) but with the delevopment of Y90 microspheres the significance of radioembolization started to increase.

Salem et al. (2011) [17] performed a comparative analysis of patients treated with Y90 radioembolization (123 patients) and TACE (122 patients) to test if significant differences in the outcome occur. Results of the study showed that Y90 radioembolization and TACE lead to similar survival of the patients after the treatment. However, Y90 radioembolization induced a prolonged time-to-response. This can not directly be related to the survival time but is of high interest if the treatment is used as a bridge to resection or transplantation. Addtionally three main advantages of Y90 radioembolization were observed. First, it is especially suitable for elderly patients because a postembolization syndrom, which is often mentioned in combination with TACE, does not occur. This leads to reduced abdominal pain. The postembolization syndrom usually requires a hospitalization of patients after the treatment with TACE. Whereas Y90 radioembolization patients are usually released on the day of treatment. Finally, portal vein thrombosis is a contraindication for TACE but given the

lower embolic effect of microspheres, Y90 radioembolization offers a new option for patients with compromised portal flow. Patients with or without portal vein thrombosis can be treated.[2] The authors of the study concluded that Y90 radioembolization can be used safely and provides a possible alternative to TACE with similar survival outcome [17].

Y90 radioembolization and Sorafenib®

The effect of Y90 microspheres in combination with sorafenib®, which is an oral multikinase inhibitor, was tested [18]. Sorafenib® reduces tumor cell proliferation and is a drug used to expand the life span of a patient or as a bridge to liver transplantation, it is often used in an advanced stage of the disease. Since Sorafenib® in combination with TACE leads to conflicting results it was hoped that Sorafenib has no negative effect on Y90 radioembolization. A first randomized study concluded that on one hand lower radiation doses for Y90 microspheres were required after the additional use of Sorafenib®. But on the other hand a possible transplantation of the liver after pretreament failed more often when using Sorafenib® and Y90 microspheres together [18].

Y90 radioembolization and chemotherapy

The effects of a combination of Y90 therapy and chemotherapy in comparison to chemotherapy alone on liver malignancies was compared in several studies [19]. Different chemotherapeutical drugs in combination with the microspheres were tested. Overall results concluded that response rates and mean survival time was higher when Y90 therapy was done as an addition to chemotherapy. Qualtiy of live and time-to-progression are reduced in patients who were treated with chemotherapy alone [19].

In general all of the clinical studies concluded that Y90 radioembolization is safe and efficient. A all of the authors mentioned, the evaluations can not be proven statistically significant due to the low number of patients compared in the studies.

5. Limitations

First of all, it must be mentioned that Y90 radioembolization is limited to palliative treatment. A complete cure or healing of the patients is extremely rare. Therefore Y90 radioembolization is used to improve quality of life and extend the time of survival. In addition it is used as a bridge to resection, transplantation or ablation procedures.

Portal vein thrombosis was seen as a contraindication for Y90 radioembolization in the past. But several studies have now concluded that the use of Y90 microspheres is not limited in patients with portal vein thrombosis. An accurate imaging of the microspheres would better evaluate the possible impact of portal vein thrombosis and could better predict the possible treamtment outcome. This leads to the most important limitation related to the injection of the microspheres. The injection procedure cannot be imaged and therefore the exact positions of the microspheres cannot be determined and a direct reaction by surgeons on the placement is not possible. The guidance is difficult and imaging is necessary to confirm the right placement. It has to draw on pre- and postoperative methods to optimize the injection of the microspheres. The introduction of the postoperative technetium-99 macroaggregated albumin scan improved the evaluation and planning procedure of the treatment.

[2]Portal vein thrombosis is listed as a contraindication in package inserts for both types of microspheres. [7], [12]. Studies showed that mirospheres can be injected in patients with portal vein thrombosis weighting the risks using the Tc-MAA scan [16].

Postoperative SPECT scans can confirm the right placement of the microspheres or depict undesired placement, but still no optimal placement imaging is achieved. Once the microspheres are injected there is no opportunity to remove them. It is of high importance to develop possibilities of an intraoperative detection of the microspheres.

6. Conclusion

Y90 radioembolization is the transarterial injection of microspheres into the hepatic artery to treat unresectable liver malignancies. It is mainly used for the treatment against unresectable hepatocellular carcinoma or unresectable colorectal liver metastases. The treatment is considered to be safe and efficient. Currently two different systems are in use, Therasphere® and SIR-Spheres®, which base on either glass or resin microspheres. Clinical results reported no significant difference between both systems and the liver malignancy they are intended to treat. Comparison studies between Y90 radioemblization and TACE showed no significant differences in survival outcome of the patients but a decreased amount of side effects in combination with the injection of the microspheres. Y90 radioembolization together with sorafenib caused no side effects and did not lower survival rates, but the acceptance of liver translpantation was slightly reduced. Y90 radioembolization together with chemotherapy had promising results. The additional treatment with microspheres prolonged time-to-progression and survival time. Clinical results of the mentioned studies have limited interpreation possibilities because they are always deemed to be statistically non-significant due to the low number of patients. Y90 microspheres cannot be detected during their injection, which is the most important limitation arising from Y90 radioembolization treament

7. Future Outlook

The main challenge for future research on Y90 microspheres is to overcome the limitation of image guidance. One one hand an additional component could be added to the microspheres which can be detected using intraoperative imaging. Possible disadvantages might be an increase in costs because of an additional processing step. On the other hand the use of other substances for microspheres, which deliver ionizing radiation and replace Yttrium-90, might be an opportunity or solution. When considering new material for microspheres the problem of leaching which occured in the past should always be in mind. In general, a depiction of the microspheres with MRI or other imaging methods is an important requirement for all used novel substances. Imaging and tracking during the injection procedure is significant for an accurate observation of the placement of the microspheres.
Furthermore clinical studies should be extended to enable statistically significant evaluation of Y90 radioembolization. Here, it might be of interest to better compare the different microspheres which are in use. In addition a significant comparison between Y90 radioembolization and TACE could be of interest. An improvement of the clinical studies could enable a better selection of the patient to optimize the treament procedure. Additionally prognostic factors which determine the possible outcome should be determinded. This could improve the choice of the right treatment for the patients and the evaluation and comparison of different studies.

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"Interventional Laser Therapy"

Abstract, Laser therapy systems, Applications, Limitations and Considerations, Summary and Future outlook

Instruments for Image Guided Procedures
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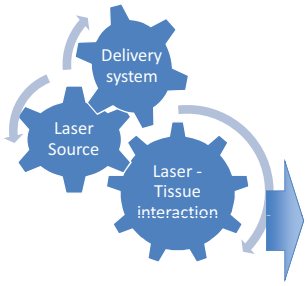
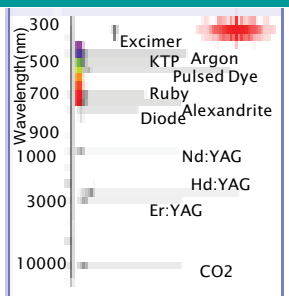
Abstract

Lasers produce intense beams of light which are monochromatic, coherent, and highly collimated. Shortly after their discovery in the 1960s, their application in the medical world was recognised and the first medical applications appeared quickly. Today, Lasers are applied in the intervention of a wide variety of diseases as well as a diagnostic tool. The basic setup of a Laser therapy system involves the laser source and the delivery system. There are various types of laser sources at different wavelengths which operate as a continuous wave and in pulsed mode. In order to develop a laser treatment system a thorough understanding of the interaction between laser type and tissue in question should be developed.

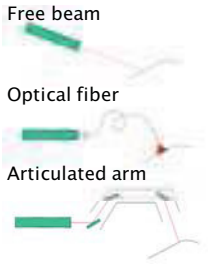
Laser therapy systems



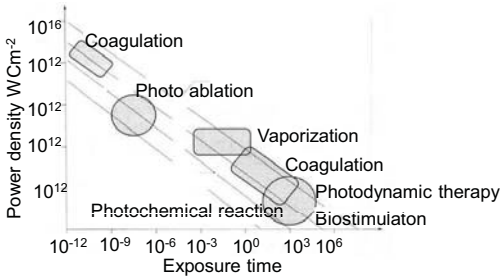
The main components of laser therapy system.



The most popular lasers applied in medicine [3]



Laser light delivery approaches [7]



Various modes of laser tissue interaction [6]

Applications

Corneal reshaping(LASIK)

http://www.doctorawwad.com/img/lasik_step_by_step_f%281%29.jpg

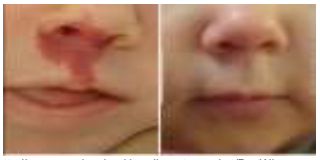
- Non-thermal Excimer ablation in the UV range
- Common issues include over or under ablation

PDT in Oncology

http://bestofbothworldsaz.com/wpcontent/uploads/2011/04/levulan_2.jpg

- Injection of photosensitizer followed by illumination producing toxic interaction.
- Main challenge is the discovery of photosensitizer that is appropriate for a particular cancer.

Destruction of blood vessels (Port Wein Stain Laser Treatment)



http://www.americanhealthandbeauty.com/art/PortWine-Brightman-B-A-Baby.jpg

- Argon laser blue-green light (488 and 514 nm) is used.
- Thermal thrombosis destroys the PWS blood vessels.
- With argon laser epidermis is not totally spared (absorption by melanin and other dermal components)
- Better selectivity is recently achieved with pulsed dye laser (PDL)(577 nm or 585 nm)

Laser Lithotripsy

http://www.kidneystoner.org/wp-content/uploads/2011/03/urs-diagram-600.jpg

- Optical fibere inserted through the urethra under endoscopic visualization
- Nanosecond pulse laser 2.1 microns from Holium:YAG source is used

Limitations and Considerations

1. Laser sources
- Ability to control energy, power fluence, and irradiance
- Better understanding of the behaviour of each laser type

2. Delivery to target area
- Penetration depth limits shallowness of ailments treated (close to the skin or on the surface of organs)
- Development of better delivery system(fibre optic and wave guides) and imaging guidance of the delivery system.
- Fibre optic currently used are not capable of transmitting high energy density pulsed laser light.

3. Laser tissue interaction.
- Deficiency in understanding of laser tissue interaction.
- Understanding of the heat distribution and penetration depth is important for the safety and accuracy of laser treatment.

4. Photosensitizer
- There are few photosensitizer that are approved by regulatory bodies.
- The discovery of new photosensitizer is important in the wide adaptation of PDT.

Summary and Future Outlook

Laser's therapeutic application is diverse and is still growing. Different wavelength lasers have different depth of penetration in human tissues. Tissue composition, which is different from one tissue to another, means that the diversity of laser types will be a boost on their adoption in the treatment room. In addition, more than one kind of laser source can generate a specific wavelength with various power output ranges. Therefore, having a wide diversity of laser sources could be a significant development which will make laser therapy more accurate. A better understanding of various tissue interaction to laser light will also play a significant role in the adoption of laser treatment. In addition, research on photosensitizer development will also increase the popularity and use of PDT.

Therefore, a more modular approach of laser system development will be more economical. In a modular system, various laser types can be combined to a various delivery system to treat different tissues according to the need. This approach decreases the cost of developing whole systems which are designed to address a particular application

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Interventional Laser Therapies

Systems used, Clinical Application, Limitation and Future Outlook

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12/17/2015

Shortly after their discovery in the 1960s, laser's application in the medical world was recognised by the research community. The first applications of laser therapy followed quickly. Today, they are applied in the intervention of a wide variety of diseases as well as a diagnostic tool. In this paper I describe a basic setup of a Laser therapy system and describe the major components, and then I will describe laser tissue interactions that facilitate lasers interventional capability. This will be followed by representative example applications which demonstrate lasers interventional use. I will then discuss the limitations of laser therapy and conclude my paper with a personal outlook on their future development.

1. Abstract

Shortly after their discovery in the 1960s, laser's application in the medical world was recognised by the research community. The first applications of laser therapy followed quickly. Today, they are applied in the intervention of a wide variety of diseases as well as a diagnostic tool. In this paper I describe a basic setup of a Laser therapy system, describe the major components and laser tissue interactions that facilitate lasers interventional capability. This will be followed by representative example applications which demonstrate lasers interventional use. Then I will discuss the limitations of laser therapy and conclude my paper with a personal outlook on their future development.

2. Introduction to Lasers in Medicine

Lasers are a special kind of electromagnetic radiation where the emission of a photon is caused by the stimulation from another photon. When electron is an excited state it will spontaneously, after some time, emit a photon to go to a lower energy level. However if a photon happens to pass by before the electron decays to lower energy level, there is a probability that the passing photon will cause the electron to decay in such a manner that a photon is emitted at exactly the same wavelength, in exactly the same direction, and with exactly the same phase as the passing photon. This process is called "stimulated emission." (Basic laser prinicple)[1].

[1] Internet file

Lasers produce intense beams of light which are monochromatic, coherent, and highly collimated. The wavelength (colour) of laser light is extremely pure (monochromatic) when compared to other sources of light, and all of the photons (energy) that make up the laser beam have a fixed phase relationship (coherence) with respect to one another.

Light have been used throughout the 20th century to treat various ailment. After the discovery of laser its unique characteristic compared to conventional light sources were assumed to bring more precise and efficient delivery of photonic treatment (Jelínková, Šulc 2013). Hence, researchers were quick to explore the usability of laser in the treatment of various illnesses.

Throughout the 1960s there were various breakthroughs and understandings on how to use lasers for medical applications for e.g. Treatment of retinal detachment by Ch. J. Campbell and then Ch. Zwengraction (Jelínková,2013), (Palanker et al. 2011), Leon Goldman, skin melanoma in 1961, surgical use of laser from 1967 to 1970 by pioneers such as T. Polanyi and G. Jako with human tissue.

Although, as mentioned in the previous paragraph, there was significant progress in the deployment of laser, there were significant issues that required further investigation. For example, in the retinal application of lasers, the deep red wavelength(694 nm) was poorly absorbed by blood, such that vascular lesions could not be treated effectively to produce vascular damage or closure without haemorrhage or intense scarring (Palanker et al. 2011) . The difficulty was found to be in controlling the power output and the delivery rate of the

laser radiation, as well as the relatively poor absorptive capacity of some types of tissue for ruby laser light. (Jelínková, 2013).

Although the above mentioned historical areas of applications demonstrated that laser could have a potential to be used for various treatments application, they also demonstrated the need for the understanding of the interaction of particular laser light with tissues that are of interest.

3. Laser Therapy System: Basic Set up

A laser treatment system can be considered as a system with two subsystems. These are the laser light source and the delivery mechanism used to take the light to the area of application. These two subsystems need to be developed in consideration of the laser tissue interaction. In the following diagram I would schematically presented a typical Laser treatment system.

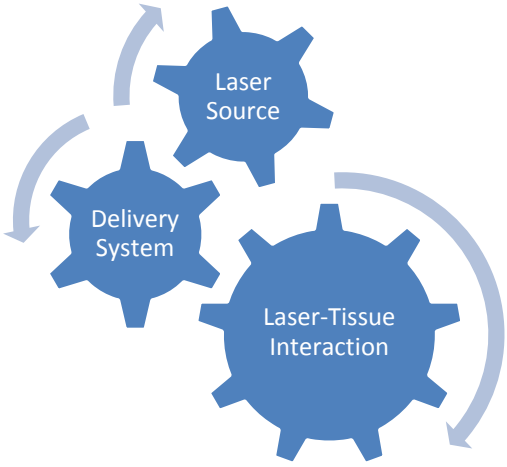

Fig 1. Basic setup of a laser

In the above diagram any laser treatment system involves the production of a particular type of the laser light, of which its choice must depend on a careful analysis of tissue laser interaction, and its effectiveness in treating the particular ailment. Then there is the delivery system which is used to take the Laser light to the area of interest. In the next few chapters I will describe three of them.

3.1. Laser types

There are various types of lasers based on the lasing material. In this chapter I will describe some of the most in medical application.

3.1.1. Gas lasers

3.1.1.1. Carbon dioxide laser

This is one of the most popular laser type and the oldest. It uses excitation of CO2 to produce a highly collimated monochromatic 10.6um wavelength radiation. It can produce a high amount of power. The molecular energy transitions that are needed for population inversions are caused by rotational and vibrational interaction which can easily be powered by thermal means. CO2 lasers have applications in surgical, ophthalmologic and cosmetic applications. The radiation from CO2 laser cannot be transmitted by silica based fibre optics. Therefore special system of mirrors made of hollow wave guides or fibres made of metal halides can be used.

3.1.1.2. Excimer laser

The excimer laser is a pulsed gas laser emitting in the UV-wavelength range from 157 to 351 nm. Its active medium is a mixture of a noble gas (argon, krypton, or xenon), a halogen(chlorine or fluorine), and a buffer gas (helium or neon). The various wavelengths emitted depend on the combination of the noble gas and the halogen. The typical pulse duration is in the region from 10 to several 100 ns at a repetition rate of up to 1000 Hz, with the average power output being up to 200 W. It has applications in ophthalmology (LASIK) as well as laser angioplasty.

3.1.1.3. Argon and krypton ion lasers

Unlike CO2 laser this type of laser is energised by electric discharge to operate. They generate less chromatic laser with wavelength at 488 and 514.5 nm. The wavelength of this laser is in the visible range and can be transmitted through fibre optic.

3.1.2. Solid state laser

3.1.2.1. Ruby laser

This is one of the early lasers and it produces 693.4 nm red light. It is a pulsed laser with pulse duration in the order of milliseconds. Being outside the absorption range of haemoglobin it is primarily absorbed by melanin containing tissue structures. It has uses in hair removal and tattoo removal. But recently its use is declining as it is replaced by alexanderite and Nd:YAG lasers.

3.1.2.2. Neodymium: yttrium aluminium garent (Nd:YAG) laser

This is the most widely used medical laser(Peng et al. 2008). It emits infrared 1064nm light. It operates in both continuous and pulsed mode. It is used for thermal ablation of malignant and benign lesions. It has also uses in oncology to treat skin cancers. By endoscopic delivery mode it can also be in urology.

3.1.2.3. Erbium: yttrium aluminium garent (Er:YAG) laser

In this laser erbium ions (Er3+) are in a solid-state matrix of yttrium aluminium garnet(YAG; wavelength 2.94 µm) or yttrium scandium gallium garnet (YSGG; wavelength 2.78 µm). According to (Knappe et al. 2004), laser emission in this medically interesting 3-µm-region is generated by an erbium concentration of 30–50%. The Er:YAG laser can work as a dental drill and in aesthetic surgery.

3.1.2.4. Alexandrite laser

This produces 700-830nm laser which can operate on both CW and pulsed mode. It is absorbed by melanin and dyes but not significantly by blood which makes it good for hair and tattoo removal as well as for the destruction of kidney stones.

3.1.2.5. Diode lasers

These are laser which are emitted when electrons which are elevated to conduction band recombine with a positive hole in the valance shell. Diode lasers are very efficient and reliable. Typical commercially available diode lasers are AlGaAS diodes at 805 nm.

3.2. Laser delivery system

Light delivery systems can be defined as systems for controlled transport of light between a light source and a target. According to (Verdaasdonk, Swol, Christiaan F P van 1997), a laser delivery system consists of entrance optics, a beam guide and target optics. The choice depends on the characteristic of the laser type and the application intended. The following diagram shows the main components of a laser delivery system.

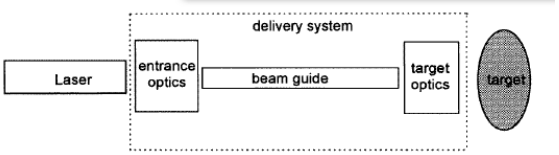

Fig 2.Diagram of a laser delivery system (Verdaasdonk, Swol, Christiaan F P van 1997)

3.2.1. Entrance optics

According to (Verdaasdonk, Swol, Christiaan F P van 1997), the first component of the delivery system provides the conditioning of the laser beam for transportation through the beam guide. For some systems, the beam only has to be deflected. When the laser light is transported through a waveguide, the beam has to be focused down to a spot of a few hundred micrometres depending on the diameter of the waveguide. The material of the focusing lens has to be transparent for the wavelength of the laser light. The lenses are usually made of material similar to the

waveguide itself and the surfaces are coated to reduce losses caused by Fresnel reflections.

3.2.2. Beam guide

This is the medium through which laser light is transmitted to reach the target region. The choice of material and construction of a beam guide is mainly determined by the wavelength of the laser, operating power and spot size of the beam and accessibility of the treatment area. According to (Peng et al. 2008), there are mainly three various systems of this type.

The first is articulated arm and lens system. This consists of a series of hollow tubes and mirrors. The laser beam is transmitted through a tube and then reflected into the next tube by an appropriately angled mirror. This system can be adapted to an operating microscope or hand piece providing excellent precision. The second type is fibre optics. These are thin, flexible optical fibres coated with opaque nylon or metal casings, which can transmit visible and near infrared radiation by reflection off the opaque casing. The optical fibres can be used in conjunction with rigid or flexible scopes to provide minimally invasive surgery. Recently flexible, biocompatible silica optical fibres with side-firing and diffusing tips for high power delivery of laser irradiation have been shown to be promising for a number of medical indications.

The third type is a waveguide. Waveguides are semi-flexible steel tubes lined by ceramic tile. Laser energy is reflected down the tube by bouncing the beam off the lateral walls. For pulsed laser systems, transportation through fiber optics can be limited by the high peak powers which could damage the fibre optics (e.g. 10^6kW per cm-2 threshold for silica). When peak power or wavelength does not permit transportation through waveguides, the laser beam has to be transported using reflecting surfaces (Verdaasdonk, Swol, Christiaan F P van 1997).

3.3. Laser tissue interaction

There are various modes of interaction between laser and tissue based on the effect they impart on tissue. Before moving on to discuss these modes of interaction, it is helpful to remember how electromagnetic radiation interacts with matter. These are reflection, transmission, scattering, and absorption. Since with laser therapy the aim is to use the energy of the photons in laser radiation to affect the molecules in cells, I would focus on the latter two radiation-matter interaction (i.e. scattering and absorption).

Absorption of laser in human tissue happens when laser photon energy is large enough to cause transitions of quantized levels of energy in molecules. Various tissues have different absorption spectra(maybe take the diagram in page 17 (Niemz 2007). The main absorbers in the tissues are nucleic acids, proteins, aromatic molecules in the UV, and melanin and hemeproteins in the visible range and water in the infrared region. (Niemz 2007), (Peng et al. 2008). Short- wave visible light penetrates typical tissues to a depth of 0.5–2.5 mm (Douplik et al., p. 69))

The second important light matter interaction which is relevant in medical intervention considerations is the scattering of light. The collimation of laser beam is disturbed very quickly when it propagates into tissues; this is due to scattering of light in every direction. The main scatters in tissue muscle fibres, skin layers, or dentin tubules; microscopic like cells or intracellular structures; and even sub-microscopic, taking into account macromolecules or nanoparticles (Peng et al. 2008).

In order to understand the overall effect of laser interaction with tissue, there are two parameters of tissue exposure to laser light which we have to consider. The first of these two parameters is the exposure rate. This is the power of the laser light which is irradiated to a particular area (that is Power per exposed area). The second parameter is the exposure duration. Based on these two parameters, various modes of interaction between laser

light and tissue can be identified. This can be seen on the following graph taken from (Raulin et al.). According to a well regarded (highly cited[2]) paper by
(Zhigilei, Garrison 2000), in addition to the above mentioned laser parameters, the interaction mode depends on the optical, mechanical and thermodynamic properties of the irradiated material. The discussion of these properties is left, as it is beyond the scope of this paper.

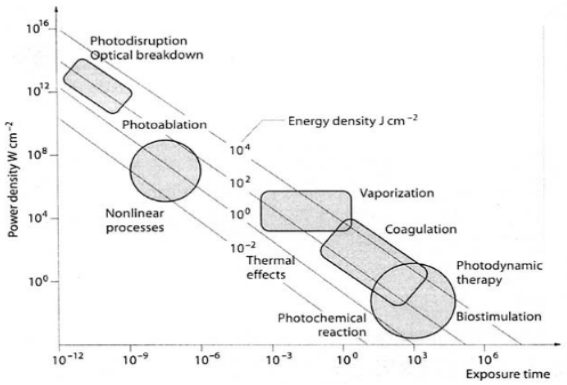

Fig 3. Diferent modes of laser tissue interaction. (Knappe et al. 2004)

Photo Disruption(Electromechanical) mode: According to (Raulin et al.), (Peng et al. 2008) this happens when tissue is exposed to a short pulsed high energy density(high photon density) in the order of 10E10- 10E12 W/cm2 laser light. In this case, the cumulative electric field of the laser right can be high enough to dislodge electrons creating a high temperature ionized spots of plasma. As the plasma expands it crates mechanical waves of supersonic speed which literally cause the explosion of the tissue. Areas of application can be in ophthalmology (Peng et al. 2008).

Ablation mode: This mode involves the evaporation of the irradiated material and the subsequent expulsion of the evaporated content. The evaporation of tissue causes explosion. If the pulse duration is short enough with enough energy to crate vaporization then the process can be clean and very accurate. Ablation mode can be used in ophthalmology, surgery of joints and angioplasty[3] and lithotripsy[4](Peng et al. 2008).

Coagulation and vaporization mode: this is the heating of tissue when exposed to laser which doesn't lead to ablation as defined in the previous paragraph. It typically happens when tissue is heated slowly, allowing heat to diffuse. Various levels of tissue thermal damage can happen according to the heating level(Peng et al. 2008).

Photodynamic mode: in this mode laser tissue interaction laser light is used to excite photosentesizer[5] material which then under goes a serious or simultaneous intersystem interaction which lead to the production of highly reactive and cytotoxic version of oxygen (1o2). In order to to use this mode the photosensitizer has to be accumulated in the target cellular structure; and the produced singlet oxygen destroys the cell. PDT have applications in tumour treatment and in precancerous stages of non malignant lesions (Peng et al. 2008) (Niemz 2007).

Biostimulation mode: According to (Niemz 2007) (Peng et al. 2008), the term biostimulation is not well defined and the mechanism and reaction of how biostimulation works is not scientifically proven yet . However it is believed that low laser level therapies help tissue to heal after a wound. It uses lower fluence rate than PDT. It is believed it can help in cancer treatment as well.

[2] 362 at the time of writing this paper(06/12/2015 from Google Scholar)

[3] *Angioplasty* (or Balloon *angioplasty*) is an endovascular procedure to widen narrowed or obstructed arteries or veins, typically to treat arterial atherosclerosis(wikepedia)

[4] **Lithotripsy** is a procedure that uses shock waves to break up stones in the kidney, bladder, or ureter

[5] A chromophore compound which is capable of causing light-induced reactions in other non absorbing molecules is called a photosensitizer(Niemz 2007.

4. Clinical laser therapy application

In medicine laser has applications in diagnostic, therapy and medical device manufacturing (Schulze 2010). In this paper, the author focuses on therapeutic applications Clinical application of laser therapy is diverse. It has therapeutic applications in dermatology ophthalmology, dentistry, otolaryngology, gastroenterology, urology, gynaecology, oncology, cardiovascular system, neurosurgery, orthopaedics (Lasers for Medical Applications 2013; Peng et al. 2008). Describing all of them is beyond the scope of the paper. So I will give some therapeutic application in fields which demonstrate some of the major categories of tissue laser interaction i.e. photodisruption(photomechanical), ablative, photothermal and photodynamic interaction.

4.1. Ophtalmology: Corneal reshaping(LASIK)

This is a procedure that can be used to surgically treat cases of Myopia (Nearsightedness), Hyperopia (farsightedness), Astigmatism. The process is carried out with a non thermal excimer ablation in the far UV wavelength.

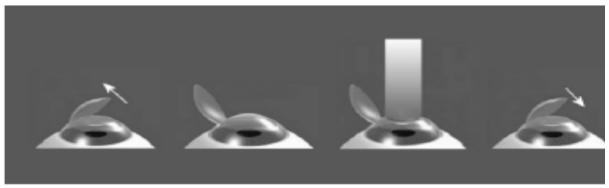

Fig 4. The ablation of cornea (Royal College of Ophthalmologists)

The above diagram demonstrates the procedure of LASIK cornea reshaping. At the start a flap is cut with a special mechanical cutter or a special laser after a suction ring is placed on the eye (painless but can cause loss of vision for 20 seconds) (LASIK). Excimer laser remodels the cornea by ablating tissue. Then the flap is returned to place. The total procedure takes about 30 minutes(Colton Smaldone). According to (Colton Smaldone) common issues in this procedure are over ablation or under ablation which requires more accurate calibration methods in the future.

4.2. PDT in Oncology

Photodynamic therapy (PDT) is increasingly being recognized as an attractive, alternative treatment modality for superficial cancer. The basics of of PDT are the initiation of toxic interaction on the target tissue to kill unhealthy cells. It involves injection of a photosensitizer subsequently followed by light illumination of the sensitized tissue at specific wavelength which can be absorbed by the photosensitizer.

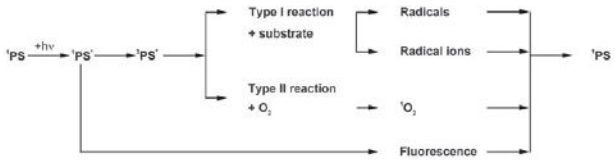

Fig 5. Interaction diagram a photosensitizer (Triesscheijn et al. 2006)

According to (Triesscheijn et al. 2006), upon absorption of the light the photosensitizer transforms the drug from its ground state (1PS) into an excited singlet state (1PS*). From this excited state the photosensitizer can either emit a photon and return to ground state or in the presence of oxygen it can react to create radical ions which then can react with oxygen to produce oxygenated products (type 1 reaction) . Alternatively, the energy of the excited photosensitizer can be directly transferred to oxygen to form singlet oxygen (type II reaction), which are very toxic species.

The main challenge in the application of laser PDT for oncology is the discovery of photosensitizer that is appropriate for a particular cancer. The following list of photosensitizer here listed as example(there are more approved) are approved in various countries (Peng et al. 2008)

- Porfimer sodium (Photofrin®): Cancer of the esophagus, non-small cell lung cancer
- Aminolevulinic acid (ALA or Levulan®): actinic keratosis (AK)
- Methyl ester of ALA (Metvixia® cream): actinic keratosis (AK)

PDT has no long-term side effects when used properly and it is less invasive than surgery and can be done as an outpatient. It can be repeated many times which makes it advantageous over Radiation therapy. In addition it often costs less than other cancer treatments.

Although it has advantages as mentioned it has some disadvantages as well. The main one being it can only be used where light can reach which means it can only be used to treat issues on skin and the lining of organs that can be reached with a light source. Research at the moment is done to apply PDT for variety of cancers and diseases. The development of better photosensitizer is also another area of focus in contemporary research.

4.3. Selective destruction of blood vessels (Port Wine Stain)

Almost always a birthmark, it is caused by a vascular anomaly (a capillary malformation in the skin). The first treatment of PWS involving lasers were developed in the 1970s with argon laser (Ortiz, Nelson 2012). The argon laser with its characteristic blue-green light (488 and 514 nm) is preferentially absorbed by haemoglobin within the PWS blood vessels. The radiant energy absorbed by the vessels is converted to heat, causing thrombosis and destruction of the PWS blood vessels.

Unfortunately, the epidermis is not totally spared (due to undesired absorption therein by melanin and other dermal components) and suffers some irreversible damage. According to (Ortiz, Nelson 2012), a better selectivity is recently achieved with pulsed dye laser (PDL). Using PDLs (577 nm or 585 nm, 0.45 milliseconds) photocoagulation of targeted blood vessels in PWS without overlying epidermal damage is achieved, hence, less side effects.

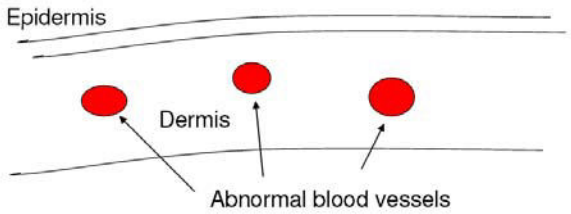

Fig 6. Laser treatment of PWS (https://www.science.mcmaster.ca/medphys/images/files/courses/4T03/4T3_lasers_revised_Compatibility_Mode.pdf)

4.4. Laser Lithotripsy

This is a minimally invasive method to pulverise kidney stones. Although there is a non-invasive alternative to treat kidney stones using high powered ultrasound pulses, it is not ideal for all stones; for e g. when the stone is big or difficult to reach with ultrasound pulses. (dornier MedTech)

The procedure involves placing optical fibere inserted through the urethra under endoscopic visualization. Once contact between fiber optic and stone is made, a nanosecond high power pulse laser 2.1 microns from Holium:YAG source is used. Based upon the principle that Holmium laser energy is strongly absorbed by water, the short laser pulses create a shock-wave that causes fragmentation of both urethral and intrarenal stones.

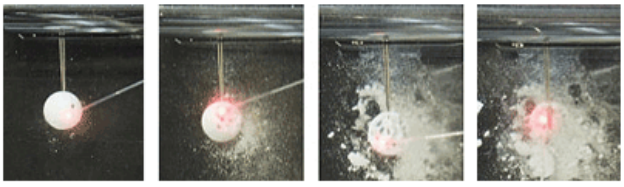

Fig7. Laser Lithotripsy (dornier MedTech) http://www.dornier.com/unitedstates/clinical-solutions/urology/kidney-stones/laser-lithotripsy-procedure/

5. Limitations and considerations

Various laser types can be used interchangeably. Which one is used depends on several factors, including patients concerns, what the research reveals in terms of efficacy and safety, reliability and optical behaviour in transmission medium. In most applications, more than one type of laser is equally suitable for the same concern; all of the various options can have their own pros and cons. The unique properties of laser light, including monochromicity, coherence, collimation, and high power, are the basis for the therapeutic applications of laser energy. The ability to control energy, power fluence, and irradiance are of paramount importance when considering specific clinical uses. Therefore a better understanding of the behaviour of each laser type is very important in choosing the right laser type for optimum result.

A second issue that should be taken into consideration is in regard to accessibility of body tissue to be targeted with laser therapy. Light unlike ionizing radiation cannot penetrate deeply into tissue and hence it can be only used for shallow ailments. That is it can be used for issues very close to the skin and also issues that arise on the surface of organs. However, in this scenario the organ have to be accessed. This obligates the development of better delivery system(fibre optic and wave guides) and imaging guidance of the delivery system. In addition fibre optic currently used are not capable of transmitting high energy density pulsed laser light. This restricts their scope of application which require photo disruptive and ablative interactions.

Third consideration and a limiting factor in the application of laser treatment is the deficiency in understanding of laser tissue interaction. This is in regard to all modes of interaction. In applications involving photo thermal interaction understanding of various tissues absorption and scattering interaction with particular wavelengths is the starting point for developing laser therapy. However in terms of safety and accuracy of laser treatment understanding the heat distribution and penetration depth is very important.

Although there is a growing understanding of the mechanism through which photodisruptive and ablative tissue vaporization occur there are still gaps in understanding in the research world. For example (Vogel, Venugopalan 2003) in their highly cited literature review regarding laser tissue interaction, they mention that "further investigations are needed to better characterize both the changes of tissue properties during pulsed laser irradiation and the dynamics of tissue deformation, fracture, and material ejection". This indicates that the lack of clear understanding could be hindering novel ways of treating various ailments.

In addition there are only few photosensitizer that are approved by regulatory bodies in various parts of the world. These only have application in a number of cancer treatments and as such with discovery of new photosensitizer treatment for diseases can be found. In addition the fact that some photosensitizer may be selective enough might decrease their chance in medical application.

6. Future of laser therapy: Outlook

Laser's therapeutic application is diverse and is still growing. One of the interesting aspects of laser light is that it can be generated at a wide range of wavelength spectrum with a different depth of penetration in human tissues. Tissue composition, which is different from one tissue to another, means that the diversity of laser types will be a boost on their adoption in the treatment room. In addition, more than one kind of laser source can generate a specific wavelength with various power output ranges.

Therefore, having a wide diversity of laser sources could be a significant development which will make laser therapy more accurate. In my opinion, a more modular approach of laser system development will be the future of laser treatment. In a modular system various laser types can be combined to a specific delivery system to treat different tissues according to the need. This approach decreases the cost of developing whole systems which are designed to address a particular application area.

A better understanding of various tissue interactions to laser light will also play a significant role in the adoption of laser treatment. In addition, research on photosensitizer development will also increase the popularity and use of PDT.

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"NUCLEAR MEDICINE IN IMAGE GUIDED PROCEDURE:REVIEW AND OUTLOOK"

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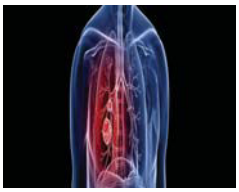
Introduction

Observation in Image guided procedures by PET/ SPECT

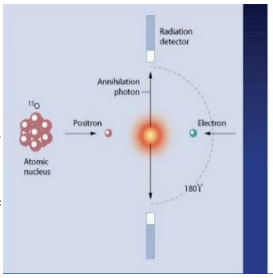


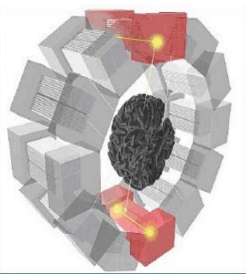
Mammography image of PET / CT

Image for Full body scan : PET

Technology + Motivation

- Start of procedure by injection of a small radiopharmaceutical into patient's body.
- Radioactive reactions inside body duplicate defects such as signs of cancer or any malignant diseases
- The PET & CT together provide information about the location, nature of, and the extent of the diagnosed cancer





Methods

Testing starts with small amounts of radiopharmaceuticals being introduced into the body by injection, swallowing, or inhalation Radiopharmaceuticals are substances that are attracted to specific organs, bones, or tissues. The amount of radiopharmaceutical used is carefully selected to provide the least amount of radiation exposure to the patient but ensure an accurate test.
A special camera (PET, SPECT or gamma camera) is then used to take pictures of your body. The camera detects the radiopharmaceutical in the organ, bone or tissue and forms images that provide data and information about the area in question. Nuclear medicine differs from an x-ray, ultrasound or other diagnostic test because it determines the presence of disease based on biological changes rather than changes in anatomy.

Radio Pharmaceuticals of importance

CHEMI CAL FORM	HALF LIFE	DIAGNOSTI C USE
Carbon- 11 Chlorine	20.334 min	prostate cancer recurrence
Fluorine -18 sodium fluoride	109.771 min	PET bone imaging agent to delineate areas of altered osteogenesis
Fluorine -18 fludeoxy glucose	109.771 min	A PET imaging agent to: Assess abnormal glucose metabolism in oncology
Iodine– 123 Ioflupan e	13.22 hours	SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS

PET & SPECT Comparison

PET	SPECT
Cyclotron or special generators	Gamma emitting radio isotope
Helpful to locate larger and aggressive tumors	Longer life radio isotopes
Difficult to locate tumors less than 8 mm	Less contrast and special resolution
Gives molecular and anatomical information	Lower cost than PET
Measures blood flow, oxygen usage and sugar metabolism	Helps to determine glucose, fatty acids, bone imaging and cerebral blood flow
PET with CT gives normal cellular activities	SPECT with CT facilitates correction of attentuation, scatter and partial volume errors

Limitations and Future outlook

LIMITATIONS
- ➢ Minimization of radiation dose.
- ➢ Short lived radio pharmaceuticals
- ➢ High cost cyclotrons
- ➢ Difficult to prepare radio isotopes

FUTURE OUTLOOK
- ➢ Metabolic imaging
  - ➢ Myocardial intermediately metabolism
- ➢ Solid State multi detector SPECT
  - ➢ High Sensitivity and capability

PET/CT scan

Parameters

Parameters	Comparison
Cost	PET > SPECT
Availability	SPECT > PET
Spatial resolution	PET > SPECT
Temporal resolution	PET > SPECT
Sensitivity	PET > SPECT
Signal and noise ratio	PET > SPECT

Conclusion

Both SPECT and PET has its own advantages and disadvantages in nuclear medicine. Even though it has limitations and drawbacks the technology is widely used nowadays and has good scope in future as well. Nuclear medicine has brought the world to a very distinct level of knowledge especially till the molecular level which really helps to find out various undefined parameters and diseases in medicine. PET and SPECT in combination with CT is made an evolution for new findings.

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NUCLEAR MEDICINE IN IMAGE GUIDED PROCEDURE:REVIEW AND OUTLOOK

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Abstract: Nuclear Medicine in image guided procedure is the cutting edge technology in medicine. This pave the way to an era of precise knowledge about certain un-curable and deadly diseases which made life simple and more secure from the past. Radio-pharmaceuticals with equipment such as PET and SPECT gives molecular level information turns the medical world knowledge to a great extent. Today both the techniques are milestones for the molecular imaging modalities. These technologies so far overcome the major drawbacks faced by the CT and MRI . This paper discuss about the various aspects, technologies , applications along with the limitations and the future of nuclear medicine technical modalities in image guided procedures. Moreover we will discuss about various parameters which influence the imaging procedures and its complexities.

Keywords : IGP , IGS

Abbreviations :

IGP :Image Guided Procedures
IGS :Image Guided Surgery

I. INTRODUCTION

Nuclear medicine procedure is sometimes described as an "inside-out" x-ray because it records radiation emitting from the patient"s body rather than radiation that is directed through the patient"s body.

Nuclear medicine procedures use small amounts of radioactive materials, called radiopharmaceuticals, that are attracted to specific organs, bones or tissues. As the radiopharmaceutical travels through the body, it produces radioactive emissions. A special type of camera detects these emissions in the organ, bone or tissue being imaged and then records the information on a computer screen or on film.

Nuclear medicine is unique because it shows how organs and tissues are working. For example, nuclear medicine allows physicians to see how a kidney is functioning, not just what it looks like. Most other diagnostic imaging tests, such as x-ray exams, reveal only anatomical structure.

Apart from the CT or MRI images it gives molecular level

information which helps the physicians to analyze the cellular reactions the formations. This will gives a clear picture of various cancerous tissues. [1]

There are more than 100 different nuclear medicine examinations to assess organ function. A thyroid uptake study shows how well the thyroid gland is working. A cardiac stress-rest test shows blood flow to the heart and helps your physician detect coronary artery disease.

II.RADIOPHARMACEUTICAL

A Radiopharmaceutical is a drug that can be used either for diagnostic or therapeutic purposes. It is composed of a radioisotope bond to an organic molecule. The organic molecule conveys the radioisotope to specific organs, tissues or cells. The radioisotope is selected for its properties.
Radioisotopes emitting penetrating gamma rays are used for diagnostic (imaging) where the radiation has to escape the body before being detected by a specific device (SPECT/PET cameras). Typically, the radiation emitted by isotope used for imaging vanishes completely after 1 day through radioactive decay and normal body excretion. The most common isotopes for imaging are:99mTc, I-123, I-131, Tl201, In111 and F18.[2]

Radioisotopes emitting short range particles (alpha or beta) are used for therapy due to their power to lose all their energy over a very short distance, therefore causing a lot of local damage (such as cell destruction). This property is used for therapeutic purposes: cancer cells destruction, pain treatment in palliative care for bone cancer or arthritis. Such isotopes stay longer in the body than imaging ones; this is intentional in order to increase treatment efficiency, but this remains limited to several days. The most common therapeutic isotopes are**:** I131, Y90, Rh188 and Lu177.[2]

Manufacturing such radio labeled molecules requires pharmaceutical industry expertise within the safety constraints of a nuclear facility. Therefore, such a facility must comply with the Good Manufacturing Practice of the pharmaceutical industry while at the same time adhering to the As Low As Reasonably Achievable principle of the nuclear industry, aimed at protecting the workers, the environment and the patient. The largest facilities for producing radiopharmaceuticals are located in Europe and North America.

Before being accessible for routine clinical use, the radiopharmaceutical has to demonstrate its harmlessness for the patient and its benefit for the treatment, like any classical drug. This demonstration process is strictly regulated by the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe. The typical duration for such a process is typically 5 to 8 years, from the initial discovery to the availability for the physicians.

II. LIST OF RADIOPHARMACEUTICALS

NAME	CHEMICAL SYMBOL	CHEMICAL FORM	HALF LIFE	DIAGNOSTIC USE
CARBON-11	11C	Carbon-11 Choline	20.334 minutes	prostate cancer recurrence
CARBON-14	14C	Carbon-14 urea	5,730 years	H.pylori infection in the stomach
FLUORINE-18	18F	Fluorine-18 florbetapir	109.771 minutes	elevated blood prostate specific antigen (PSA)
FLUORINE-18	18F	Fluorine-18 sodium fluoride	109.771 minutes	PET bone imaging agent to delineate areas of altered osteogenesis
FLUORINE-18	18F	Fluorine-18 fludeoxyglucose	109.771 minutes	As a PET imaging agent to: Assess abnormal glucose

				metabolism in oncology
GALLIUM-67	67Ga	Gallium-67 Gallium Citrate	3.26 days	Hodgkin's disease Lymphoma Bronchogenic carcinoma Aid in detecting some acute inflammatory lesions
INDIUM-111	111In	Indium-111 Capromab Pendetide	2.80 days	A diagnostic imaging agent in post-prostatectomy patients with a rising PSA and a negative or equivocal standard metastatic condition
INDIUM-111	111In	Indium-111 Oxyquinoline	2.80 days	For radiolabeling autologous leukocytes which may be used as an adjunct in the detection of inflammatory processes to which leukocytes migrate, such as those associated with abscesses or other infection
IODINE-123	123I	Iodine-123	13.22 hours	Neuroendocrine tumor
		Iobenguane		imaging.
IODINE- 123	123I	Iodine–123 Ioflupane	13.22 hours	SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS
IODINE- 125	125I	Iodine–125 Human serum albumin	59.4 days	Indicated for use in the determination of: • Total blood • Plasma volume

III. PROCEDURE

Nuclear medicine tests are safe and painless. In a nuclear medicine test, small amounts of radiopharmaceuticals are introduced into the body by injection, swallowing, or inhalation.

Radiopharmaceuticals are substances that are attracted to specific organs, bones, or tissues. The amount of radiopharmaceutical used is carefully selected to provide the least amount of radiation exposure to the patient but ensure an accurate test.

A special camera (PET, SPECT or gamma camera) is then used to take pictures of your body. The camera detects the radiopharmaceutical in the organ, bone or tissue and forms images that provide data and information about the area in question. Nuclear medicine differs from an x-ray, ultrasound or other diagnostic test because it determines the presence of disease based on biological changes rather than changes in anatomy.

IV. SAFETY

Nuclear medicine procedures are among the safest diagnostic imaging exams available. To

obtain diagnostic information, a patient is given a very small amount of a radiopharmaceutical. Because such a small amount is used, the amount of radiation received from a nuclear medicine procedure is comparable to, or often times less than, that of a diagnostic x-ray. The nuclear medicine team will carefully perform the most appropriate examination for the patient‟s particular medical problem and thereby avoid any unnecessary radiation exposure. Although we don‟t think much about it, everyone is continually exposed to radiation from natural and manmade sources. [3]

For most people, natural background radiation from air and space, rocks, soil, and even atoms in your own body, accounts for 85 percent of the radiation you receive annually. Additional exposure to radiation comes from consumer products such as household smoke detectors, color television sets, and luminous clock dials. The remaining radiation is from x-rays and radioactive materials used for medical diagnosis and therapy. Most nuclear medicine procedures expose patients to about the same amount of radiation as they receive in a few months of normal living.

Nuclear imaging uses low doses of radioactive substances linked to compounds used by the body's cells or compounds that attach to tumor cells. Using special detection equipment, the radioactive substances can be traced in the body to see where and when they concentrate. Two major instruments of nuclear imaging used for cancer imaging are PET and SPECT scanners.[3]

V. SCANNING METHODOLOGY

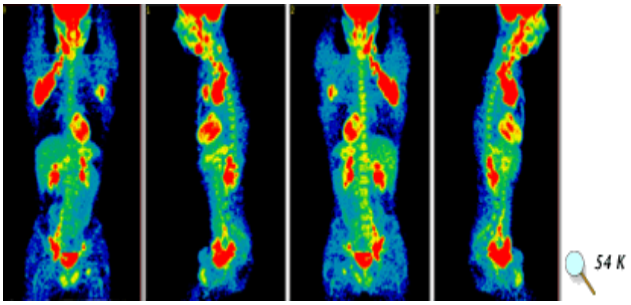
1) PET Scan

The positron emission tomography (PET) scan creates computerized images of chemical changes, such as sugar metabolism, that take place in tissue. Typically, the patient is given an injection of a substance that consists of a combination of a sugar and a small amount of radioactively labeled sugar. The radioactive sugar can help in locating a tumor, because cancer cells take up or absorb sugar more avidly than other tissues in the body.

After receiving the radioactive sugar, the patient lies still for about 60 minutes while the radioactively labeled sugar circulates throughout the body. If a tumor is present, the radioactive sugar will accumulate in the tumor. The patient then lies on a table, which gradually moves through the PET scanner 6 to 7 times during a 45-60-minute period.

The PET scanner is used to detect the distribution of the sugar in the tumor and in the body. By the combined matching of a CT scan with PET images, there is an improved capacity to discriminate normal from abnormal tissues. A computer translates this information into the images that are interpreted by a radiologist.[4]

PET scans may play a role in determining whether a mass is cancerous. However, PET scans are more accurate in detecting larger and more aggressive tumors than they are in locating tumors that are smaller than 8 mm and/or less aggressive. They may also detect cancer when other imaging techniques show normal results.



PET scans. Uptake of tracer in the lymph nodes involved with lymphoma in the groin, both axilla, and neck (red areas). Image courtesy of Dr. Jorge Carrasquillo, Nuclear Medicine Department, Clinical Center, National Institutes of Health.

Nuclear medicine imaging procedures are noninvasive and, with the exception of intravenous injections, are usually painless medical tests that help physicians diagnose and evaluate medical conditions. These imaging scans use radioactive materials called radiopharmaceuticals or radiotracers.

Depending on the type of nuclear medicine exam, the radiotracer is either injected into the body, swallowed or inhaled as a gas and eventually accumulates in the organ or area of the body being examined. Radioactive emissions from the radiotracer are detected by a special camera or imaging device that produces pictures and provides molecular information.[3]

In many centers, nuclear medicine images can be superimposed with computed tomography (CT) or magnetic resonance imaging (MRI) to produce special views, a practice known as image fusion or co-registration. These views allow the information from two different exams to be correlated and interpreted on one image.

A PET scan measures important body functions, such as blood flow, oxygen use, and sugar (glucose) metabolism, to help doctors evaluate how well organs and tissues are functioning.CT imaging uses special x-ray equipment, and in some cases a contrast material, to produce multiple images or pictures of the inside of the body. These images can then be interpreted by a radiologist on a computer monitor. CT imaging provides excellent anatomic information.

Today, almost all PET scans are performed on instruments that are combined PET and CT scanners. The combined PET/CT scans provide images that pinpoint the anatomic location of abnormal metabolic activity within the body. The combined scans have been shown to provide more accurate diagnoses than the two scans performed separately.

Machinery and Working


[5]

A PET scanner is a large machine with a round, doughnut shaped hole in the middle, similar to a CT or MRI unit. Within this machine are multiple rings of detectors that record the emission of energy from the radiotracer in your body.

The CT scanner is typically a large, box-like machine with a hole , or short tunnel, in the centre. The patient will lie on a narrow examination table that slides into and out of this tunnel. Rotating around you, the x-ray tube and electronic x-ray detectors are located opposite each other in a ring, called a gantry. The computer workstation that processes the imaging information is located in a separate control room, where the technologist operates the scanner and monitors your examination in direct visual contact and usually with the ability to hear and talk to you with the use of a speaker and microphone.

As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, an antiparticle of the electron with opposite charge. The emitted positron travels in tissue for a short distance (typically less than 1 mm, but dependent on the isotope), during which time it loses kinetic energy, until it decelerates to a point where it can interact with an electron.

The encounter annihilates both electron and positron, producing a pair of annihilation (gamma) photons moving in approximately opposite directions. These are detected when they reach a scintillator in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD). The technique depends on simultaneous or coincident detection of the pair of photons moving in approximately opposite directions (they would be exactly opposite in their center of mass frame, but the scanner has no way to know this, and so has a built-in slight direction-error tolerance). Photons that do not arrive in temporal "pairs" (i.e. within a timing-window of a few nanoseconds) are ignored. [7]

Positron emission tomography (PET)

- very expensive
- uses positron emitting radioisotope (tracer) 18F
- better contrast and spatial resolution

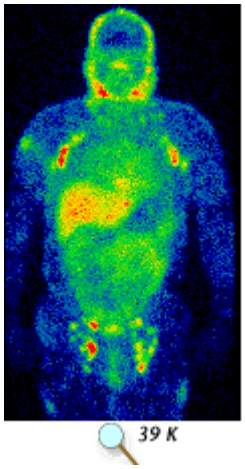
B. SPECT Scan

As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, an antiparticle of the electron with opposite charge. The emitted positron travels in tissue for a short distance (typically less than 1 mm, but dependent on the isotope), during which time it loses kinetic energy, until it decelerates to a point where it can interact with an electron.

The encounter annihilates both electron and positron, producing a pair of annihilation (gamma) photons moving in approximately opposite directions. These are detected when they reach a scintillator in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD).[6]

The technique depends on simultaneous or coincident detection of the pair of photons moving in approximately opposite directions (they would be exactly opposite in their center of mass frame, but the scanner has no way to know this, and so has a built-in slight direction-error tolerance). Photons that do not arrive in temporal "pairs" (i.e. within a timing-window of a few nanoseconds) are ignored.

PET will always gives the isolated images which really helps for the interventional procedures such as biopsy.



SPECT scan. High levels of antibody in pelvis and axilla (red) and uptake in skin of the thigh and right shoulder (green) showing areas of cutaneous T-cell lymphoma. Image courtesy of Dr. Jorge Carrasquillo , Nuclear Medicine Department, Clinical Center, National Institutes of Health.

Single-photon emission computed tomography (SPECT)

- lower cost
- uses gamma emitting radioisotope (tracer)
- technetium-99m
- iodine-123
- iodine-131
- less contrast and spatial resolution (c.f. PET)

VI. COMPARISON OF PET AND SPECT

The most important advantage of PET imaging over SPECT is that of exhibiting a much higher sensitivity (by approximately two to three orders of magnitude); i.e., the ability to detect and record a higher percentage of the emitted events, which has very important implications (see coincident detection in PET subsection). This is because, in single-photon imaging (planar and SPECT), physical collimators are needed in order to reject photons that are not within a small angular range (otherwise the angle of incidence will not be known).[8]

Collimators therefore exhibit low geometric efficiencies (defined as the percentage of detected

to emitted photon), of the order of B0.01%. On the other hand, SPECT offers the possibility to widen the observational time window (owing to the longer half life of single photon emitters) thus allowing biomedical scientists to observe biological processes in vivo several hours or days after administration of the labeled compound(1)

VII. LIMITATIONS

The minimization of radiation dose to the subject is an attractive feature of the use of short-lived radionuclides. Besides its established role as a diagnostic technique, PET and SPECT has an expanding role as a method to assess the response to therapy, especially cancer therapy, where the risk to the patient from lack of knowledge about disease progress is much greater than the risk from the test radiation.

Limitations to the widespread use of PET arise from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning and the need for specially adapted on-site chemical synthesis apparatus to produce the radiopharmaceuticals after radioisotope preparation.

Organic radiotracer molecules that will contain a positron-emitting radioisotope cannot be synthesized first and then the radioisotope prepared within them, because bombardment with a cyclotron to prepare the radioisotope destroys any organic carrier for it. Instead, the isotope must be prepared first, then afterward, the chemistry to prepare any organic radiotracer (such as FDG) accomplished very quickly, in the short time before the isotope decays. Few hospitals and universities are capable of maintaining such systems, and most clinical PET is supported by third-party suppliers of radiotracers that can supply many sites simultaneously.

This limitation restricts clinical PET primarily to the use of tracers labelled with fluorine-18, which has a half-life of 110 minutes and can be transported a reasonable distance before use, or to rubidium-82 with a half-life of 1.27 minutes, which is created in a portable generator and is used for myocardial perfusion studies. Nevertheless, in recent years a few on-site cyclotrons with integrated shielding and „hot labs" have begun to accompany PET units to remote hospitals. The presence of the small on-site cyclotron promises to expand in the future as the cyclotrons shrink in response to the high cost of isotope transportation to remote PET machines. In recent years the shortage of PET scans has been alleviated in the US, as rollout of radio pharmacies to supply radioisotopes has grown 30%/year.

Because the half-life of fluorine-18 is about two hours, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent calibration of the remaining dose and careful planning with respect to patient scheduling.

VIII. FUTURE OUTLOOK

1.Metabolic Imaging

The primary emphasis of metabolic imaging in clinical practice has been in the study of myocardial intermediary metabolism, using either PET or SPECT imaging.

Several different radiolabeling strategies have been employed for clinical PET imaging of metabolism. The most widely used PET imaging approach is to radiolabel a substrate analog with fluorine-18 (18F). The best example in this category is 2-[18F] fluoro-2-deoxy-D-glucose (FDG). Evaluation of the myocardial kinetics of FDG provides an in vivo approach for imaging glucose uptake by the myocardium, but can also track myocardial or vascular inflammation.

Several 18F-labeled PET agents have been proposed for evaluation of fatty acid metabolism that would have the potential for widespread metabolic imaging of the heart. These agents have already entered into clinical trials. The

evaluation of different patterns of myocardial glucose and fatty acid metabolism with these 18F-labeled agents may have important diagnostic, prognostic, and therapeutic implications for management of patients with cardiovascular disease.[7]

Alternatively, naturally occurring metabolic substrates can be radiolabeled in specific carbon locations with carbon-11, such as various fatty acids (1-11C-palmitate or 1-11C-acetate), glucose (1-11C-glucose), and lactate (l-3-11C-lactate). An advantage of this approach is that the metabolism of the radiolabeled substrate is identical to the unlabeled substrate. With the application of appropriate mathematical modeling schemes, the myocardial uptake and downstream metabolism of these substrates can be assessed in vivo. Disadvantages of this approach relate to the limitation of radiolabeling with 11C, including the requirement for an onsite cyclotron and advanced radiochemistry capabilities. Both of these issues have significantly limited the widespread clinical utilization of the 11C PET imaging approaches.[7]

SPECT radiolabeled tracers have also been utilized to assess myocardial glucose and fatty acid metabolism, and offer practical clinical advantages. One of the first successful SPECT approaches for evaluation of oxidative fatty acid metabolism involved the use of 15-(p-iodophenyl)-pentadecanoic acid (IPPA), which contains an aromatic ring at the omega position radiolabeled with radioiodine.

Unfortunately, conventional SPECT imaging systems did not have the sensitivity or temporal resolution to effectively evaluate the rapid kinetics of IPPA, and this approach was never widely applied. This limitation may disappear with the recent introduction of solid-state multidetector SPECT systems that provide high sensitivity and the capability for dynamic "PET-like" imaging.

An alternative solution to the challenges associated with rapid clearance kinetics of IPPA was the development of branched-chain analogs of IPPA, such as 123I-beta-methyl-p-iodophenylpentadecanoic acid (BMIPP). Alkyl branching inhibited beta-oxidation, thereby increasing radiotracer retention and improving SPECT image quality. It recently reported the results of a large multicenter clinical trial that applied BMIPP SPECT imaging for the detection of acute myocardial ischemia in patients presenting to the emergency department with chest pain.

This molecular-based metabolic imaging approach provided comparable sensitivity to other imaging approaches, while providing incremental value in the early detection of acute coronary syndrome and a retained performance even after resolution of symptoms. Thus, metabolic imaging may offer unique advantages over more conventional imaging of regional myocardial function or perfusion. The existing technical limitations of SPECT image quantification may be overcome with the availability of hybrid SPECT/CT imaging systems that facilitate correction of attenuation, scatter, and partial volume errors, allowing for determination of absolute radiotracer retention.

Metabolic imaging is likely to play an important role in the evaluation and management of ischemic myocardial injury, hypertrophic heart disease, and heart diseases associated with diabetes and obesity, and complement conventional imaging of perfusion and function.

2.Neuro-receptor Imaging

Another classic targeted molecular imaging approach that has entered multicenter clinical trials involves the imaging of cardiac neuroreceptors in the heart. This work has primarily focused on in vivo imaging of sympathetic function in the myocardium.

Important alterations in pre- and post-synaptic cardiac sympathetic function occur in several cardiovascular diseases, including ischemic heart disease and heart failure, and may be predictive of risk for sudden cardiac death or death from heart failure, as well as for response to

therapeutic interventions. Pre-synaptic function can be measured using radiolabeled norepinephrine analogs such as 11C-meta-hydroxyephedrine (11C-HED), a PET radiotracer, or 123I-meta-iodobenzylguanidine (123I-MIBG), a SPECT radiotracer. Post-synaptic function can be assessed with 11C-CGP12177, a radiolabeled beta-blocker for PET imaging.

Many clinical studies have demonstrated that 123I-MIBG SPECT imaging provides powerful diagnostic and prognostic information in patients with heart failure. In these patients with heart failure, 123I-MIBG scans typically show a reduced heart–mediastinum uptake ratio, heterogeneous distribution within the myocardium, and increased 123I-MIBG washout from the heart. A large, prospective, industry-sponsored trial, the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study of 123I-MIBG imaging for risk stratification of patients with symptomatic heart failure on contemporary therapy was recently published (4), and demonstrated a highly significant relationship between the time to heart failure–related events and the heart-to-mediastinal ratio, which was independent of other commonly measured parameters such as left ventricular ejection fraction (LVEF) and B-type natriuretic peptide (BNP). This clinical study also showed a clear association between severity of myocardial sympathetic neuronal dysfunction and risk for subsequent cardiac death (4).

If the value of cardiac autonomic assessment using 123I-MIBG or 11C-HED imaging in combination with other conventional or molecular imaging indexes is confirmed, this neuroreceptor imaging approach may help in the selection of patients who would benefit the most from an implantable cardioverter-defibrillator by means of identification of those at increased risk for potentially fatal arrhythmias, leading to more cost-effective implementation of this life-saving device.[9]

Molecular imaging in the future with expanded clinical impact

Molecular imaging is moving forward in many other areas relevant to the cardiovascular system. Some of these approaches involve targeted imaging of critical biological processes associated with cardiovascular disease, including inflammation, thrombosis, angiogenesis, apoptosis, necrosis, fibrosis, atherosclerosis, and remodeling. Figure 1 summarizes the complex cascade of events associated with the progression from early to advanced atherosclerosis, ischemic injury, and subsequent post-infarction remodeling, along with some of the potential molecular targets for imaging these molecular processes in temporal relation to conventional imaging approaches that focus on evaluation of physiology and changes in anatomic structure. Many probes targeted at these processes remain under development, although some have already reached clinical testing, or have even completed clinical testing and have received FDA approval

IX. CONCLUSION

Both SPECT and PET has its own advantages and disadvantages in nuclear medicine. Even though it has limitations and drawbacks the technology is widely used nowadays and has good scope in future as well. Nuclear medicine has brought the world to a very distinct level of knowledge especially till the molecular level which really helps to find out various undefined parameters and diseases in medicine. PET and SPECT in combination with CT is made an evolution for new findings.

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Brain tumor resection using IIGP:

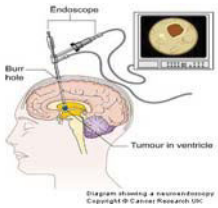
Introduction: Neurosurgery was the first surgical discipline to adopt image guidance. Why Image guidance during surgery? Preoperative scan display of tumour location differs from the actual location as craniotomy shifts the brain.

Types of Treatment
- Surgery
- Radiation therapy

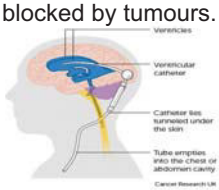
Surgery

1.)Guided Biopsy- CT or MRI used to guide to the location of tumour.
2.) 5-ALA- chemical used to florescence the tumour cells.
3.) Ultrasonic Aspiration: Use of ultrasonic waves to break down the tumour.

4.)Neuroendoscopy



5.)Ventricular access devices using shunts:A reservoir to drain the CSF blocked by tumours.



A needle is put into the reservoir to drain the CSF to relieve the pressure.(5)

Radiation Therapy:

1.)Stereotactic Radiosurgery: A head frame has fiducials marked on the brain to realize where the tumour is located and then high dose of radiation is given to the tumour.
Can be used with:
- Linear accelerator: using high energy particles.
- Gamma knife: uses gamma rays
- Cyber knife: robotic device to guide to the tumour target.

Patient undergoing stereotactic radiosurgery(7)

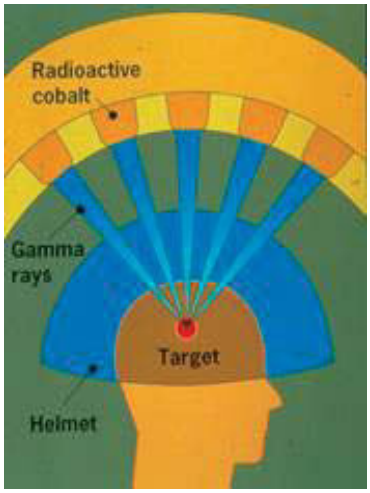
Stereotactic frame(7)

2.)3D CT Radiosurgery: irradiating a tumor target volume defined in a 3D anatomical image of the patient with a set of x-ray beams individually shaped to conform to the 2D beam's-eye-view (BEV) projection of the target.

3.)Proton Therapy: High energy protons destroy cancer cells

4.)Intensity Modulated Radiation Therapy: Radiation Beam broken into smaller intensified beams.

5.)Brachytherapy



Stereotactic radiation(5)

What is the future?

1.)Frameless, armless stereotactic wand for brain tumour localization.

2.)3-D neuronavigation

3.)Resection using molecular imaging.

4.)GliaSite Radiation Therapy System-balloon placed near tumour in which radiation is delivered.

5.) Laser Interstitial Therapy: MRI guided laser to cause thermal injury to tomour.

6.)Robotics for resection: neuroARM designed in Canada, ROSA from MEDTECH.

ROSA(7)

Conclusion

Neurosurgery limits to deep seated tumours; radiation therapy entails high dose of radiation; stereotactic radiosurgery used for small tumours; surgery with adjuvant therapy is the most successful treatment.

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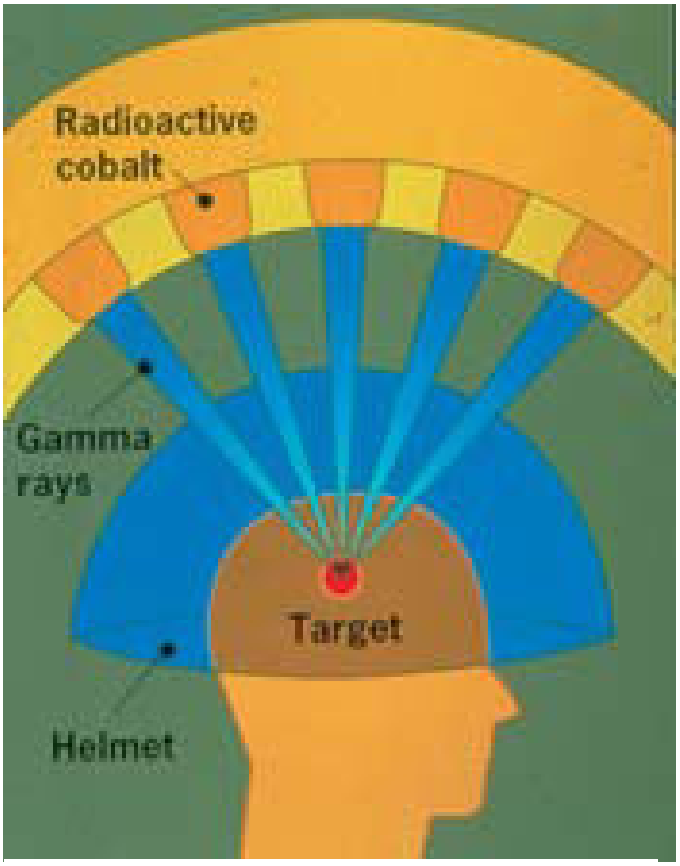
INNOPROFILE UNTERNEHMEN REGION

Bundesministerium für Bildung und Forschung

Prof. Michael Friebe
CHAIR CATHETER TECHNOLOGIES
+ IMAGE GUIDED THERAPIES



Stereotactic radio surgery, source: http://www.oncolink.org/types/article.cfm?id=9536

Brain Tumour Resection using IGP

WHAT IS POSSIBLE AND WHAT CAN BE POSSIBLE?

GUTHA VAISHNAVI REDDY | MEDICAL SYSTEMS ENGINEERING | DECEMBER 17, 2015

Abstract

Neurosurgery was the first surgical discipline to adopt image guidance in any concerted manner, and the first application was for minimally invasive procedures. Image guided neurosurgery is well established and is successfully used in everyday neural applications. Tumour surgery requires craniotomy under whose conditions, the pressure equilibrium inside the cranial vault is changed and significant brain shift may occur. This means that the position of the tumour as indicated on the preoperative scan no longer represents the actual position of the lesion. This again means that surgery of this nature can only be performed with real time image guidance. The report presents different types of brain tumour resection using image guided procedures which are broadly treated in three ways using: Surgery, Radiotherapy and Chemotherapy.

Introduction:

There are about 130 different types of brain tumours. They are generally named after the type of cell they are developed from. The central nervous system consists of neurons and glial cells. Neurons constitute about half the volume of the CNS and glial cells make up the rest. Glial cells provide support and protection for neurons. Most brain tumours develop from the cells that support the nerve cells of the brain called glial cells. A tumour of glial cells is a glioma. ***Today nearly 700,000 in the United States are living with a primary brain tumor, and more than 69,000 others will be diagnosed this year***. Some types of brain tumours grow rapidly; other tumours grow slowly. Successfully treating brain tumours can be challenging. The body's blood-brain barrier normally protects the brain and spinal cord from harmful chemicals entering those structures through the bloodstream. The main method used against brain tumours is Surgery. Most of the tumour cells are manually surgically removed. Image guided techniques are used to pin point and painstakingly resolve the location of these tumour cells. Surgery is enough for low grade tumours and adjuvant treatment can be supplemented for high grade tumours. Additional treatment options for high-grade tumours include:

- **Radiation therapy:** X-rays and other forms of radiation can destroy tumour cells or delay tumour growth.
- **Chemotherapy:** The use of drugs to kill rapidly dividing cells. It can be taken orally or intravenously.
- **Targeted therapy:** The focus on a specific element of a cell,

such as molecules or pathways required for cell growth, in order to use them as a target.

- **Tumour Treating Fields:** (A wearable device) Locally or regionally delivered treatment that produces electric fields to disrupt the rapid cell division exhibited by cancer cells by creating alternating, "wave-like" electric fields that travel across their region of usage in different directions. Because structures within dividing cells have an electric charge, they interact with these electric fields.

We see ahead different kinds of treatments for resection of brain tumours with image guided methods.

Surgery:

Surgery entails removing the tumour cells by cutting and opening up the brain. It involves incision with physical removal or manipulation of the diseased or injured part of the body. For brain surgery, a neurosurgeon performs craniotomy which means he removes a part of the skull and cuts the tumour off after which he uses the patient's own bone in covering the opening of the skull.

Types of Brain Surgery:

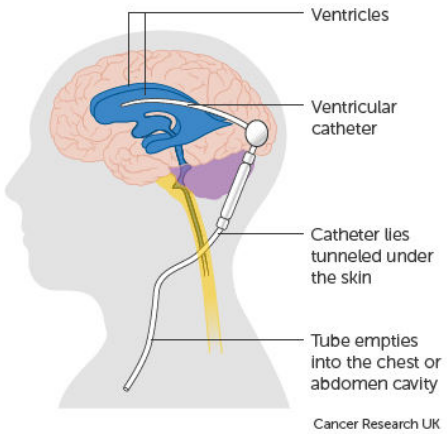
Guided Biopsy: The surgery is guided by MRI or CT scan. The scan lets the surgeon know where exactly he has to place his needle. There are two types: *Stereotactic biopsy and neuro navigation*. For stereotactic biopsy, you have a head frame fitted. Once you've had the scan, the doctors use the scan and the reference points from the head frame to work out exactly where they need to guide the needle. The surgeon makes a very small hole in the skull with a drill, as they would for any brain biopsy. Then the frame is set to guide a fine needle into exactly the right position to take the tissue sample. For neuro navigation, the surgeon takes the biopsy with a fine needle in much the same way. But you don't wear a head frame, instead a computerized system, into which a planning scan has been loaded, helps the surgeon guide the needle into the correct position. You may have markers called fiducials stuck to your head before you have the scan. Sometimes surgeons use the natural landmarks of your nose, eyes and ears to help the computer locate the correct position.

Microsurgery: The surgeon uses a high powered microscope to discriminate between healthy and tumourous tissue.

5-ALA: 5-aminolevulvenic acid hydrochloride when taken in by glioma patients is absorbed by the tumour cells. When the brain is viewed under special light, the tumour cells glow which is called fluorescence. This helps the surgeon

to delineate the tumour and hence successfully resect it. 5-ALA is taken 3 hours before surgery. It can cause side effects such as making you more sensitive to light (photosensitivity), lower your blood pressure and affect your liver function.

Shunts: Some tumours block the normal circulation of CSF, the fluid builds up inside the skull and might lead to hydrocephalus. To drain this fluid in such conditions, shunts are used. A shunt is a drainage tube which is also called a ventricular catheter. Shunts drain away the extra fluid from the ventricles of the brain, to other parts of the body, where it is harmlessly absorbed. The most common type is the ventriculo peritoneal shunt, which is a tube from the brain ventricles into the abdomen (tummy). Another type drains the fluid into the chest cavity.



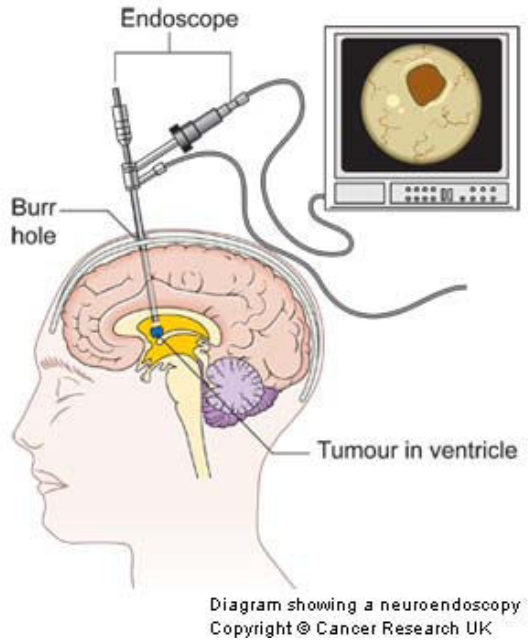
Ventricular access device, source: http://www.cancerresearchuk.org/about-cancer/type/brain-tumour/treatment/surgery/about-brain-tumour-surgery

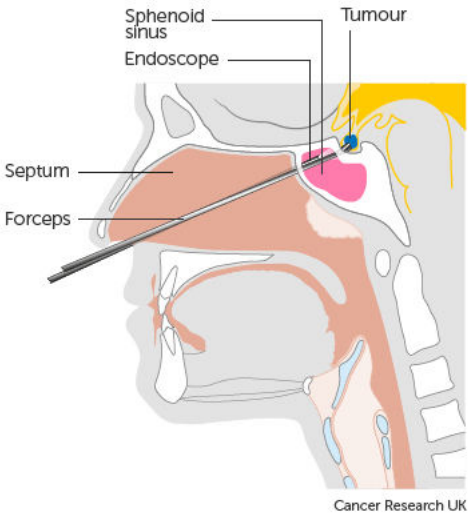
Ventricular access devices: It is a dome shaped reservoir. The device has thin tubing attached to the underside that goes into the fluid filled spaces (ventricles) of the brain. By putting a needle through your skin and into the reservoir your doctor can take away fluid to relieve pressure in the brain. Or they can use the reservoir to give access to chemotherapy drugs.

Ultrasonic aspiration: This is a procedure that uses ultrasonic waves to break down the tumour and then remove it. It produces sound waves that vibrate into the tumour and break it down. The surgeon uses a gentle suction to take out the tumour bits.

Neuroendoscopy: An endoscope is a medical device made of a long tube, camera and an eyepiece. The surgeon can see what is at the tip of the endoscope either through the eyepiece or on a TV screen. At the end of the endoscope, tiny forceps and scissors are used to cut the tumour.

Neuroendoscopy; source: http://www.cancerresearchuk.org/about-cancer/type/brain-tumour/treatment/surgery/about-brain-tumour-surgery





Removing a pituitary tumour through the nose; source: http://www.cancerresearchuk.org/about-cancer/type/brain-tumour/treatment/surgery/about-brain-

Radiation therapy:

It uses high doses of X-rays or other particles to destroy cancer cells The most common type of radiation treatment is called external-beam radiation therapy, which is radiation given from a machine outside the body. When radiation treatment is given using implants, it is called internal radiation therapy or brachytherapy. A radiation therapy regimen (schedule) usually consists of a specific number of treatments given over a set period of time. External-beam radiation therapy can be directed at the tumour in the following ways:

* **Conventional radiation therapy**: The treatment location is determined based on anatomic landmarks and x-rays. In certain situations, such as whole brain radiation therapy for brain metastases, this technique is appropriate. For more precise targeting, different techniques are needed. The amount of radiation given depends on the tumour's grade.

* **Three-dimensional conformal radiation therapy** (3D-CRT): Using images from CT and MRI scans , a three-dimensional model of the tumour and healthy tissue surrounding the tumour is created on a computer. This model can be used to aim the radiation beams directly at

the tumour, sparing the healthy tissue from high doses of radiation therapy.

* **Intensity modulated radiation therapy (IMRT)**: IMRT is a type of 3D-CRT that can more directly target a tumour, delivering higher doses of radiation to the tumour while giving less to the surrounding healthy tissue. In IMRT, the radiation beams are broken up into smaller beams and the intensity of each of these smaller beams can be changed. This means that the more intense beams, or the beams giving more radiation, can be directed only at the tumor.

* **Proton therapy**: Proton therapy is a type of external-beam radiation therapy that uses protons rather than x-rays. At high energy, protons can destroy cancer cells. Proton beam therapy is typically used for tumours when less radiation is needed because of the location. This includes tumours that have grown into nearby bone, such as the base of skull, and those near the optic nerve.

Stereotactic radiosurgery: Stereotactic radiosurgery is the use of a single, high dose of radiation given directly to the tumour and not healthy tissue. It works best for a tumour that is only in one area of the brain and certain noncancerous tumours, but it can also be used when a person has more than one metastatic brain tumour. There are many different types of stereotactic radiosurgery equipment, including:

* A modified linear accelerator is a machine that creates high-energy radiation by using electricity to form a stream of fast-moving subatomic particles.

* A gamma knife is another form of radiation therapy that concentrates highly focused beams of gamma radiation on the tumour.

* A cyber knife is a robotic device used in radiation therapy to guide radiation to the tumour target—particularly in the brain, head, and neck regions.

Frame of a stereotactic radiosurgery; source: http://www.cancerresearchuk.org/about-cancer/type/brain-tumour/treatment/radiotherapy/stereotactic-radiotherapy-for-brain-tumours

This technique is used for tumours located close to sensitive structures, such as the optic nerves or brain stem.

* **3D CT radiosurgery** : In general, 3D conformal radiation therapy (3DCRT) is a method of irradiating a tumour target volume defined in a 3D anatomical image of the patient with a set of x-ray beams individually shaped to conform to the 2D beam's-eye-view (BEV) projection of the target. The reduction in normal tissue irradiation when moving from 2D to 3D should theoretically improve the therapeutic ratio and allow the tumour target volume to be treated to a higher dose, thereby improving the probability of tumour control.

Future:

There has been use of a frameless , armless stereotactic wand for Brain tumour localization with two dimensional and three dimensional neuroimaging, neuronavigation using three dimensional ultrasound, flouroscence image guided brain tumour navigation with photodynamic therapy, resection using molecular imaging strategy using a new triple modality MRI photoacoustic-Raman nanoparticle, Vector Vision Neuro Navigation. A few technologies like: The GliaSite Radiation therapy system: The GliaSite RTS involves placing an inflatable balloon in the area of the brain tumour at the time of surgery; low-dose-rate radiation is delivered through a catheter (tube) into the balloon; the advantage is a shorter period of stay for post-op. It is approved by the U.S. Food and Drug Administration for usage. *Laser interstitial thermal therapy* (LITT) – This uses MRI guided laser to achieve irreversible thermal injury to the tumour tissue. This technology is

not yet available in Australia, but there are increasing cases that support the use of LITT; and Robotics for resection of the tumour are some of the new emerging technologies that can find more scope in future. One of the most innovative image-guided neurosurgery applications is the neuroArm,an MR compatible robot designed by Dr. Garnette Sutherland at Foothills Hospital in Calgary, Canada. The neuroArm comprises two remote 7-degrees-of-freedom, MR-compatible slave manipulators on a movable base designed to hold a variety of surgical tools.

Conclusion:

Conventional neurosurgery is limited in its ability to treat deep seated tumors because of the necessity of cutting through normal brain and vasculature to obtain access to the tumor. Radiation therapy carries with it the problems of high dose ionizing radiation which is both destructive to normal tissue and like chemotherapy oftentimes ineffective in stopping tumor growth. Whole brain radiotherapy is mostly used as part of palliative care when a patient has more than five metastases and showed progression on systemic central nervous system treatment therapy. Stereotactic radiosurgery is usually used in cases with less than five brain metastases. Whole brain radiotherapy has no impact on overall survival, however stereotactic radiosurgery improves overall survival in patients with one brain metastases and for those with more tumours, can help reduce steroid use and improve quality of life.

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Intra Operative Radiation Therapy Technologies & Systems - Current & Future

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INTRODUCTION – Rational for IORT

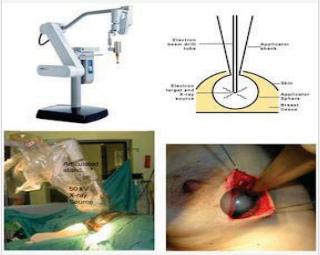
External Beam Radiation Therapy (EBRT)	➢EBRT is the current standard of care for the treatment of early-stage tumors and the survival rate has increased overall [1] ➢Women undergo post-operative EBRT for weeks consecutively. Many Patients miss therapy due to various reasons. ➢Patients usually decline RT or even choose mastectomy in order to avoid EBRT.
Intra Operative Radiation Therapy.(IORT)	➢IORT is the delivery of irradiation (>20Gy) during operation significantly reducing time(3min-45min). [2] ➢IORT focuses all dose to the tumor (1cm-2.5cm) without significantly increasing normal tissue damage. [2] ➢Given newer and lower cost treatment devices, the use of IORT in clinical practice will likely grow

INTRA OPERATIVE RADIATION

IORT - Current Systems and Technologies

Low Energy X-ray System

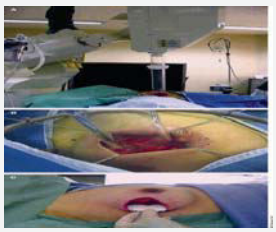
INTRABEAM


From top right (a) The INTRABEAM System (b) Application principle (c & d) during application in OT[3]

➢ Miniature system
➢Compatible with current OR
➢Lead Screens and aprons for OT staff
➢20Gy dose
➢ treatment time 20-40 mins

Intra operative Electron Beam System

NOVAC-7


The Novac-7 System (a) The arm of the mobile linear accelerator (b) Target Application (c) Lead shield between muscle and breast. [3]

➢Mobile system
➢Compatible with current OR
➢Shelf Shielded but OT staff must leave room
➢21Gy Dose
➢Treatment time 3-5 mins

High Dose Rate - After loaders

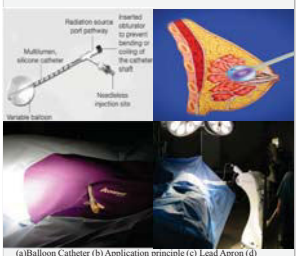
HDR - IORT


(a)The flexible Harrison-Anderson- Mick applicator used in HDR-IORT (b)HDR brachytherapy units remote after loading devices[2]

➢Mobile System
➢Dedicated OR requirements
➢Heavy shielding requirements
➢18Gy Dose
➢Treatment time 20-40 min

Catheter Technologies

Axxent Balloon Catheter


(a)Balloon Catheter (b) Application principle (c) Lead Apron (d) Axxent Electronic Balloon Brachtherapy System[4]

➢Flexible Balloon catheters
➢Compatible with any OR
➢ Lead Apron Shielding for staff
➢20Gy Dose
➢Treatment Time 20 mins

RESULTS

A Comparative Technological and Clinical trial Analysis[3][4][5][6]

Device	SOURCE	RADIATION TYPE	DOSE DEPTH AT 1 cm	APPLICATOR TYPE	CLINICAL TRIALS	LOCAL REGIONAL RECURRENCE
INTRABEAM	Miniature X-ray	50KV X-rays	5Gy	Solid Spherical	Targit-A (Phase III)	3.3% (IORT) VS 1.3% (EBRT)
NOVAC-7	Miniature Linac	Electrons at 4-12Mev	6Gy	Collimators	Eliot (Phase III)	4.4% (IORT) VS 0.4% (EBRT)
High Dose Rate Afteloader (HDR-IORT)	Iridium (192)	β- Radiation	5.8Gy	H.A.M applicator	MSKCC Evaluation (Phase I & II)	7% (IORT) = Non Radiation patient
Axxent Balloon Catheter	Miniature X-ray	50KV X-rays	9-10Gy	Balloon Spherical	1 Case only up to date	+ve post op margin over 2mm

➢20 Gy @ 1cm needed for effective IORT

➢Targit A & Eliot only Phase III trials conducted

➢HDR limited due to low Efficiency & High cost

➢Very Limited research

➢Further research data required for technology improvement & clinical implementation

➢Clear Advantages of Single dose RT

➢Complimentary & Non Inferior Status to EBRT

FUTURE OUTLOOK

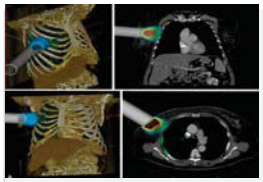
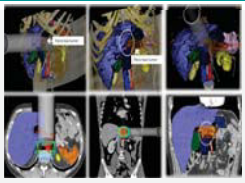
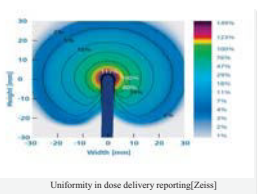


Image Guided IORT simulation[7]


Multi-tracking camera concept[7]


IORT simulation with RADIANCE[7]


Uniformity in dose delivery reporting[Zeiss]

CONCLUSION

In conclusion, in light of the existing data, IORT should be now considered as an alternative to EBRT for selected patients. The current striving is to deliver 'minimum effective treatment' to patients. Analyzing the results of research a number of limitations should be noted. Reports describing the use of IORT in Local and Regional Recurrences do not constitute sufficient evidence for all the technologies and there is a lack of evidence for comparable studies based on this research can only an engineer develop future technologies capable for delivering the results required. More focus is required on the dose accuracy and integration of Image guidance to attain more satisfactory results & for the development of optimum IORT technologies

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INNOPROFILE UNTERNEHMEN REGION
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CHAIR CATHETER TECHNOLOGIES
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Intra Operative Radiation Therapy

Technologies & Systems- Current & Future

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Instruments for Image Guided Procedure.

Abstract— Intraoperative radiation therapy (IORT) is the delivery of irradiation at the time of an operation. This is performed by different techniques which include Low-energy miniature X-ray IORT (X-ray IORT), intraoperative electron beam techniques (IOERT), high-dose rate brachytherapy (HDR-IORT), balloon devices (CATHETERS) without chemotherapy and surgical resection. IORT excludes part or all dose limiting sensitive structures to the tumor bed and the local control without significantly increasing normal tissue damage. The IORT treatment methods have improved local control as well as survival in many disease sites in both the primary and locally recurrent disease settings. More recently, there has been interest in the use of IORT as a technique of partial breast irradiation for women with early breast cancer. Given newer and lower cost treatment devices, the use of IORT in clinical practice will likely grow, with increasing integration into the treatment of nonconventional malignancies. The available methods of delivering IORT are low-energy X-ray systems, electron beam radiation therapy, high dose rate after loaders or specific balloon devices. Low-energy X-ray IORT is delivered by the Intrabeam device (Carl Zeiss, Germany). Mobile linear accelerators can deliver IOERT, Novac7 (Hitesys, Italy). High-dose-rate (HDR-IORT) afterloaders (Mick Radio-Nuclear Instruments, USA). Xoft electronic brachytherapy (eBx, Xoft, USA). Phase III randomized trials have been carried out to prove its efficacy in these disease sites. Only 2 large randomized controlled trials of intra operative radiotherapy (IORT) in breast-conserving surgery (TARGIT-A and ELIOT) have been published 14 years after their launch. Neither the TARGIT-A trial nor the ELIOT trial results have changed the current clinical practice for the use of IORT.

I. BACKGROUND

External beam radiation therapy (EBRT) following tumor resection surgery is the standard of care for the treatment of early-stage tumors. It has been shown to reduce local recurrence (LR) and improve overall survival [1-2].

Women undergoing post-operative EBRT are required to attend the radiation treatment 5 days a week for weeks consecutively. Almost one-third of patients who undergo for early breast cancer in North America do not receive post-operative breast irradiation because they live far from a treatment centre and cannot attend daily RT [3].

This issue affects patients suffering from breast cancer all over the world and is particularly challenging for the elderly people. In some countries, patients decline RT or even choose mastectomy in order to avoid EBRT [4].

IORT and some other shortened and localized radiotherapy treatments that can be delivered prior to tissue displacement and a direct visualization of the tumor bed can guarantee an accurate dose delivery. The growing body of scientific evidence, in which IORT was given as a boost, has provided outstandingly low local recurrence rates [5].

II. INTRAOPERATIVE RADIATION THERAPY (IORT)

Firstly, it is observed that over 90% of local recurrence after BCS occur at or near the original operation site. Secondly, the risk of new primaries is equal to the risk of contra lateral breast cancer. In an effort to offer both shortened and more localized RT regimens, partial breast irradiation (PBI) that directly targets the index quadrant has been under clinical investigation Partial Breast Irradiation (PBI) treatments and Intraoperative radiotherapy (IORT). Among the various PBI techniques, the largest randomized controlled trials were conducted on IORT [5].

Many of the major clinical advances in radiation therapy have been related to improvements in the radiation dose distribution delivered to the tumor volume [6]. Several single institution cohort studies have been published on IORT, but only two phase-III trials have been launched and completed recruitment, the targeted intraoperative radiotherapy-alone (TARGIT-A) trial and the electron intra operative treatment (ELIOT) trial.

One of the most important advantages of IORT is the delivery of a single fraction of RT at the time of surgery, directly into either the tumor cavity or the index quadrant. Because IORT is performed during surgery, it always is given as a single radiation fraction. The biologic effectiveness of this single fraction is equivalent to at least a dose factor of two to three times greater than that delivered by conventional fractionation. Thus 20Gy administered by IORT has been estimated to have the cell-killing equivalence of 40 to 60Gy given by conventional EBRT [6].

In the past, the main limitation in the widespread adoption of IORT had been the need for the patients to be moved from the sterile operating room environment to the radiation oncology department for their radiation treatment. The patient must then be transported back to the operation room (OR) for surgical closure after radiation treatment. For such workflow to move effectively, sterile transport pathways have to be established between the OR and the radiation oncology department (which itself is not considered sterile).

Thus, extensive surgical draping of the patient and equipment will be required. It is also laborious and time consuming to aseptically move sterile patients around the hospital as many members of the clinical staff have to be committed to escort such patients to and from the OR.

In the past few years, however, promising technologies have been developed that have eliminated or reduced the need for the shielding within the operating rooms. These new radiation therapy systems have also been designed to be reasonably mobile so that they can be moved from one OR to the next for radiation treatment delivery

By employing these new IORT systems, waiting times for RT are reduced, and departments can focus on more complex radiotherapy treatments, since the workload of RT departments constitutes EBRT for breast cancer. On the other hand, a disadvantage of IORT is the longer operating time required, the equipment cost, the service cost, and the cost of the additional staffing.

III. Current Technologies and Systems

The available methods of delivering IORT are Electron beam radiation therapy, low-energy X-ray systems, High dose rate after loaders, & specific balloon devices.

A. IO Electron Beam Radiation Therapy-(IOERT)

Electron beam radiation therapy (EBRT) or intraoperative electron radiation therapy (IOERT) is the application of electron radiation directly to the tumor bed at the time of surgery. Electron beams can deliver the required dose much more rapidly than other devices [4]. To treat breast tumors, it has been estimated that 12MeV energy is sufficient.

These systems are designed with the concept of being utilized to deliver radiation in non-shielded operating rooms and are provided with a beam stopper. The beam stopper for certain mobile IORT units is designed to track the movement of gantry in all directions so that it will always intercept the primary beam, whereas other beam stoppers must be manually positioned.

The Novac7 have been employed in the phase-III trial, the ELIOT trial. The entire irradiation procedure is completed in 2 minutes, and the delivered dose is 21Gy with the depth of 90% Iso-dose ranging from 13 (3MeV) to 24 mm (9MeV) [7]. Fig 1 shows the unit during the treatment of the IORT of the breast. Fig 2 shows us the dose depth of the radiation in tissue.

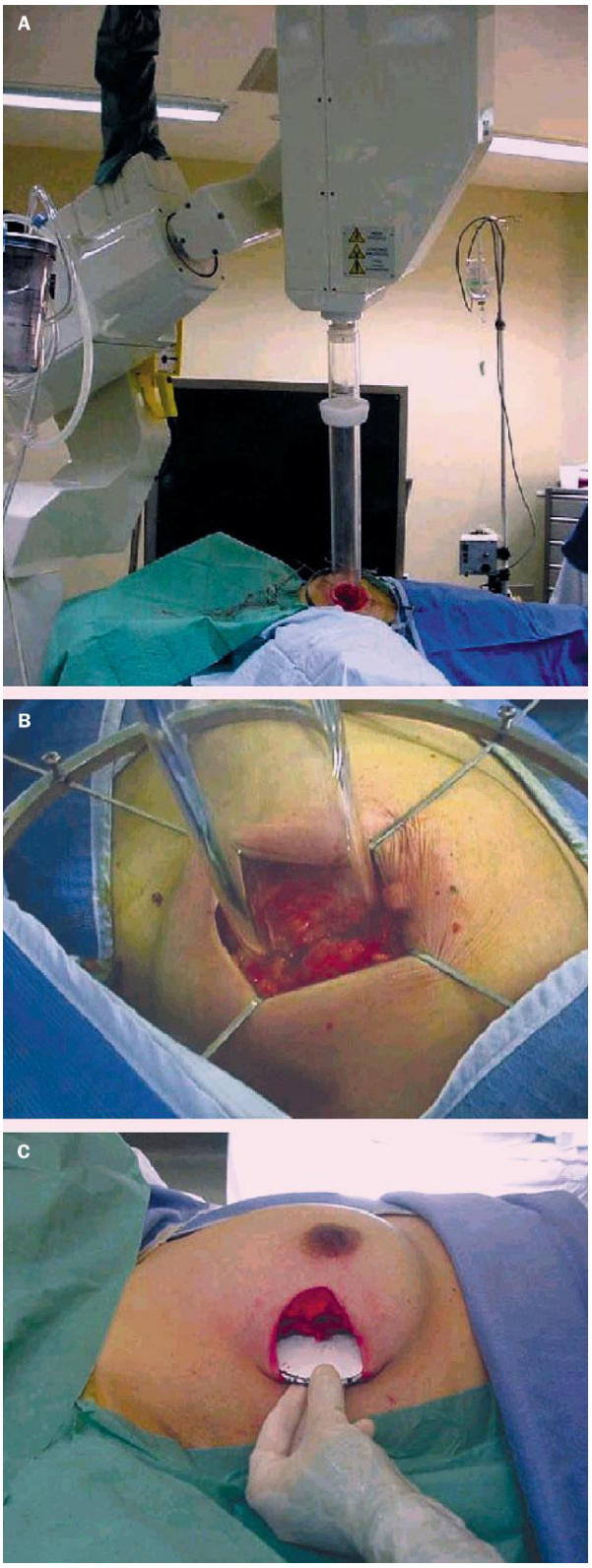

Fig1. The Novac-7 system. (a) The arm of the mobile linear accelerator is attached to a Perspex cylinder that is introduced in the breast wound (b). The breast tissue is mobilized from the chest wall and overlying skin, and apposed in the wound after placing a lead shield between the breast and pectorals muscle (c).

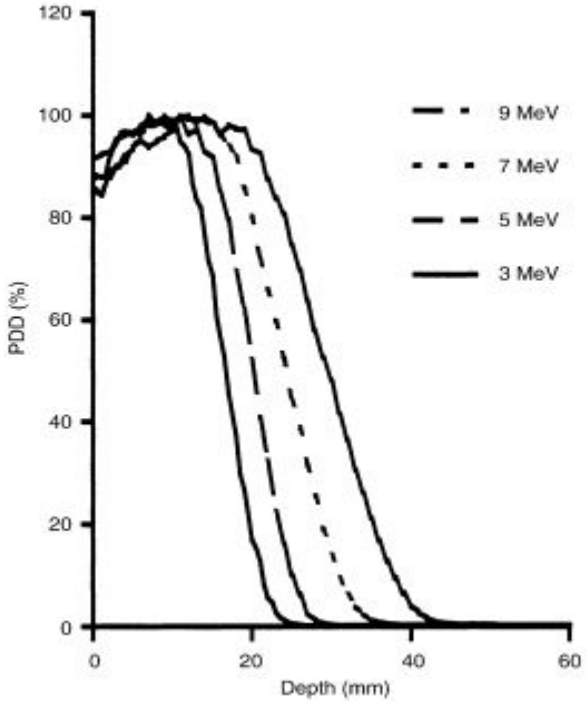

Fig.2 Per cent Depth Dose (PDD) as a function of depth in water. The photon behavior is compared to the electron delivered dose. In a few cm the electron dose is absorbed while a greater depth is needed to absorb the photon dose

The Eliot Trial

The ELIOT trial recruited its first patients in November 2000 at the European Institute of Oncology (EIO) in Milan (Italy). It was a prospective single-centre randomized phase-III equivalence trial. The aim of this trial was to compare a 21Gy single-dose IOERT delivered using the ELIOT technique [7] to conventional whole breast EBRT.

The LRR was found to be 4.4% in the ELIOT arm and 0.4% in the EBRT [7], at 5.8 years median follow-up. The LRR just fell within the pre-defined non-inferiority margin of 4.5%. The hazard ratio (HR) for Local Recurrence rate (LRR) in the ELIOT trial was 9.3% for women allocated to receive IOERT compared with those allocated to receive EBRT [7]. It was found that there was no significant difference in the 5-year overall survival rate in two arms, that is, 96.8% in the ELIOT arm and 96.9% in the EBRT arm (p = 0.59) [7].

After American Society for Radiation Oncology (ASTRO) and Groupe Europèen de Curietherapie of the European Society of Therapeutic Radiology and Oncology (GEC-ESTRO) recommendations were made available in 2009. Patients who fit the ASTRO ‘suitable’ group guidelines and the GEC-ESTRO ‘low-risk’ group guidelines, were found to have a LRR of 1.5% and 1.9%, respectively [4], confirming that IORT should be restricted to selected patients on the basis of tumor characteristics.

In terms of cost-effectiveness, despite the higher initial device-related costs, the cost per patient treated with IORT by using electron beams linear accelerators is effective when considering the reduction in radiotherapy waiting lists, pre-treatment planning and delay, but a specific cost-effective analyses is required, since IORT devices remain unaffordable for many hospitals worldwide.

B. High Dose Rate - After loaders-(HDR-IORT)

High-dose-rate (HDR) after loader (Mick Radio-Nuclear Instruments, Inc., Mount Vernon, NY) within a dedicated shielded operating facility (Brachytherapy Unit) was evaluated by Memorial Sloan–Kettering Cancer Centre (MSKCC), New York, USA in patients older than 60 years (median age 67 years) treated with BCS. At the time of surgery, HDR intraoperative radiotherapy (HDR-IORT) is delivered to the tumor bed by an iridium 192 (192Ir) Flexible applicators of various source connected to a quadrangular silastic template applicator named Harrison–Anderson–Mick (H.A.M) fig .

A dose of 18Gy was used since 20Gy doses were associated with a higher rate of side effects in a prior pilot study [9]. Treatment time varies between 20 and 40 minutes. At five years (median follow-up 68 months), local recurrence rate was 7% [9], and this was similar to the rate one would expect with no radiation treatment as shown in the CALGB 9343 trial [10]. HDR-IORT is also very limited by the high cost of specialized shielded operating room facilities.

Fig3. High-dose rate brachytherapy units are remote after loading devices that use an iridium-192 source

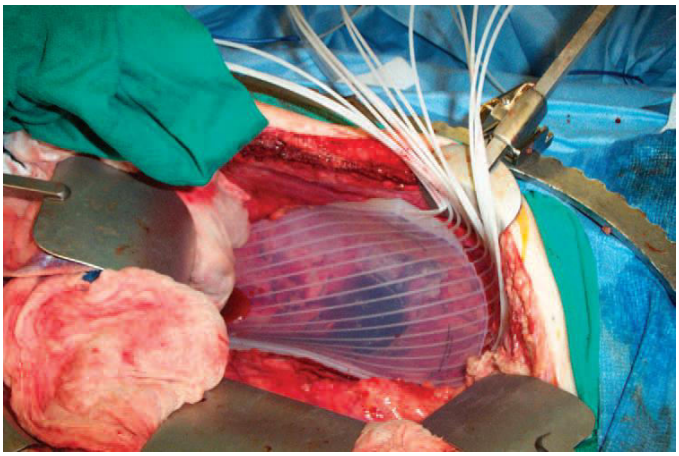

Fig 4. The flexible Harrison-Anderson- Mick applicator used in high-dose rate intraoperative radiation therapy allows more conformal treatment along curved body surfaces (eg, large pelvic sidewall fields, lateral abdominal wall, and thoracic cage.

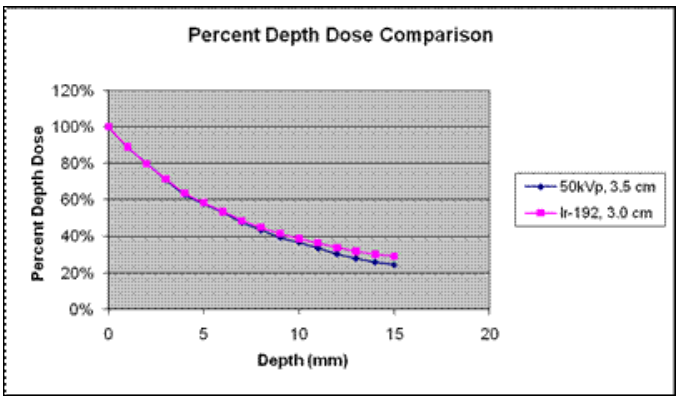

Fig5: Percent Depth Dose Comparison between 50 kV eBx and Ir-192.

C. Low Energy X-ray System- X-ray IORT

Low-energy X-ray IORT is delivered by the Intrabeam device (Carl Zeiss, Oberkochen, Germany). It is a miniature low-energy X-ray source employed for IORT during surgery after removal of the tumor. With the Intrabeam device treatment time ranges from 20 to 40 minutes, delivered dose is 20Gy at the surface of the applicator and 5–6Gy at 1 cm depth [11]. Tungsten-impregnated sheets are used to shield the wound prior to treatment. These block 95% of radiation, but radiation doses within the operating room remain potentially significant and necessitate control of access to the room during treatment and further shielding for the anesthetist and medical physicists. Existing walls will often provide sufficient shielding for the low-energy X-rays, and thus, it is often possible to use existing operating rooms. Before introducing the Intrabeam system, it is thus important to consider control of access to the operating room, to undertake a shielding assessment and to measure environmental radiation dose rates around the theatre.

The X-ray tube in the Intrabeam is powered by a 12 V supply, a miniature electron gun, and an electron accelerator.

Radiation in the form of soft X-rays (low energy, 50 kV) [11] is emitted from the point source and is modulated by spherical applicators to give a uniform dose of radiotherapy in a spherical field in the tumor bed. There is rapid attenuation of the radiation within tissues, which both reduces the damage to surrounding healthy tissues.

Another advantage of soft X-rays is rather elegantly, the pliable breast tissue around the cavity of surgical excision wraps around the radiotherapy source i.e. the target is conformed to the source. This simple, effective technique avoids the unnecessarily complex and sophisticated techniques of interstitial implantation of radioactive wires, or the even more complex techniques necessary for conformal radiotherapy by external beams with multi-leaf collimators from a linear accelerator. Use of soft X-rays eliminates geographical miss and delivers radiotherapy at the earliest possible time after surgery. Fig 6,7, 8 & 9 is shows the sytem during the application and the miniature.

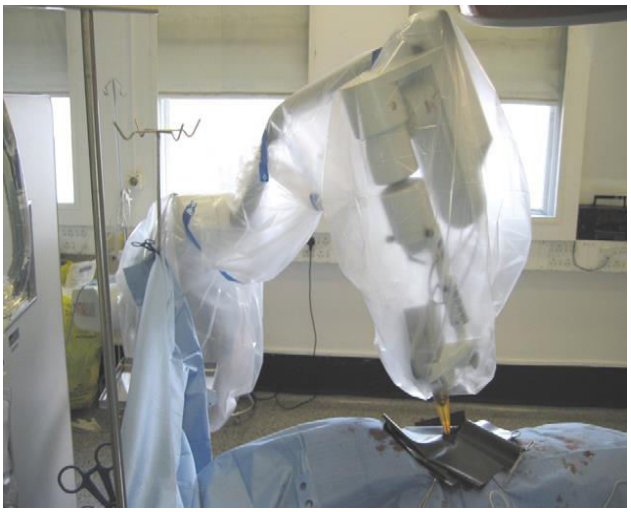

Fig6. The Intrabeam system An X-ray source is placed in the breast wound; an electron generator and accelerator are held by an articulated robotic arm. Only the shaft of the applicator can be seen; the tip of the device is in the breast tissue. A tungsten-impregnated polyurethane sheet is used to localise irradiation.

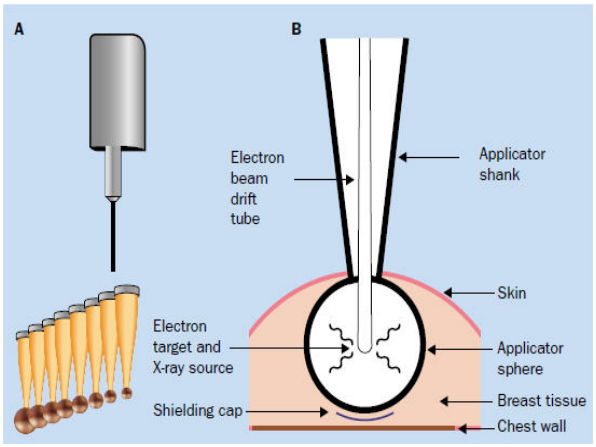

Fig7. (a) The Intrabeam X-ray source (upper) and applicators (lower). (b) Schematic diagram showing how target tissues are irradiated from within the breast and how intrathoracic structures can be protected with a thin shield.

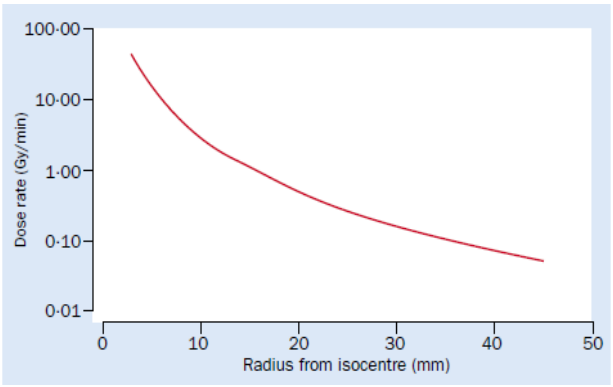

Fig8. Intrabeam: dosimetry around the bare probe in water

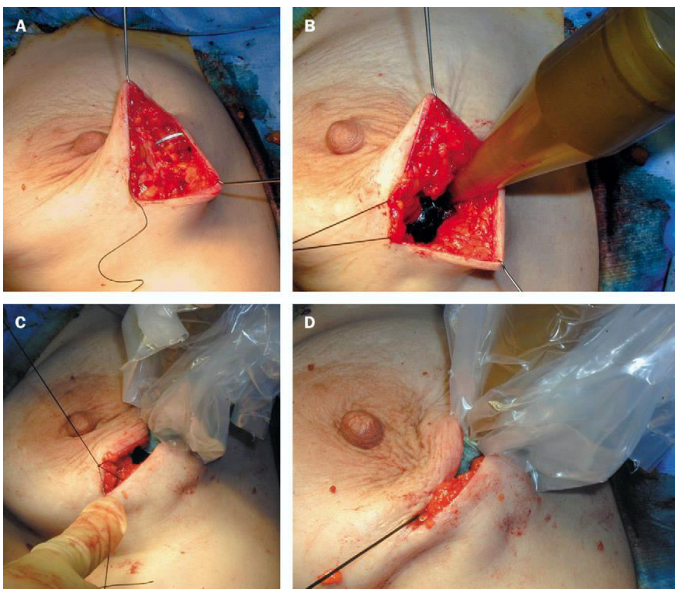

Fig 9. After wide local excision of the primary tumor (a), the applicator is inserted into the tumor bed (b). The applicator is secured with a purse-string suture (c) so that the target breast tissue wraps around the applicator, giving true conformal brachytherapy (d).

The TARGIT-A Trial

The TARGIT-A trial compared a strategy of a single fraction of IORT delivered using the Intrabeam system to conventional 3–6 weeks of EBRT after BCS. It was a prospective phase-III trial that commenced in March 2000, enrolling 2,232 patients over 45 years old with clinically T1–T2 ≤ 3.5 cm, N0–1 invasive tumors [12]. The pre-specified non-inferiority margin was 2.5% (80% of statistical power at 5% significance level), based on an estimated LRR of 6% with EBRT. Patients were ineligible if they were diagnosed with a lobular tumor or if they had an extensive *in situ* component. Eligible patients were treated with BCS and were randomized to either IORT or EBRT prior to surgery (pre-pathology cohort) or after surgery (post-pathology cohort). A 'risk-adapted approach' was used for IORT meaning that if the final pathology showed pre-specified adverse features, EBRT was administered after surgery. In these cases, IORT served as a tumor-bed boost [12].

In June 2012, the first results were published with a median follow-up of 25 months. The LRR in the conserved breast was 1.20% (95% CI: 0.53–2.71) in the IORT arm and 0.95% (95% CI: 0.39–2.31) in the EBRT arm (p = 0.41). In order to allow accrual in sub protocols, while data matured further, the sample size was extended from 2,232 to 3,451 and recruitment continued until 2012. In November 2013, the latest results from the TARGIT-A trial were published [12], again with a short median follow-up (2 years and 4 months) due to the trial recruitment extension. The LRR with IORT was 3.3% (95% CI: 2.1–5.1%) and with EBRT, 1.3% [(95% CI: 0.7–2.5%) with a p = 0.042] but met the non-inferiority margin of 2.5%, set at the outset. Overall, breast cancer mortality in the IORT arm was 2.6% (95% CI: 1.5–4.3%) versus 1.9% [(95% CI: 1.1–3.2%) in the EBRT arm; p = 0.56] [26]. However, non-breast cancer deaths were found to be significantly reduced in the IORT arm [1.4% (95% CI: 0.8–2.5%) versus 3.5% (95% CI: 2.3–5.2%) p = 0.0086] [12]. In terms of survival, although the log-rank statistics show a significant difference in non-breast cancer deaths that were found to be reduced in the IORT arm, these deaths also included stroke, bowel ischemia, and other events unrelated to breast irradiation. Additionally, the median follow-up of most patients was too short to observe differences in cardiac deaths (attributable to RT) which would be expected to occur between 10 and 20 years after radiation treatment. With IORT, there was a lower rate of Radiation Therapy Oncology Group (RTOG) grade 3–4 side effects and a higher rate of wound complications including seroma.

TARGIT-A trial lacks long-term follow-up data specifically on LRR. Only 1,222 patients (35%) completed 5 years of follow-up, and 611 (18%) of these received IORT. These results were more favorable for the pre-pathology stratum, and this group met the 2.5% non-inferiority margin [IORT 2.1% (1.1–4.2) versus EBRT 1.1% (0.5–2.5)], while the post-pathology did not met [IORT 5.4% (95% CI: 3.0–9.7) versus EBRT 1.7% (95% CI: 0.6–4.9; p = 0.069)] [12]. However, the data are still too immature to draw a definitive conclusion on LR.

Cost-effective analysis is also important in view of the equipment cost and potentially small number of eligible patients at some centers. A significant investment in equipment would be required to make IORT technology available across the National Health Service (NHS) in the United Kingdom (UK) or other European countries. In United States, two cost-effective analyses have been reported. *It was* concluded that when considered against the cost of EBRT, the Intrabeam system is more cost-effective. It offered more quality-adjusted life years (QALYs) than the 6-week EBRT regimen. The effectiveness analysis showed that IORT was slightly preferred over the whole breast EBRT strategy when measured in QALYs (a difference of 0.00026 QALYs)
This result was driven by the improved utility values for the proportion of women who have salvage lumpectomy after IORT, whereas all women who undergo EBRT have a salvage mastectomy based on cost-minimization analyses.

IORT represents a potential cost savings in the management of early-stage breast cancer. However, absolute reimbursement is misleading, because when additional medical and non-medical costs associated with IORT are factored in, EBRT represents the cost-effective modality based on cost per QALY analyses.

D. Balloon Catheter IORT

Balloon catheters have been employed as intracavitary brachytherapy devices for PBI. They can be inserted into the tumor bed at the time of surgery or postoperatively. Typically, RT is delivered by balloons in 10 fractions twice a day over five consecutive days.

Balloon-based APBI methods were developed to simplify the brachytherapy procedure. The MammoSite(MS) brachytherapy applicator was the first balloon catheter to be developed for APBI. The catheter contains an inflation channel and a channel for the passage of an Iridium-192 (Ir-192) [13] radiation source. It can be inserted through a single incision at the time of surgery or post-lumpectomy using ultrasound guidance.

A modified form of balloon-based brachytherapy called Xoft Axxent Electronic Brachytherapy (XB) received FDA clearance for the treatment of breast cancer in January, 2006. This device uses a mobile controller, which generates kilovoltage (kV) x-rays

Xoft electronic brachytherapy (eBx, Xoft,) [13] represents the balloon device which is now being tested to deliver RT as a single fraction, totally intraoperatively, at the same dose used with the Intrabeam system (50kpV low-energy X-rays, 20Gy).

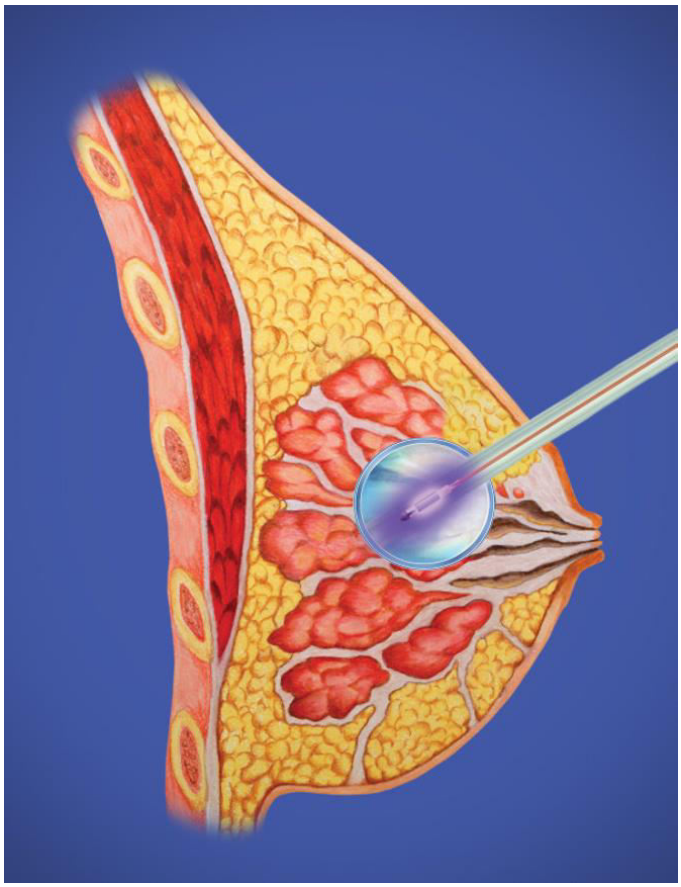

Fig 10 Electronic brachytherapy balloon inflated with source active in place with adequate skin spacing

A prospective phase-IV (post-marketing) trial is underway, but data are still immature, to introduce Xoft as IORT, in the current clinical practice [13].

To date, XB has been utilized only in an outpatient setting to deliver APBI in 10 fractions over 5 days [13] report on the first patient treated using XB to deliver IORT as part of an IRB approved single-institution trial.

Attached the XB controller to the catheter, and inserted the radiation source into the balloon. The radiation therapy was then initiated. A total of 20 Gy to the balloon surface was delivered in approximately 20 minutes (Fig 10). The duration of the entire procedure including lumpectomy, sentinel lymph node biopsy, balloon catheter placement, radiation therapy, and closing the incisions was approximately 2 hours [14].

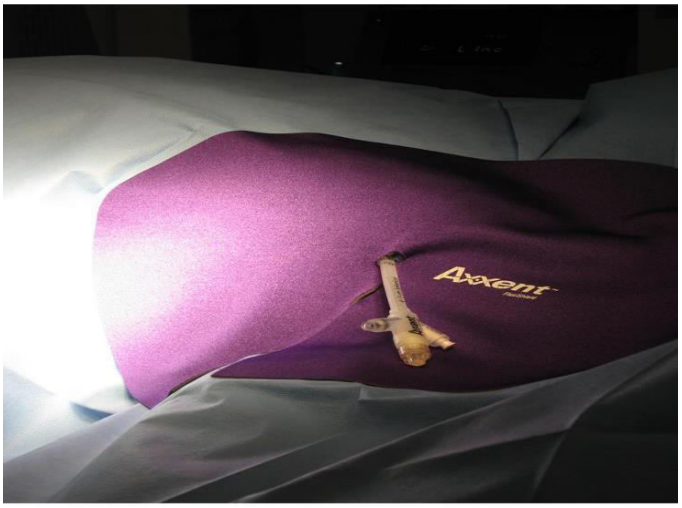

Fig10 A sterile drape is placed over the operative field and a FlexiShield™ is placed on top of the drape to minimize radiation transmission

Margin status was assessed by permanent section after the completion of the surgery. Negative microscopic margins are required in the protocol for treatment with IORT alone. Patients who are found to have microscopically positive margins of excision are offered re-excision and whole breast EBRT. The patient was found to have margins of excision of over 2-mm [14].

IV Discussion and Results

Very few of trails other than the TARGIT-A and ELIOT trials demonstrated that IORT and IOERT are not inferior to EBRT in selected patients. A subset of low-risk women for whom IOERT is acceptable in terms of LRR at 5.8 years of median follow-up has emerged from the ELIOT trial. Data from the TARGIT trial are encouraging and promising at 29 months of median follow-up with IORT, but longer follow-up is required. Data from totally intraoperative intracavitary balloon application by Xoft technology are still immature, while HDR-IORT demonstrated that ASTRO recommendations are ineffective for patients treated with this approach. Moreover, Intrabeam and both LIAC and Novac7 devices employed in these trials have been validated, whereas it is not clear the level of clinical evidence of the rest of novel devices introduced into the market.

However, there are some clear advantages of single-fraction RT for patients, and the level of evidence available on IORT is significant enough to share with them. Patients deemed at low risk of LR or those deemed suitable for PBI, according to the GEC-ESTRO and ASTRO recommendations, could be considered as candidates for IORT delivered under strict protocol, even though more specific guidelines for IORT would be helpful to assist clinicians in patient optimal selection. Both TARGIT-A and ELIOT techniques have been evaluated within phase-III trials launched over 14 years ago, and although further follow-up will increase confidence with the data, it will also further delay clinical implementation. National registries should be set up in order to monitor LR events occurring after IORT treatments off-trial, prospectively and might be useful to accumulate data.

V Future Outlook

Dose Deliverance

The radiation dose administered was 5Gy, at a distance of 1 cm from the applicator surface for Intrabeam. A dose in Nova 7 is given to the depth of 0.5-1 cm. However, there is no uniformity in terms of the dose delivery reporting process. Generally, a dose is calculated to the surface or at a certain distance chosen by the study team [15]. The dose of IORT is very important, because it allows in a measurable way to increase the total dose used in the treatment in order to eradicate the tumor to achieve a satisfactory treatment outcome [15]. In the case of IOERT it does not extend a total time of the entire treatment. The duration of IOERT irradiation is short (3-5 minutes) but preparations for the procedure with treatment usually take 30-45 minutes. In HDR-IORT, the operative time is extended by about 90 minutes due to the time of preparation and treatment [15]. Precise adherence between the tumor lodge and the applicator surface is extremely important. If the applicator is not fitted closely, the dose delivered to the lodge surface may vary markedly, resulting in the areas with insufficient dose coverage.

Image Guidance in IORT

Intraoperative electron beam radiation therapy (IOERT) procedures involve the delivery of radiation to a target area during surgery by means of a specific applicator. This treatment is currently planned by means of specific systems that incorporate tools for both surgical simulation and radiation dose distribution estimation [16].

VI CONCLUSION

In conclusion, in light of the existing data, IORT and IOERT should be now considered as an alternative to EBRT for specifically selected and well-informed patients. The higher risk of local recurrence should be widely discussed and compared with the great advantage of a single-fraction radiation treatment. The current striving is that of to deliver ‘minimum effective treatment’ to patients with cancer, and with this in mind, it is necessary to inform suitable patients about the options for the treatment of their cancer. Analyzing the results of research a number of limitations should be noted. Reports describing the use of IORT in Local and Regional Recurrences do not constitute sufficient evidence for all the technologies and there is a lack of evidence for comparable studies. Only 2 major multicenter clinical trials have taken place based on this research only can an engineer develop future technologies capable for delivering the results required for optimum IORT. More research focus is required on the dose accuracy and distribution to attain more satisfactory results for the development of IORT technologies.

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Interventional Trauma Procedures:
Summary of Procedures Systems Used with a Future Outlook

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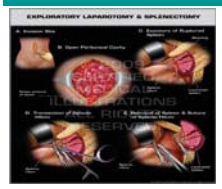
I. Introduction

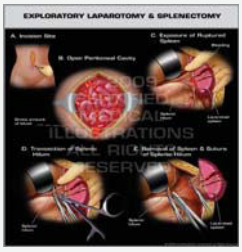


Exploratory Laprotomy [4]

Problem:	Trauma is a leading cause of mortality with over 5 million people succumbing to it each year. Unrecognized and and uncontrolled haemorrhage is the primary cause of early mortality.
Solution:	The aim of good trauma care is to prevent early trauma mortality. Early trauma deaths may occur because of failure of failure of oxygenation of vital organs or central nervous system injury, or both.
Challenges:	The initial assessment and management of seriously injured patients is a challenging task and requires a rapid and rapid and systematic approach
Aim of this poster:	This poster presents the interventional trauma procedures which are in use and their limitations.

II. Common Trauma Surgery Procedures

A. Exploratory Laprotomy



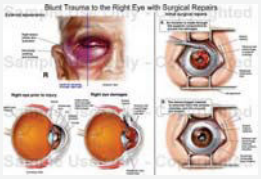
Exploratory Laprotomy[3]

▪ Common used approach
\+ Cost-effective
– Uncomfortable position

Trauma Conditions

- 2 types

Blunt trauma



Blunt trauma of the eye [2]

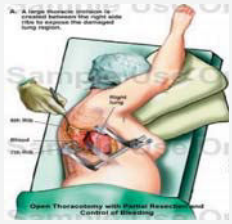
-internal injuries to the eye
-difficult procedure

Penetrating Trauma

Transnasal flexible endoscopy [2]

- The tract may be too small to appreciate with a finger or even a cotton-tip swab

B. Emergency thoractomy



Emergency thoracotomy technique[1]

▪Availability of high-quality digital subtraction angiographic equipment, preferably with digital road mapping and/or fade-fluoroscopic capabilities;

III. Methods

A. Ballon Occlusion

Ballon Occlusion for trauma[2]

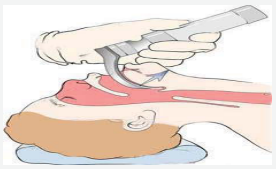
▪ Inflation of an angioplasty balloon proximal to or at a major arterial injury may temporarily stop or reduce life-threatening haemorrhage and thereby stabilize the patient while definitive surgical or endovascular repair is being arranged

B. Trans-Arterial Embolization

Trans-arterial Embolization[2]

▪TAE can stop arterial haemorrhage, thus improving unstable haemodynamic and often avoiding the need for surgery. Prompt, effective, and safe TAE requires skill and knowledge of the available equipment, arterial anatomy, role of collateral arterial flow, and risks

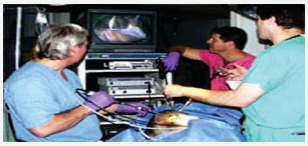
C. Orotracheal intubation



Orotracheal intubation [3]

- Tube position is confirmed
  -Auscultation/Chest excursion
  -Capnography
  -CXR
  Tube is secured

IV. Future Outlook



Endoscopic procedure for trauma[6]

- The initial findings indicate that there is a substantial radiation dose reduction without any change in the way of working or inconvenience during interventional procedures. According to these preliminary results, up to 75% of the radiation dose to staff and patient could be reduced. Image quality remained excellent.
- Advances in endovascular therapy aim to improve patient outcome and procedural success. However, with the latest generation in imaging systems, we also see promise in increasing patient and staff safety without sacrificing the imaging quality required to provide optimal care.[5]

V. Conclusion

Interventional radiology has much to offer in the evaluation and treatment of traumatic injuries. Current literature suggests that this role may expand in time due to desire for organ preservation and avoidance of surgery as well as due to improvements in trans-catheter equipment. A solid understanding of the benefits and risks of the different trans-catheter therapies is required to provide patients with the best care possible.[7]

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Interventional Trauma Procedures

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Abstract

Injuries and illness associated with major trauma that require lifesaving procedures, such as surgical airway, chest tube thoracotomy, emergency department thoracotomy, early recognition and treatment of compartment syndrome, and venous cut down, are seen in the emergency department. The emergency medicine physician must be proficient in recognizing these injuries and their associated complications and be able to provide appropriate management. This article discusses the most common trauma-related procedures in which emergency physicians must be proficient. A description of each procedure is discussed as well as the indications, contraindications, equipment, technique, and potential complications. [7]

1. Summary

Trauma is a leading cause of mortality with over 5 million people succumbing to it each year. Unrecognized and uncontrolled haemorrhage is the primary cause of early mortality. Whilst surgery remains the standard of care in patients with haemodynamic instability and abdominal injury, embolization is making rapid strides in this area. Trauma management is now a multidisciplinary team approach and interventionalists are finding themselves in a position where they are asked to unexpectedly help manage trauma patients with increasing frequency. Success rates of greater than 90% have been reported when embolization was used either as a first line therapy [3], after a vascular complication, or after surgical failure to achieve haemostasis. Success of the interventional procedure requires both prompt recognition of sometimes subtle signs as well as adequate emergent treatment. Unnecessary surgery can often be avoided or the procedure can assist the surgeon in the creation of a relatively bloodless field, particularly for pelvic trauma. [5]

The initial assessment and management of seriously injured patients is a challenging task and requires a rapid and systematic approach. [2]

This systematic approach can be practised to increase speed and accuracy of the process but good clinical judgement is also required. Although described in sequence, some of the steps will be taken simultaneously. [12]

The aim of good trauma care is to prevent early trauma mortality. Early trauma deaths may occur because of failure of oxygenation of vital organs or central nervous system injury, or both. [6]

Courtesy: NBC-Trauma-Keyart_1

Injuries causing this mortality occur in predictable patterns and recognition of these patterns led to the development of advanced trauma life support (ATLS) by the American College of Surgeons. A standardised protocol for trauma patient evaluation has been developed. The protocol celebrated its 25th anniversary in 2005. Good teaching and application of this protocol are held to be important factors in improving the survival of trauma victims worldwide. [6]

1.1 Clinical Findings

As a level I trauma centre, IR at our institution is involved in managing multiple types of trauma. We undertake embolization both in the angio suite and in the operating theatre just prior to surgery. The goal of this presentation is to familiarize the reader to various angiographic signs of traumatic injury such as active extravasation, pruning of vessels, traumatic AV fistulas, to name a few Case examples will be presented and will include subtle findings which can easily be missed. Imaging will cover various organ systems like the pelvic, hepatic, and splenic vasculature. Discussion will cover techniques and pitfalls in imaging. Controversial topics such as management of pruned vessel, the need for being super selective, and embolization in the operating theatre will be discussed. [4]

1.2 Aims of the initial evaluation of trauma patients

- Stabilise the patient.

- Identify life-threatening conditions in order of risk and initiate supportive treatment.
- Organise definitive treatments or organise transfer for definitive treatments.[1]

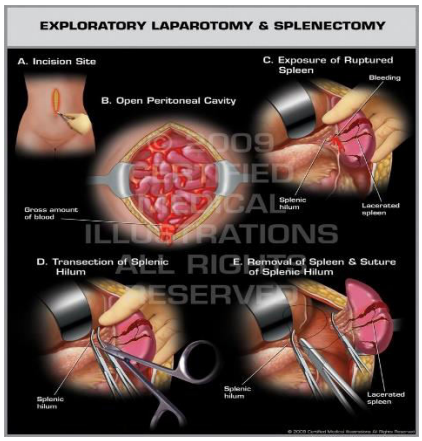
2. Common Trauma Surgery Procedures

Trauma Conditions

• **Blunt:** Motor vehicle crash, falls, all-terrain vehicle crashes, assaults
• **Penetrating:** Gunshot wounds, stab wounds, farm implement injuries [5]

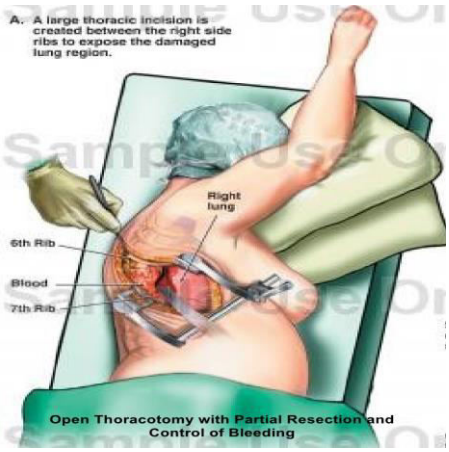
Trauma Procedures

- Trauma evaluation (level 1 and level 2)
- Exploratory laparotomy [10]



Courtesy: certifiedmedicalillustrations.com

- Emergency thoracotomy



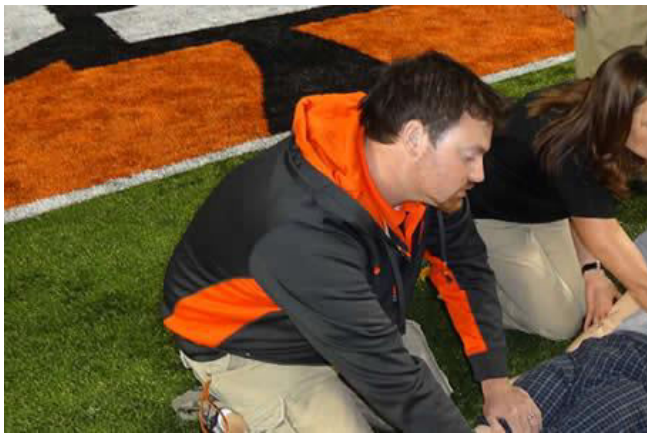
Courtesy: slideshare.net

2.1 Role of interventional radiologists

Interventional radiologists (IRs) are ideally qualified to play an important role in the management of trauma patients. Aside from their specialized training in the delivery of trans-catheter therapies, IRs receive broad-based multimodality imaging training, which renders them highly capable of correlating findings from pre-procedural imaging studies to speed diagnosis and treatment of trauma patients in the emergency setting. However, an interventional practice must meet the following criteria to be an effective player in the team management of trauma patients:
(1) A skilled IR who is available for consultation on urgent notice;
(2) Availability of high-quality digital subtraction angiographic equipment, preferably with digital road mapping and/or fade-fluoroscopic capabilities;
(3)Availability of skilled nursing and equipment needed for monitoring of critically ill patients; and
(4) Ability to ready these resources within 30 to 60 minutes.

Equally important, treatment of trauma patients requires efficient use of resources as well as cooperation and communication among a multidisciplinary team. Patients need to be rapidly and accurately assessed to determine the nature of their injuries with treatments prioritized by injury severity. Angiography

and trans-catheter therapy can be time-consuming and may delay other important procedures, so it is critical that delays in interventional treatment are minimized. [10]



Courtesy: isu.edu

3. Methods

Interventional Treatment Modalities

The following interventional treatment methods are commonly utilized in the trauma setting:

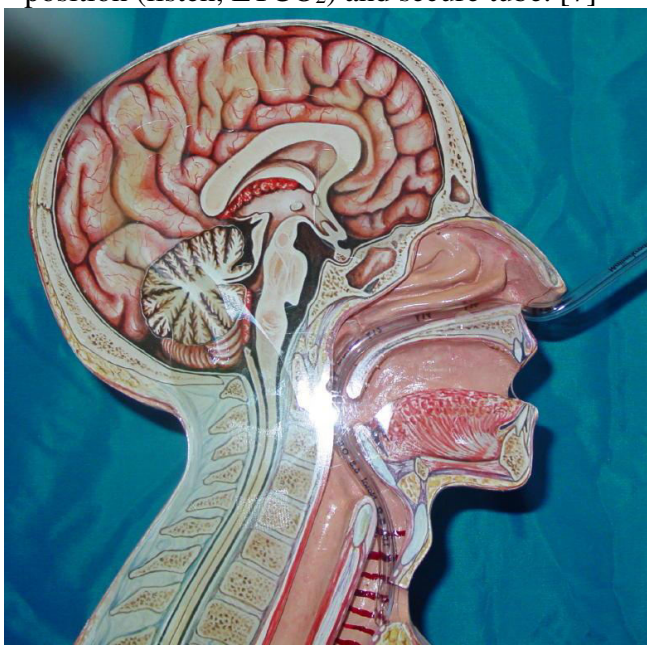
1. *Balloon occlusion*: Inflation of an angioplasty balloon proximal to or at a major arterial injury may temporarily stop or reduce life-threatening haemorrhage and thereby stabilize the patient while definitive surgical or endovascular repair is being arranged.
2. *Trans-arterial embolization (TAE)*: TAE can stop arterial haemorrhage, thus improving unstable haemodynamic and often avoiding the need for surgery. Prompt, effective, and safe TAE requires skill and knowledge of the available equipment, arterial anatomy, role of collateral arterial flow, and risks. A variety of catheters, including coaxial micro catheters, are available for selective catheterization to virtually all parts of the arterial circulation. Embolic agents vary in their permanency and the anticipated level of arterial occlusion. The choice of embolic agent will vary based on the site and nature of the injury, the desire to preserve collateral flow, and operator preference. Gel foam, particles (e.g., polyvinyl alcohol), and coils are some of the most commonly selected embolic agents in trauma. Care must be taken to avoid no target embolization.
3. *Stent-grafts*: Stent-grafts are increasingly being applied to the treatment of large vessel injuries and may enable one to avoid complex surgical vascular repairs in areas with trauma-related anatomic distortion and in patients who may be unstable. These considerations must be weighed against the long-term sequelae of device implantation, which are largely unknown.[16]

Common interventional imaging modalities include fluoroscopy, computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI) as well as traditional (plain) radiography:

- Fluoroscopy and computed tomography use ionizing radiation. However, both methods have the advantages of being fast and geometrically accurate.
- Ultrasound is frequently used to guide needles during vascular access and drainage procedures. Ultrasound offers real-time feedback and is inexpensive. Ultrasound suffers from limited penetration and difficulty visualizing needles, catheters and guidewires.
- Magnetic resonance imaging provides superior tissue contrast, at the cost of being expensive and requiring specialized instruments that will not interact with the magnetic fields present in the imaging volume. [11]

Nasotracheal Intubation – Technique

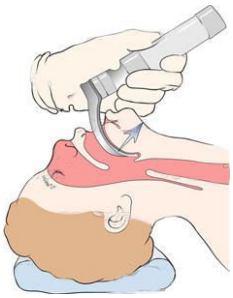
- Ask the patient to take deep breaths and slowly advance the tube past the vocal cords with inspiration
- When phonation is lost, inflate cuff, confirm position (listen, $ETCO_2$) and secure tube. [7]



Courtesy: Slideshare.net

Orotracheal Intubation – Technique

- The endotracheal tube is inserted through the cords and the cuff is inflated.

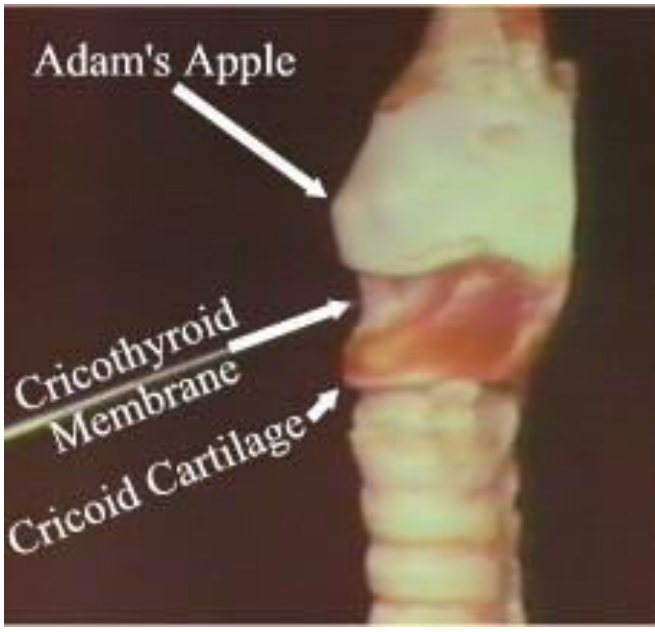


Courtesy: http://patienteducationreferencelibrary.com/generateexhibit.php?ID=22307&TC=&A=

- Tube position is confirmed
  - Auscultation/Chest excursion
  - Capnography
  - CXR
- Tube is secured [9]

Cricothyroidotomy

- Prep the neck
- Palpate the cricothyroid membrane below the thyroid cartilage in the midline
- Stabilize the thyroid cartilage firmly with one hand and make a transverse incision 2 cm in length down to and incising the cricothyroid membrane.

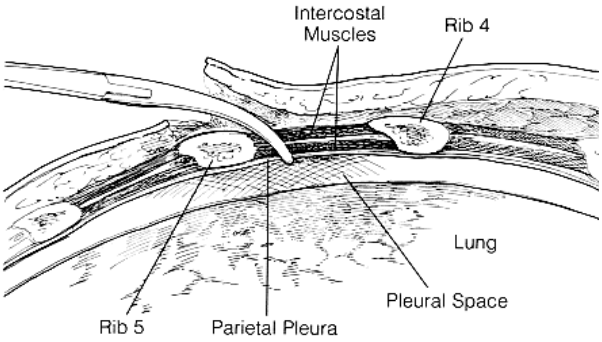


Courtesy: https://en.wikipedia.org/wiki/Cricothyrotomy

- Insert either a tracheal spreader or the back end of the scalpel handle and gently dialate
- Insert a tube (tracheostomy, endotrachial, BIC pen)
- Confirm ventilation
- Suture tube to secure
- Obtain hemostasis if necessary [3]

Tube Thoracostomy

- Prep and drape hemothorax
- Infiltrate skin, subcutaneous tissue and pleura with 1% lidocaine
- Place finger in track to confirm intrapleural positioning and lyse any adhesions.
- Insert tube via track (with or without clamp) towards apex of lung.
- Attach tube to pleuravac.
- Secure tube to patient with heavy silk suture and tape all connections. [6][8]



Courtesy: http://medical-dictionary.thefreedictionary.com/thoracostomy

4. Risks and Benefits

1. Damage to Internal Organs:

- Bowel
- Urinary Organs
- Blood Vessels
- Ovaries
- Nerves

2. Need for larger incision: If your exploratory laparotomy is planned to be laparoscopic or vaginal and we encounter scarring in your abdomen or excessive bleeding, we may need to make a larger incision.

3. Bleeding: requiring transfusion or further surgery to correct. 4. Infection: requiring antibiotics and in rare cases, surgery, to correct

5. Poor wound healing: some patients don't heal well, due to smoking, diabetes or other disorders. Antibiotics and frequent surgical dressing changes would be needed. Pain of the wound can also occur

6. Development of blood clot in legs or lungs: Deep Venous Thrombosis and Pulmonary Embolism occur rarely.

7. Reaction to anaesthesia: Can have nausea or vomiting after anaesthesia. [11]

The Benefits of IR in Trauma Care

Trauma patients are often young, active patients, and being able to improve survival rates for patients who are otherwise in their prime has obvious social and economic benefits. Interventional radiology can actively contribute to reducing the rate of accident fatalities, and should be considered by any accident and emergency department which does not already benefit from this unique skill-set, and by any healthcare authority which wishes to improve its trauma outcomes.

Offering cutting-edge IR therapies positively contributes to the reputation and performance of any trauma centre. This helps not only the patients themselves, but also the hospital as a whole, preventing patients from entering that rapid downhill spiral of acidosis, hypoxia, and hypothermia, keeping them out of intensive care or reducing the length of their stay there. [7]

5. Conclusioms

- Knowledge about simple surgical procedures can be lifesaving – however pure knowledge is not a substitute for repeated practice.
- Take every opportunity to practice these procedures with senior and/or attending supervision under controlled circumstances. [9]
- When positive vascular findings of contrast medium extravasations are found on the angiography in children with blunt renal

injury, our results suggest that intervention of TAE is indicated, which is a useful treatment option to minimize renal parenchyma damage. This study was based only on the experience of one hospital; further multiple medical centres' studies should focus on redefining indications and comforting level of interventional radiologists for TAE in paediatric blunt renal trauma patients. [11]

- The paradigm for management of traumatic injuries is shifting. Until the late 1970s, operative management was considered the only legitimate course for blunt and penetrating abdominal and extremity vascular injuries. Many studies suffer from the lack of inclusion of angiography and embolotherapy in evaluation of nonsurgical management of patients. A therapeutic alliance between trauma surgeons and interventional radiologists will advance the standard of care for trauma patients who might require embolization. Much work remains; specifically, although angiography has decreased the false-negative rate of surgical exploration, angiography itself can suffer the same problem. Ongoing investigation of non-invasive imaging and its correlation to angiographic findings will improve the yield and effectiveness of interventional techniques. [7]

- Interventional radiology has much to offer in the evaluation and treatment of traumatic injuries. Current literature suggests that this role may expand in time due to desire for organ preservation and avoidance of surgery as well as due to improvements in trans-catheter equipment. A solid understanding of the benefits and risks of the different trans-catheter therapies is required to provide patients with the best care possible.

6. Future Outlook

The initial findings indicate that there is a substantial radiation dose reduction without any change in the way of working or inconvenience during interventional procedures. According to these preliminary results, up to 75% of the radiation dose to staff and patient could be reduced. Image quality remained excellent.

Advances in endovascular therapy aim to improve patient outcome and procedural success. However, with the latest generation in imaging systems, we also see promise in increasing patient and staff safety without sacrificing the imaging quality required to provide optimal care.

Courtesy: http://www.getholistichealth.com/2889/how-endoscopic-procedures-revolutionized-pituitary-surgery/

ENDO procedures for arterial injury have increased over time while mortality for arterial injury subtypes has significantly decreased. Early ENDO procedures are common and are independently associated with a lower risk of mortality. These results suggest outcomes after vascular injury may benefit from ENDO expertise and that ENDO techniques should be incorporated into the early treatment algorithm of trauma patients

with vascular injury, particularly those that require difficult operative exposure. [9][16]

Urethral stenting is considered a palliative procedure for malignant obstructions. Urethral stents can also be placed for benign diseases such as proliferative urethritis, urethral strictures and pelvic lymphadenopathy. Malignant urethral obstructions can cause pain, dysuria and life threatening azotaemia. The two most common malignant urethral obstructions are derived from transitional cell carcinomas (TCC) and primary prostatic carcinomas (PPC). About 85% of patients with TCC will have dysuria and about 10% of those patients will develop a complete urinary tract obstruction. PPC has a worse prognosis compared to TCC. Survival time after urethral stenting with chemotherapy is reported to be greater than 250 days. With stent placement alone, survival time is 80 days. To determine the severity of the obstruction, a cryptogram is performed using a 50/50 saline solution to contrast solution. The urinary bladder needs to be distended with the solution in order to see the ureter vesicular junction (UVJ). An urethrogram is then performed to allow for maximum urethral distention. The cryptogram and urethrogram are performed under the guidance of fluoroscopy. Once the obstruction is located and measured, the appropriate size urethral stent is deployed through a transurethral approach, which is safe and reliable in male and female dogs. Vet Stent-Urethra™ comes in various sizes from 6mm – 12mm in diameter, and 40mm – 80mm in length. There are 5mm diameter stents available for cats. After the stent is deployed a cyst urethrogram is repeated to ensure that the urethra is no longer obstructed. When the patient has recovered from anaesthesia, often times the dysuria is significantly improved; however, maximum benefit may not be seen until two weeks post stent placement. Approximately 25% of canines diagnosed with a malignant urethral obstruction will have mild to moderate incontinence post stent placement. Urethral stents are not replaced; it is rare to have tumour growth through the stent, but there may be tumour obstruction that develops in front of or behind the stent. If those obstructions occur, additional urethral 610 stents may be placed. There are no reported complications with indwelling urethral stents; urethral stents do not tend to migrate or cause a foreign body reaction. Ureteral and urethral stenting improves the quality of life in animals, while relieving life-threatening obstructions. Interventional Radiology provides a minimally invasive alternative with a high rate of success in animals that would otherwise be humanely euthanized. [3]

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Technical Systems For Heart Valve Replacements under Image Guidance - Now and the Future

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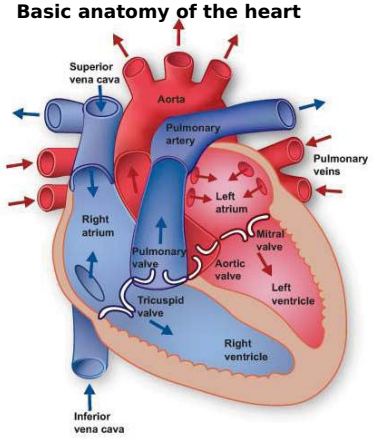
Abstract: In all developed countries aortic stenosis represents the vast majority of all medical conditions concerning the heart valves, followed by mitral valve stenosis. The ammount of patients afflicted is projected to increase drastically within the next decades due to an ever aging population yet currently there is no complete overview of prevalence of Aortic Stenosis. In 2002 the first transcatheter aortic valve replacement (TAVR) has been performed. In 2007 TAVR gained Conformité Européenne (CE) mark approval. Since then TAVR has become an established procedure with a steadily increasing percentage of heart valve replacement surgeries being performed with this method. It is the prefered method for patients deemed to high at risk for complications during open heart surgery. TAVR is expected to grow as a general alternative to open heart surgery for valve replacement. The aim of this work is to present the reader with an introduction and overview for the fast growing technology that is TAVR.

Introduction

Basic anatomy of the heart



State of the art and benefits of TAVR

- currently open heart surgery is still the most frequent method of heart valve replacement
- increasing numbers of patients deemed too unstable and fragile to withstand the stress due to open heart surgery lead to a need for minimally invasive approaches
- innovations in the development of artificial heart valves such as durable and elastic designs have opened the door for applications of catheter based placement methods

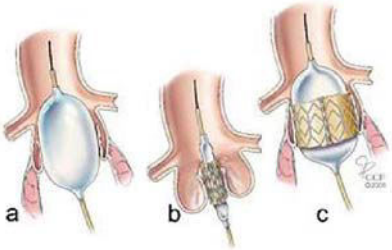
Stenosis:

represents a thickening of the tissue of a heart valve

Stenotic Valve

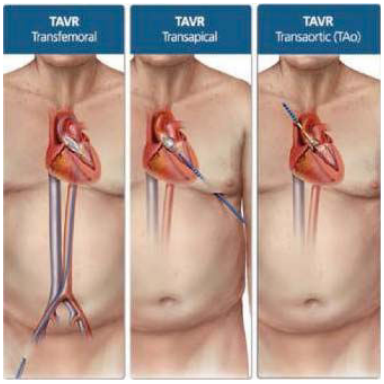
Methods

Transfemoral approach: For patients whose Aorta is in good condition. A sheath is inserted into the right femoral artery and a guide wire is led through it, from the femoral artery to the Aorta. Via the Aorta the guide wire is placed in the left ventricle.



Transcatheter placement of balloon and artificial heart valve

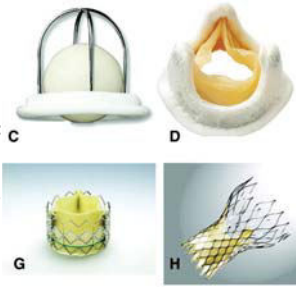
The three different approaches for Transcatheter Valve Replacement



Transapical approach: Depending on the individual condition of the patient, especially the condition of the femoral artery and or the Aorta the surgeons involved may decide to perform the transapical version of the procedure. In this approach a small incision is made in the ribcage and the ball catheter with the valve is inserted through the Apex of the heart.

Transaortic approach: Patients with inherently small arteries or severe vascular disease the transaortic method can be an alternative after the transapical access route.

Examples for Artificial Valves
C: caged ball valve;
D: stented porcine bioprosthesis;
G: percutaneous bioprosthesis expanded over a balloon;
H: self-expandable percutaneous bioprosthesis



Summary and Conclusion

About 30% of patients suffering from aortic stenosis do not undergo open surgical aortic valve replacement due to medical conditions, advanced age, left ventricular dysfunction or other coexisting conditions. To provide an alternative and decrease risk in this mostly elderly and frail population, TAVR strategies of aortic valve replacement will most likely steadily grow in importance. With an increasing number of clinical studies and use of TAVR the projected growth of usage seems to be a sound development. TAVR has potential for the expansion to a patient population with severe aortic stenosis from inoperable to high - risk patients and patients who have intermediate to low risk of complications.
The contemporary patient population for TAVR only represents a small subset of patients with severe aortic stenosis. Improvements in TAVR technology will expand the use of TAVR to younger and healthier patients. Current challenges for second generation TAVR models include: steep learning curves for the surgical procedure, difficulties with precisely placing the device, difficult repositioning of the device, inability to remove the device without the necessity to open the patient if necessary and a risk of perivalvular leakages, permanent pacemaker implants and stroke. At least eight next generation aortic valves compatible with TAVR are in development. Further studies will likely support regulatory approvals. With the general goal to reduce open and more invasive surgery, minimally invasive procedures are almost certain to replace the open surgery completely.

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TECHNICAL SYSTEMS FOR HEART VALVE REPLACEMENTS UNDER IMAGE GUIDANCE - NOW AND THE FUTURE

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ARTICLE INFO

Keywords:

Heart Vavle Stenosis

Abrevations:

SAVR	Surgical Aortic Valve Replacement
TAVR	Trans Aortic Valve Replacement

ABSTRACT

In 2002 the first transcatheter aortic valve transplantation (TAVR) has been performed. Since then TAVR has become an established procedure with a steadily increasing percentage of heart valve replacement surgeries being performed with this method. It is the prefered method for patients deemed to high at risk for complications during open heart surgery. The aim of this work is to present the reader with an introduction and overview for the fast growing technology that is TAVR.

1. Introduction

About 67,500 surgical aortic valve replacements (SAVR) are performed every year in the United States alone. In all developed countries aortic stenosis represents the vast majority of all medical conditions concerning the heart valves, followed by mitral valve stenosis. The ammount of patients afflicted is projected to increase drastically within the next decades yet currently there is no complete overview of prevalence of Aortic Stenosis. [1]

In 2007 TAVR gained Conformité Européenne (CE) mark approval. The number of patients undergoing the procedure in Europe has increased exponentially since then and will definitelly increase further. [2]

The heart functions as the general motor of the bloodsystem, pumping nutrient and oxygen-rich blood through the body and transporting blood with low oxygen content to the lungs. A healthy heart transports about 5 litres of blood each minute. The mammalian heart consists of four different chambers the right atrium, right ventricle, the left atrium an the left ventricle.

To pump blood into the heart it first relaxes which fills the right and left ventricles with blood from the right and left atrium. When it contracts again the valves at each chamber prevent the blood from flowing back into the veins by quickly closing again which forces it into the pulmonary artery and the Aorta.

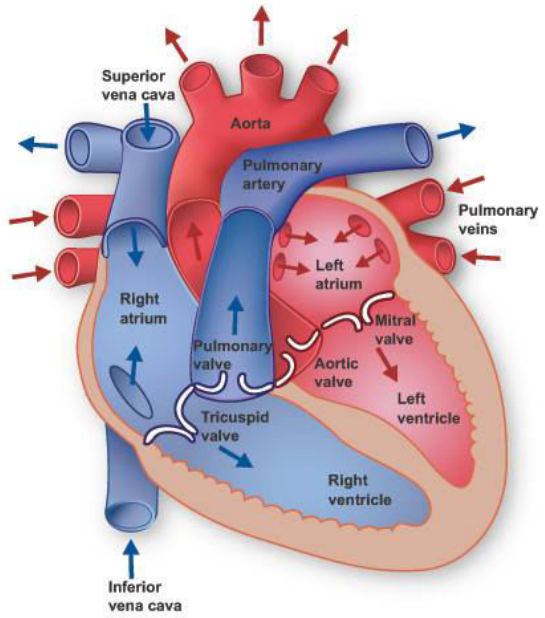

Fig.: 1 Anatomy of the heart [4]

These valves are the tricuspid, pulmonary, mitral and aortic valves. Any disruption in this normal flow will make it difficult for the heart to effectively pump the blood where it needs to go. The pulmonary valve directs blood flow from the right ventricle into the pulmonary artery, which splits into two arteries and leads the blood to both lungs. The aortic valve directs blood from the left ventricle into the aorta. The aorta is the major blood vessel that leads from the left ventricle out to the rest of the body. The mitral valve sits between the left left atrium and left ventricle. The mitral valve directs blood flow from the left atrium into the left lower chamber. Finally the tricuspid valve sits between the right upper chamber and right lower chamber. The tricuspid valve directs blood flow from the right atrium to the right ventricle. [3]

2. **Heart Valve Stenosis**

Severe aortic stenosis occurs when, mostly due to calcification, a heart valve does not open properly.

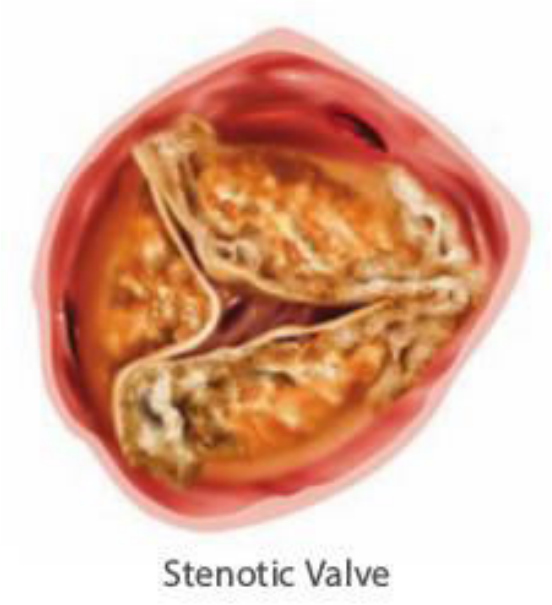

Fig.: 2 Stenotic Valve [3]

The flaps of the valve have thickened or are fused together. Causes can be age, a buildup of mineral (calcium) deposits narrowing the aortic valve, radiation therapy, a history of a bacterial infection of the heart (rheumatic fever) or increased fat in the blood vessels (high cholesterol).

As a result the heart has to work harder to pump blood through the valve, and the body may suffer from a reduced supply of oxygen. Over time, the heart muscle weakens which affects the overall health and keeps the patient from taking part in normal daily activities.

Left untreated, severe AS is a very serious, life-threatening condition, leading to heart

failure and increased risk for sudden cardiac arrest. Often AS is not preventable and causes narrowing of the aortic valve and may also be related to a number of symptoms such as Chest pain or tightness, feeling faint or fainting with activity, dizziness, general fatigue, shortness of breath, irregular heart beat (palpitations) and or unusual sounds heard during a heartbeat (murmur). [3]

3. **State of Art: Medication and Valvuloplasty**

High risk patients with severe AS may be prescribed medication to control symptoms. These medications may help control symptoms for a short time, however without aortic valve replacement, AS will most certainly worsen over time. In addition to medications a Balloon valvuloplasty can be performed to relieve symptoms. A valvuloplasty is performed by placing a balloon into the aortic valve and inflating the balloon.

This procedure can only relieve symptoms and does not remove the stenosis, which can worsen to a more serious condition without valve replacement. [3]

4. Open Surgery

Even today most heart valve surgeries are still performed as open surgeries. Surgical aortic valve replacement is effective and life-saving for patients who are healthy enough to withstand a highky invasive procedure. Depending on risk factors, such as health, diagnosis, and age it will be decided to recommend the appropriate valve replacement procedure. A traditional aortic valve replacement surgery often requires sternotomy, where the sternum is split down the middle. The surgeon will open up the ribcage of the patient above the sternum for about 25 cm with special retractors. This provides the surgeon with necessary access to the heart and chest cavity. During surgery the heart is temporarily stopped and the blood flow is delegated to a heart-lung machine to maintain circulation. The surgeon will then remove the damaged valve and sew in a replacement. After the replacement has been installed the heart is restarted with a defibrilator and the ribcage is shut closed with wires. Valve replacement is typically finished after about 2-4 hours and the patient spends about 12 days in hospital stay.

The highly invasive nature of this surgery prevents a lot of heart valve procedures from happening. [5]

5. Transcatheter Aortic Valve Replacement

Transcatheter Aortic Valve Replacement takes approximately 1-2 hours. Itttreats aortic stenosis by displacing and functionally replacing the native valve with a bioprosthetic valve delivered on a catheter through the femoral artery or transapical through the left

ventricular apex. Each patient is different, therefore a doctor may determine whether or not the patient should be fully anaesthetized for the procedure. When the end of the balloon is in the aortic valve, the balloon will be inflated and will force the narrowed aortic valve open to prepare it for the valve prosthesis. The interventional cardiologist or cardiac surgeon will make an incision and guide a sheath into place. Again, using the imaging equipment at hand, the doctor will place the prosthesis in position over the diseased aortic valve.

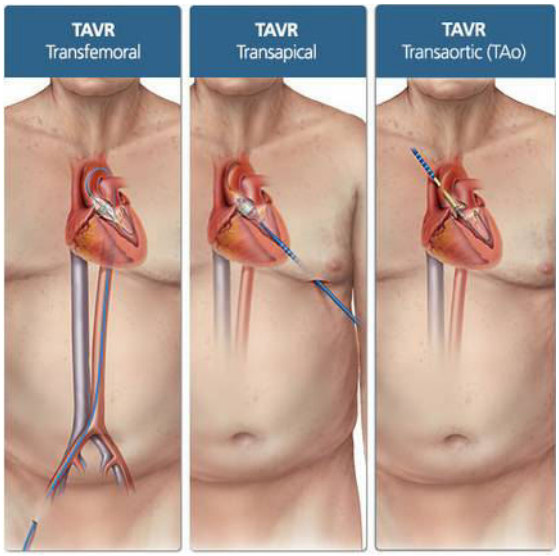

Fig.: 3 Different approaches for TAVR [6]

1. **Transfemoral**

For patients with severe aortic stenosis and those who are at high risk for open surgery. The transfemoral approach is performed in a cardiac operating room or hybrid catheterization lab under general anesthesia and fluoroscopic guidance. Delivery access is achieved through transfemoral cannulation. A sheath is inserted into the right femoral artery and a guide wire is led through it, from the femoral artery to the Aorta. Via the Aorta the guide wire is placed in the left ventricle. In the next step a balloon catheter is placed in the aortic valve and inflated. The aortic valvuloplasty is performed prior to implantation. The valve is then placed on its the delivery system and crimped over a balloon to allow insertion into the body through the sheath. In the last step the valve prosthesis is placed over another balloon catheter, placed in the valve and also inflated. During the procedure the other femoral artery has to be used to inject contrast agent and to place a pacemaker. Temporary pacing is performed to allow delivery of the valve in a stable environment. [7][8]

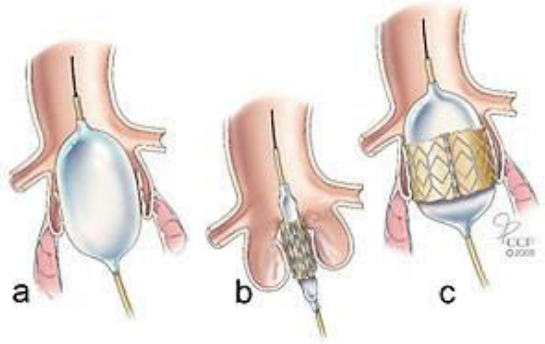

Fig.: 3 Balloon Placement and inflation [9]

2. **Transapical**

Depending on the individual condition of the patient, especially the condition of the femoral artery and or the Aorta the surgeons involved may decide to perform the transapical version of the procedure. In this approach a small incision is made in the ribcage and the ball catheter with the valve is inserted through the Apex of the heart. [8][10]

3. Transaortic

The trans-femoral route is the preferred approach for TAVR yet some patients who have insufficient femoral access need additional alternatives. Patients with inherently small arteries or severe vascular disease the transaortic method can be an alternative after the transapical access route. [11] [12]

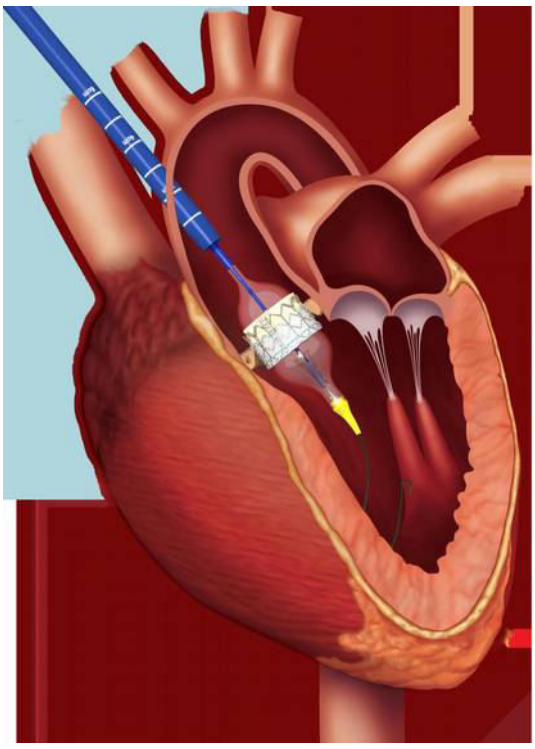

Fig.: 4 Tranaortic approach [12]

6. **Prosthetic Valves**

The valves involved in transcatheter procedures are generally biological, which means they come from either human or animal donors.

Fig.: 5 Edwards SAPIEN 3 Transcatheter Heart Valve [13]

The biological type is prefered for catheter delivery methods since it is easily shapeable and can fit onto a catheter. For the tissue either porcine or bovine tissues are harvested and treated to prevent antigene reaction as good as possible. Naturally human donor tissue would also be an option. A major backdraw as compared to strictly mechanical valves is the shortened lifetime of biological valves.

7. **Examples for mechanical and biological valves:**

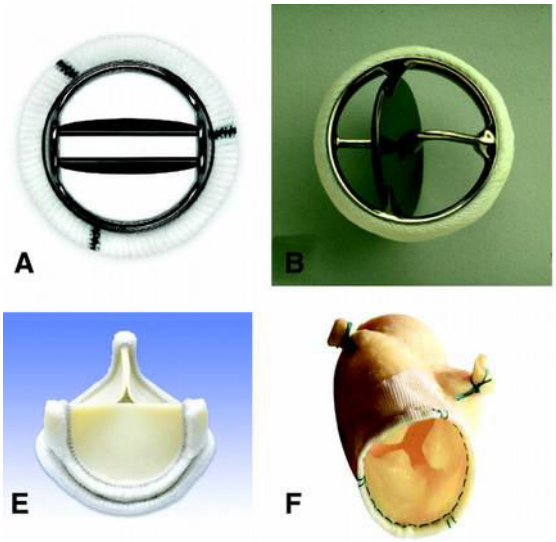

Fig.: 6 A: Bileaflet mechanical valve; B: monoleaflet mechanical valve; E: stented pericardial bioprosthesis; F: stentless porcine bioprosthesis [14

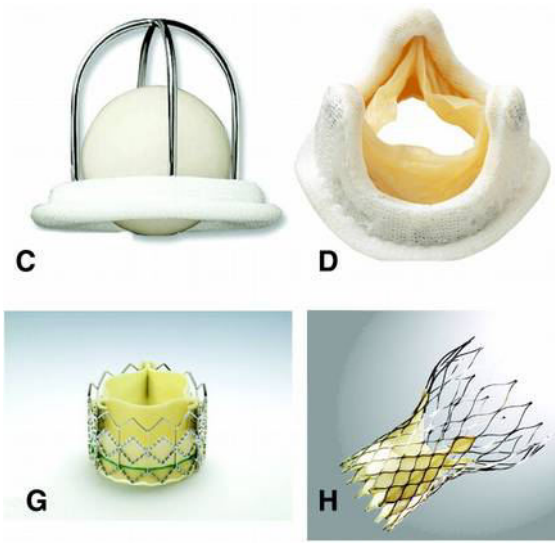

Fig.: 7 C: caged ball valve; D: stented porcine bioprosthesis; G: percutaneous bioprosthesis expanded over a balloon; H: self-expandable percutaneous bioprosthesis

8. **Intraoperative Imaging**

Conditions are generally the same for all transcatheter procedures. They utilize non invasive imaging (e.g., echo, vascular US, CT, MR) Sufficient space in sterile enviroenment. All imaging modalities found, that are used in TAVR approaches were C-Arm fluoroscopy in a hybrid approach combined with Ulrtrasound to monitor positioning and possible leakage of the placed valves.

This is according to a conventional catheter prozedure in any catheterization laboratory. [3] [15]

9. **Future Outlook**

About 30% of patients suffering from aortic stenosis do not undergo open surgical aortic valve replacement due to medical conditions, advanced age, left ventricular dysfunction or other coexisting conditions. To provide an alternative and decrease risk in this mostly elderly and frail population, TAVR strategies of aortic valve replacement will most likely steadily grow in importance. With an increasing number of clinical studies and use of TAVR the projected growth of usage seems to be a sound development. TAVR has potential for the expansion to a patient population with severe aortic stenosis from inoperable to high - risk patients and patients who have intermediate to low risk of complications.

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With the general goal to reduce open and more invasive surgery, minimally invasive procedures are almost certain to replace the open surgery completely. [16]

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2. Safety and Restrictions in MRI Environment

Safety should always be considered when using an MRI, because it creates a hazardous environment due to the expeditious increase of the field strength from the outside to the center of the magnet. Metal scans of persons entering the room are performed and special tools need to be used [1]. Furthermore, implants of patients have to be MR-compatible.

The magnet affects electrical devices and inhomogeneities in the magnetic field can cause distortions in the image [1]. Additionally, the restricted workspace in the MRI tube is challenging to perform accurate interventions. Therefore, different MRI configurations have been developed.

3. Steps of an Image-Guided Procedure (IGP)

1. Medical imaging and image processing: 3D volume is created from a set of 2D cross sectional images [2]
2. Data visualization: Images have to be presented in an appropriate way and additional information like tools models are provided [2]
3. Segmentation: Fragmentation of the image into non overlapping connected regions, which then represent explicit anatomical structures [2]
4. Registration: Junction of multiple data sets to one specified coordinate system in order to coincide the spatial locations of corresponding points [2]
5. Tracking systems: Gain knowledge about the position and orientation of tools and anatomical structures at each point in time [2]
6. Human Computer Interaction (HCI): Interaction technique and the information presentation [2]

MR-Guided Interventions – A Review and Future Issues

1. Introduction

Since Minimally Invasive Surgeries are increasing, the need for image guidance raises as well. Magnetic Resonance Imaging (MRI) provides a good soft tissue contrast and can be an appropriate method in clinical applications like neurosurgery and prostate biopsy. However, MRI is also challenging as it requires special tools and the space is limited. At the moment this guidance method is not in widespread use and some changes in development have to be done to make this method more affordable.

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4. Intra-operative Magnetic Resonance Imaging (iMRI)

Operating room configuration with visualization via MRI during surgery, which
- → Helps the surgeon to execute the surgery appropriately
- → Lowers the risk of damaging surrounded tissue
- → Enables to confirm the success before completing the surgery

An idealized intra-operative MR system combines:
- → Optimal access to the patient
- → High image quality
- → Fast acquisition and monitoring

iMRI is not in widespread use up to now. This is because of the need for MRI-compatible tools, the high costs for the change of the operating suite to MR-compatibility and the operating costs [3].

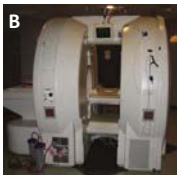

Image 1. MRI configurations
A Medtronic PoleStar MRI [6]
B GE double donut MRI [6]
C Oasis open MRI [7]

Image 2. IMRIS IGP suite with two operation rooms and a movable MRI in the middle [3]

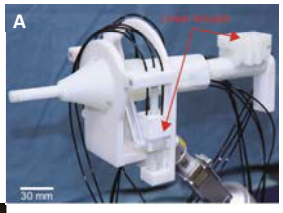

Image 3. MR-compatible tools
A Manipulator for neurosurgery [4]
B Prostate biopsy device [8]

5. Clinical Applications

Neurosurgery:
- Visualize brain shifts and identify residual tumor [4]
- Precise imaging required for successful surgery
  → Maximal lesion resection without damaging healthy tissue and causing sequelae [4]

Prostate Therapy:
- Magnetic resonance imaging-guided transrectal biopsy (MRGB) has high potential to enhance cancer detection rates [5]
- Image-guidance prevents needle dispalcement due to movements [5]

6. Conclusion and Future Outlook

MR-guided interventions are currently not standardized and affordable in the daily clinical process. Influencing factors:
- High costs (required special tools, high safety issues and large needed space for these setups)
- Balance between image quality and real-time use
- Restricted use of one system

However, it has several advantages like the missing of radiation exposure, imaging slices in all directions, the high resolution imaging of soft tissue structures and a good differentiation between healthy and nectrotic tissue.
The focus in future should be to make current systems commercially available. Moreover, the development of more widespread applicable systems rather than specialized systems should be considered to accomplish a balance between cost and benefit.

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MR-Guided Interventions: A Review and Future Issues

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Abstract — **Since Minimally Invasive Surgeries are increasing, the need for image guidance raises as well. Magnetic Resonance Imaging (MRI) provides a good soft tissue contrast and can be an appropriate method in clinical applications like neurosurgery and prostate biopsy. However, MRI is also challenging as it requires special tools and the space is limited. At the moment this guidance method is not in widespread use and some changes in development have to be done to make this method more affordable.**

Keywords:
Intra-operative MRI
Minimally Invasive Surgery
Magnetic Resonance Imaging
Neurosurgery
Prostate biopsy
Image-guided procedures

Abbreviations:

IGP	Image-Guided Procedure
MIS	Minimal Invasive Surgery
MRI	Magnetic Resonance Imaging
iMRI	Intra-operative MRI
Mp-MRI	Multi-parametric MRI
MRT	Magnetic Resonance Therapy
OR	Operating Room
RF	Radiofrequency
TRE	Target Registration Error

I. INTRODUCTION

NOWADAYS, surgeries become more minimally invasive in order to reduce the patient´s risk and to improve the health conditions of the patient. That is why, the need of image guidance increases, since the complexity of the Minimally Invasive Surgeries (MIS) raises [1]. Traditional guidance is carried out with either X-ray or ultrasound. Especially ultrasound is widely available and it illustrates a cost-effective imaging modality. Despite the fact that Magnetic Resonance Imaging (MRI) provides good soft tissue contrast and does not have to deal with radiation exposure like X-ray, it had not been consider as an appropriate method for image-guided interventions. The reason for that was its acquisition time and the closed magnets did not provide good access to the patient. However, this changed due to faster acquisition velocity and different magnet configurations to give more space to the surgeon. For this reason, MRI was not anymore a research modality in the field of guided interventions and became a preclinical method. [1]
Today MR-guided interventions are still rare due to cost issues and they require the use of compatible tools and devices. Nevertheless, there are already systems in clinical use in the field of neurosurgery. Interventional radiology is also considered as a future application for MR-guidance.

In the following, features of MRI, special requirements, safety aspects and challenges are characterized. Furthermore, a standard image-guided procedure with its implied technology is described and Image-Guided Procedure (IGP) systems are presented. Additionally, current and possible future applications of intra-operative MRI (iMRI) are depicted.

Advantages	Disadvantages
- Good soft tissue contrast and tissue differentiation - Nectrotic tissue well visible - No nephrotoxic contrast media - No radiation exposure - Morphological and functional information (e.g. blood flow and temperature changes) - Imaging slices in all directions (oblique as well)	- Risks like projectile effect or heat development - Sensitivity towards external magnetic and electric fields (wrong image information) - Special compatible systems and tools necessary - Complex and expensive investment, installation and running costs

Table 1: *Advantages and disadvantages of MRI [1], [2]*

II. Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a medical diagnostic technique and provides cross-sectional grey value images of internal structures, which can also be presented in a 3D model. The intensity of the grey value depends on the proton density of the corresponding tissue. Because of that, MRI provides good soft tissue contrast. Table 1 shows more advantages and disadvantages of the MRI technique.

The measurement principle is based on the directional magnetic field cohesive with moving charged particles. In the human body the hydrogen nuclei have a precession. Due to their charge, a small magnetic moment produced. In an MRI a large amount of these get aligned with the main magnetic field and the so called Larmor precession takes place, which frequency is proportional to the magnetic field strength. This alignment causes a net magnetic moment parallel to the main magnetic field of the MRI and by applying a radio-frequency (RF) pulse perpendicular to the field a change in orientation is done. The elimination of the pulse leads to a realignment of the nuclei (relaxation). The freed energy out of this relaxation process is an RF signal from the nuclei and is called free-induction decay (FID), which is measured by a conductive coil and reconstructed to an image. The system consists mainly of three magnetic fields; the main high static magnetic field, an alternating magnetic gradient field and radiofrequency (RF) electromagnetic fields [1]. There are series of coils to transmit and receive the radio waves from the imaged region, whereas the set of gradient coils manipulate the magnetic field dynamically and spatially. Therefore, the gradients are used to encode location through the variation of frequency and phase because the resonant frequency of the nuclei is dependent on the magnetic field strength. [1], [2]

1. Restrictions, challenges and safety issues

For medical devices and implants in the MRI environment, three categories of safety were defined by the American Society for Testing and Materials (ASTM) [2]:

1. MR-Safe: item that poses no known hazards in all MRI environments and includes non-conducting, non-metallic and non-magnetic materials.
2. MR-Conditional: item that has been demonstrated to pose no known hazards in a specified MRI environment with specified conditions of use.
3. MR-Unsafe: item that is known to pose hazards in all MRI environments and include magnetic items.

A **B** **C**

Figure 1: *Signs for (A) MR-Safe, (B) MR-Conditional and (C) MR-Unsafe [4]*

Safety should always be considered when using an MRI. The magnetic field creates a hazardous environment because of the expeditious increase of the field strength from the outside to the center of the magnet. This provokes an attraction of ferromagnetic objects like scalpels and small things like paperclips can turn into dangerous projectiles. Consequently, MR compatibility has always to be taken in account and special tools have to be used in MR-guided interventions. To prevent accidents, a metal scan of the personal is performed before the entrance in the MR environment [1]. Another aspect is pregnancy. Yet it is not proven sufficiently if MRI has an impact on pregnancy. For this reason, particular in the first trimester, the woman should only be taken to an MR procedure when there is a critical risk or a benefit in comparison to other imaging modalities. Furthermore, implants of patients should be MR-compatible For example it can contain conducting materials, which then lead to excessive heating due to the induction of electric current by RF fields [1]. Additionally, patients with tattoos can emerge cutaneous swellings or transient skin irritations. To prevent this cold compresses may be applied during the imaging process. Another effect of the magnet is the affection of electrical devices, which causes them to fail, work incorrectly or produce artifacts [2].

Except from safety there are other challenges due to the use of MRI. One aspect is that the image can be distorted as a result of inhomogeneities in the magnetic field, which can be caused by the patient itself, worn objects, implants or surgical devices. This is challenging in image-guided interventions because these irregularities are difficult to characterize in advance [2]. Besides, the restricted workspace in the MRI tube makes it difficult to perform interventions. Hence, new technical solutions like the "double-donut" magnet, open MRIs or MRI systems with a larger tube diameter have been introduced but are not in widespread use up to now.

2. *Intra-operative MRI*

The term Intra-operative Magnetic Resonance Imaging (iMRI) describes an operating room configuration. A visualization via MRI can be done during the surgery and the MRI helps the surgeon to execute the surgery appropriately and lowers the risk of damaging surrounded tissue. Additionally, it can be used to confirm the success before completing the surgery. Another term is interventional MRI, which describes the use of an MRI in an interventional radiology procedure. This surgical radiology outlines a minimally invasive image-guided diagnosis and treatment. [5]

Figure 2: *Different MRI configurations (A) General Electric "double donut" MRI [6], (B) Medtronic PoleStar MRI [6], (C) closed bore MRI [7] and (D) open MRI [8]*

An idealized intra-operative MR system would provide optimal access to the patient in combination with a high image quality and fast acquisition and monitoring [1]. Intra-operative MRI is not in widespread use up to now. The main reason for that is the need for MRI-compatible tools, the high costs for the change of the operating suite to MR-compatibility and the operating costs. Another important aspect is the typically lower quality of the interventional MR images compared to diagnostic MRI due to the use of low-field magnets. The optimization focus in diagnostic imaging is in the image quality whereas in iMRI systems real-time imaging is more important than high quality images. This leads to different research fields and makes it more difficult to create affordable technology. [2]

It is discriminated between low-, mid- and high-field procedures. Low-field imaging systems (0.1 T magnet field strength) are compact, moveable and the required room modifications become less, which could make the MRI guidance more widely available. However, they have limited imaging capabilities. Mid-field systems (0.5 T magnet field strength) can be seen as a tradeoff between imaging capabilities and the restrictions of the operating room. High-field systems are fixed systems which provide high quality images. But the required number of images is restricted because of the movement of the patient to the MRI scanner, which can be in an adjacent room or behind another form of shielding. These systems are the most expensive and complex models due to the large space requirements. [2]

Figure 2 shows different MRI system configurations. The double donut from GE (figure 2 A) has two vertically oriented low-field magnets with an operation gap in between. This allows near real-time image acquisition without moving the patient during the surgery. The Medtronic Polestar (figure 2 B) is as well a low field iMRI with a U-shaped magnet configuration, which can be removed when imaging is not required and therefore the used equipment does not have to be MR-compatible. [6], [7], [8]

III. IMAGE-GUIDED PROCEDURES

In general three procedure steps are distinguished. The pre-operative image is made to develop a surgical plan prior to the surgery with the use of additional information like implant geometry and functional data. The plans are specified for each patient and procedure respectively. The intra-operative plan execution implies the alignment to the operating room coordinate system and a visual assistance to the physician is created by tracking tools and anatomical structures and visualization of the spatial relations. Intra-operative images can be taken to update and adopt the surgical plan. The third step is the post-operating assessment, where the success of the surgery is confirmed by comparing the pre-operative image with a post-operative image. [9]

Due to Z. Yaniv and K. Cleary [9] there are 6 key technologies involved in all Image-Guided Procedures (IGP):

1. Medical imaging and image processing
2. Data visualization
3. Segmentation
4. Registration
5. Tracking systems
6. Human Computer Interaction (HCI)

In the following, these technologies are described briefly with the focus on MRI. The information are mainly taken from source [9].

1. Medical imaging and image processing

Firstly, images have to be taken and processed to make use of them. MRI is a tomographic imaging modality, which means that a three-dimensional volume is created from a set of two-dimensional cross sectional images. As a result of the slice-based scheme, the object has to be stationary during the process of collecting data or rather systematic motion can be gated. Otherwise, the volumetric data gets distorted. MRI implies geometric and intensity distortion. Geometric distortion is the result of inhomogeneity of the main magnetic field and non-linearity of the magnetic gradients. Geometric distortion correction should compensate these effects.

The intensity change can also be induced by inhomogeneity of the main magnetic field, but additionally the patients' anatomy can cause intensity distortions.

2. *Data visualization*

After imaging procedure the images have to be presented in an appropriate way. Furthermore, additional information is added like models of tools. Tomographic images are visualized with the help of surface rendering, volume re-slicing or direct volume rendering. These methods are not described further and for more information I refer the reader to [10]. To visualize three-dimensional data understandable in 2D, different views are required to reach the goal of concisely conveying the relevant information, which are necessary to complete the intervention successfully. Volume re-slicing creates the familiar views of physicians (axial, sagittal and coronal) and therefore it is the favored visualization method up to now, but three-dimensional visualization becomes more and more attractive for them with medical training in this field.

3. *Segmentation*

In Image-Guided Procedures (IGP) segmentation describes the fragmentation of the image into non-overlapping connected regions, which then represent explicit anatomical structures. There are in principle two types of segmentation algorithms. In the first one the desired segmentation is specified by the physician and therefore an interactive process with direct modification to reach correct results is acquired. In the second one the specification is implemented in the algorithm, which is hard to realize appropriately due to noisy and complex images and this leads to the use of algorithms with prior knowledge.

4. *Registration*

Registration is the junction of multiple data sets to one specified coordinate system in order to coincide the spatial locations of corresponding points. A good registration implies accuracy, speed and robustness. Accuracy can be determined by the comparison of the predicted position with the current position, which is called Target Registration Error (TRE). The speed is essential to ascertain the time needed to allocate the solution. Robustness shows if the algorithm is non-sensitive to noise and outliers.

5. *Tracking system*

Tracking systems are applied to gain knowledge about the position and orientation of tools and anatomical structures at each point in time.

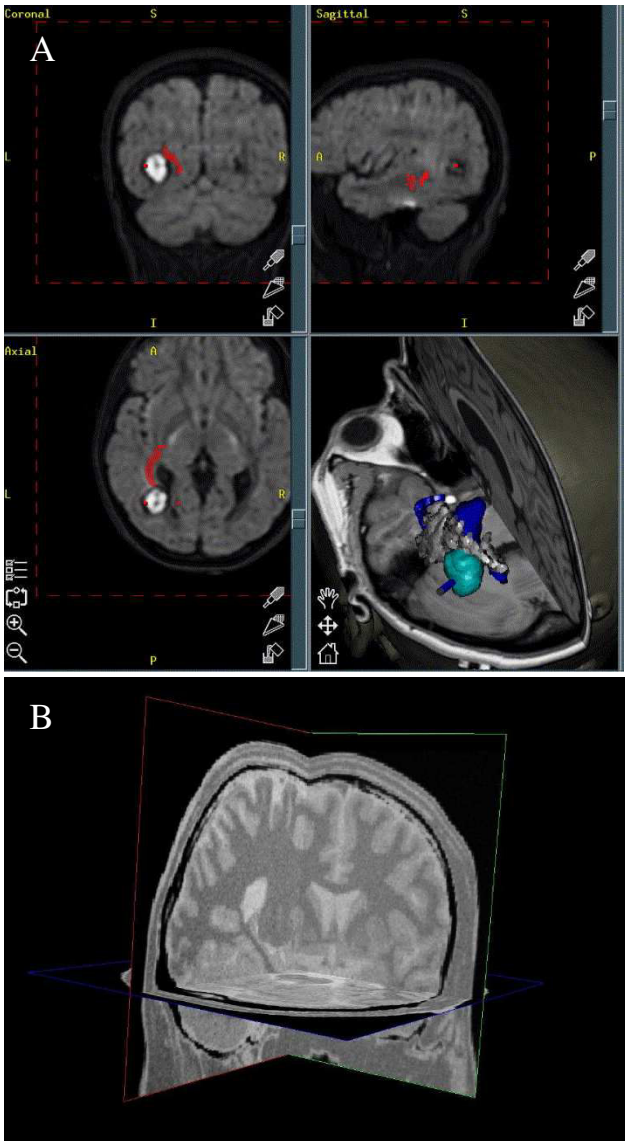

Figure 3: *Different visualization methods (A) four quadrant method with coronal, sagittal and axial slice cut and 3D model [11], (B) coronal, sagittal and axial slice cut combined in a 2D/3D model [12]*

This technology is therefore an important aspect in image-guided surgery. For medical applications mechanical-, optical-, ultrasonic- and electromagnetic tracking methods are common. They can be categorized in tracking systems for single objects and tracking systems for multiple objects at the same time. For MRI different materials like gold are used as a marker, which causes an artifact in the image. These can also be marker wires or marking clips.

6. *Human computer interaction*

Human computer interaction is divided into two main parts; the interaction technique and the information presentation. While Sterilization plays a huge role in surgery as well as the restricted space to interact with technique, the standard keyboard, mouse and computer monitors are not suitable for interventions. That is why IGP systems are developed to become more interactive. Already existing approaches are touch screens, trigger input devices (e.g. foot switches), tracked virtual keypads, speech recognition systems and computer vision based gesture recognition techniques.
A standard visualization method is the four quadrant data visualization, where three quadrants represent the axial, sagittal and coronal view respectively and the fourth quadrant is used for 3D rendering of the anatomy. The reasons for the widespread use are the wide range of application for this visualization and the physicians being already familiar with this way of data presentation, which can be seen in figure 3 A. Another approach is the presentation of the three planes in a combined 2D/3D model (figure 3 B).

IV. IGP Systems and Suites

The systems have to be imbedded in special rooms because of requirements for MR.
IMRIS developed an IGP suite with two operation rooms (OR) and a movable MRI in between, which is shielded with doors. The MRI is rail-mounted to the ceiling and can be turned around 180° in order to be used for each of the operating rooms. Additionally, it is possible to use it for diagnostic purposes when there is no current use in one of the operating rooms. The operating rooms include a MR-compatible operating table and special head fixation devices for the system. [3] In 2014 nearly 90 of these ORs existed worldwide, where the most ones were found in North America and due to IMRIS 40 % of the procedures benefit from this suite [13]. Another operating room type is the Advanced Multimodality Image Guided Operating (AMIGO), which is a three room suite. In figure 5 the structure can be seen, while the left room contains of a CT, the right room incorporates an MRI and the room in the middle is the operating room with the operating table and other surgical equipment. [3]

Figure 4: *IMRIS IGP suite with two operation rooms and a movable MRI in the middle [15]*

Figure 5: *Operating room type Advanced Multimodality Image Guided Operating (AMIGO) including a CT (left) and an MRI (right) [15]*

V. Clinical Applications

MR systems are used in neurosurgery, as well as to guide biopsies and monitor catheter interventions. Below, some clinical applications, where iMRI is already in clinical or preclinical use are presented.

1. *Neurosurgery*

According to K. Miki an K. Masamune [16], intra-operative MR images are useful to get information about brain shifts and identify the residual tumor. Precise imaging is required to reach a successful surgery, which might be challenging. Uncertainty leads to inaccurate resection and can for example provoke neurological damage due to aggressive resection. It is also possible that tumorous tissue stays within the body because the surgeon does not risk resection of healthy tissue [3].

Intra-operative imaging in neurosurgery enables real-time image-guided surgery, which results in maximal lesion resection without damaging healthy tissue and causing sequelae [3].

To face the accuracy problem due to low image quality, the MR-compatible acquisition system illustrated in figure 6 was developed and tested by K. Miki and K. Masamune [16]. This was integrated in a low-field MRI scanner and contained a pneumatic manipulator and a small planar RF coil. It illustrates a small field-of-view with high resolution. The results showed that the system grants accurate tumor observation and the resection with this system was stated to be precise [16].

2. *Interventional radiology*

For interventional radiology natural pathways, mostly the circulatory system, are used. A navigation of inserted catheters and probes through the vascular system to the target region is performed by an imaging modality. Traditionally X-ray-based methods were used, but MRI implements several advantages. As the needed space for radiology interventions is small, the limited space of the MRI does not cause spatial problems. Furthermore, this imaging technique does not cause harm in form of radiation for neither the patient nor the staff. Additionally, it is important to mention that the visualization of vessels is better in MRI compared to fluoroscopy without using contrast agent [2]. MRI showed a good performance especially in cardiovascular procedures and also 3D MRI showed good results in complex vessel structures like in procedures of thoracic aortic dissection [17]. Moreover the ongoing costs of iMRI are expected to be higher than in a traditional interventional radiology procedure [2]. MRI can also provide improved visualization of the myocardium for many procedures, including delivery of therapeutic materials, placement of prosthetic devices, and electrophysiological corrections [17].

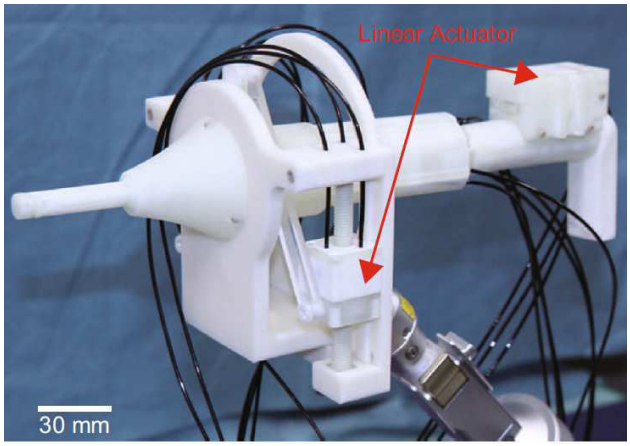

Figure 6: *MR-compatible manipulator [16]*

3. *Prostate Therapy*

Prostate cancer is the most common malignant tumor and second most frequent cause of death in men in the U.S. and Europe [18]. The prostate-specific antigen (PSA) level provides early identification of prostate cancer [18]. When patients have a high level, a biopsy is made to make sure if there is evidence for cancer. The current standard modality for prostate biopsy to diagnose cancer is the transrectal ultrasonography guided biopsy (TRUSGB) [18]. In this approach a false-negative biopsy occurs in 20–30 % [18]. Due to the good soft tissue contrast, the boundaries of the prostate and the tumor extension are well visible with MRI [2]. For this reason, magnetic resonance imaging-guided transrectal biopsy (MRGB) shows high potential to enhance the detection rates, which

then enables an early treatment [18]. Furthermore, movement of the prostate during biopsy procedures is likely and therefore image-guidance would be helpful to prevent needle displacement. Currently, multi-parametric Magnetic Resonance Imaging (mp-MRI) is stated to be the most reliable imaging biomarker for diagnosis of prostate cancer [18]. This technology combines anatomical T2-weighted imaging with diffusion-weighted imaging to highlight cell proliferation, dynamic contrast-enhanced imaging to show neoangiogenesis and MR spectroscopic imaging to display cell metabolism [18].

According to V. Panebianco et al. [18], many studies reported mp-MRI to be a method for identifying tumors, which were missed on biopsies. This is due to the fact that the location of the tumors is more inside the prostate, which cannot be observed with TRUSGB. Figure 7 shows an MR-compatible portable biopsy device, which is used for the adjustment and fixation of the needle guide [19]. The device facilitates rotation, angulation and translation of the needle and it contains no active fiducial coils (markers); however, it is visible in the MR image [19]. MRGB technology is more raising to get available; nonetheless, there is no current consensus on the optimal technique. One problem of image-guidance during biopsy is the lower quality of the image due to the use of low-field open MRI systems. V. Panebianco et al. [18] stated that at least 1.5 T images are required to reliably identify the target. This is why, in-bore MRGB is more reliable and additionally it is a relatively easy task [18]. MRI methods are initially more expensive, which is compensated by the reduced treatment costs as a result of less false negative diagnosis and an improved estimation of the tumors' aggressiveness.

4. *Other applications*

One promising application is the monitoring of the electric field distribution during electroporation. Electroporation is applied before cancer drug delivery to make the cell membrane more permeable for these drugs. But this electric pulse should just be delivered to the tumorous tissue. That is why, the visualization

Figure 7: *Prostate biopsy device [19]*

of the electric field during the examination would be helpful. This is proposed with Current Density Imaging (CDI) combined with Magnetic Resonance Electrical Impedance Tomography (MREIT). [20]

The University Clinic of Berlin (Charité) [21] introduced a new method called MR-guided Percutaneous Intradiscal Thermotherapy (MRgPIT). This technology combines a Percutaneous Laser Discus Decompression (PLDD) and annuloplasty to treat degenerative disc disease in an open MRI. This method showed precise results and was stated to be safe. No heat development in sensitive regions was observed. [21]

5. *Robotics*

Another improvement of surgical procedures is robotics because robots might be more accurate and real-time imaging is provided. An additional benefit is the use of it inside the MRI, where the space for a physician would be too small [2]. However, the MR environment involves a lot of requirements in robotics like limited access, material restrictions due to MR-compatibility and the limited use of actuator and sensor types. Therefore, the ideal material is non-magnetic and dielectric; for example plastics ceramics and glasses whereas the ideal actuator is made with pneumatics and light. Another challenge is to design a robot-to-image registration to give precise guidance

based on the MR image feedback. Moreover, robots in medical field have to fulfill requirements for sterility, safety, size and ergonomics. [22]
A development of robots for brachytherapy seed placement or other needle-based therapies in the prostate was done, which can be applied in conventional diagnostic MRI scanners [23].

VI. Conclusion and Outlook

MR-guided interventions are not standardized currently due to high cost issues and special demands for the MR environment. The high costs result from the required special tools, the high safety issues and the large needed space for these setups. Furthermore, finding a balance between image quality and real-time use is challenging. On the one hand, it is easier to operate in a low-field magnetic environment, on the other hand the image quality decreases in this case. Another aspect is the restricted use of one system because mostly the iMRI systems are designed for special procedures or body regions. iMRI is still in the development stage and up to now not affordable in the daily clinical process. However, it has several advantages like the missing of radiation exposure, imaging slices in all directions, the high resolution imaging of soft tissue structures and a good differentiation between healthy and nectrotic tissue.

The focus in future should be to make the current systems commercially available. Moreover, the development of more widespread applicable systems rather than specialized systems should be considered to accomplish a balance between cost and benefit.

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Sinja Lagotzki was born in Kiel, Germany, in 1992. She received the BSc. degree in electrical engineering from the Otto-von-Guericke University Magdeburg in 2015 and started the master "Medical Systems Engineering" in Magdeburg in the same year.
From 2011 to 2014, she was a student research assistant in metraTec. Since 2014, she has been a student research assistant in the Berlin company W.O.M. WORLD OF MEDICINE GmbH, which has a cooperation with the University Hospital of Dermatology and Venerology Magdeburg. In this Project Sinja Lagotzki supervised the two photon microscope VertiSCAN in a clinical trial, which is used in dermatology diagnostics. Her bachelor thesis was done at the same device, where the task was to develop a solution for a test procedure for the optical unit of the two photon microscope.
Her research interests are image-guided interventions, biomechanics and diagnostic imaging technologies.

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Covered stent vs drug eluting stent vs cardiac stent vs endovascular stent:
Short comparison of systems and delivery tools plus Outlook

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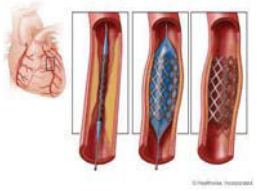
M.Friebe, Department of Catheter Technologies, Otto-von-Guericke University, Magdeburg, Germany

I. Introduction



Stent for cardiac disease[1]

▪In medicine, a stent is a tube or other device placed in the body to create a passage between two hollow spaces, and stenting is the placement of a stent. There is a wide variety of stents used for different purposes, from expandable coronary, vascular and biliary stents, to simple plastic stents used to allow the flow of urine between kidney and bladder. Stent is also used as a verb to describe the placement of such a device, particularly when a disease such as atherosclerosis has pathologically narrowed a structure such as an artery.[1]

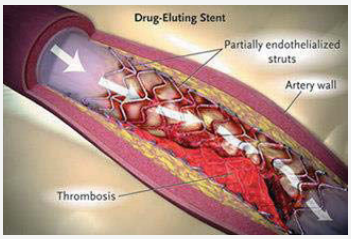
II. Types of stents

A. Covered stents

Covered stent for cardiac purpose[2]]

▪Covered stents are composed of fabric or graft material, such as polytetrafluoroethylene (PTFE), covering a metal stent. They have various clinical applications in peripheral arterial disease management. Applications include treatment of atherosclerotic disease.[2]

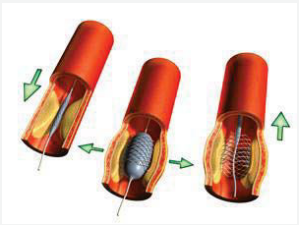
B. Drug eluting stents



Drug eluting stent [2]

A **drug-eluting stent** (**DES**) is a peripheral or coronary stent (a scaffold) placed into narrowed, diseased peripheral or coronary arteries that slowly releases a drug to block cell proliferation[5]

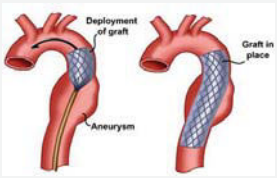
C. Cardiac stents



cardiac stent [2]

A **coronary stent** is a tube-shaped device placed in the coronary arteries that supply blood to the heart, to keep the arteries open in the treatment of coronary heart disease.[4]

D. Endovascular stents

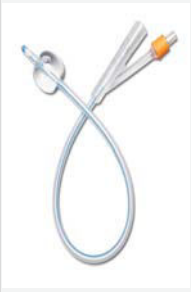


Endovascular stent graft[1]

An endovascular stent graft is a tube composed of fabric supported by a metal mesh called a stent. It can be used for a variety of conditions involving the blood vessels, but most commonly is used to reinforce a weak spot in an artery called an aneurysm.[6]

III. Tools used for stents

A. Catheters



Catheters for stent[3]

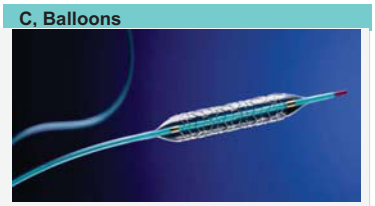
▪A **catheter** is a slender, plastic tube that can be threaded into a blood vessel to deliver treatments inside that blood vessel. During a diagnostic **angiogram**, x-ray dye flows through the catheter into the arteries so that your cardiologist can view images of any blockages in the artery. During **angioplasty**, a balloon or another device is mounted on the catheter's tip and guided to the narrowed section of the artery over a guidewire.[3]

B. Guidewires

Guidewires for stents[3]

▪A **guidewire** is a long and flexible, fine metal wire used to place balloons or stents. The guidewire is threaded through a blood vessel to the site where treatment will be delivered. A balloon or **stent** is then fed over the guidewire until it is in the desired position. A guidewire does just as it name implies: it helps your interventional cardiologist guide devices into place.[3]

C, Balloons



Balloon Stents[3]

▪An **angioplasty balloon** is attached at the end of a special balloon catheter, the balloon is at one end and can be inflated from the other end outside the body. An interventional cardiologist threads the balloon catheter over a guidewire to the area of the artery that has become blocked with a fatty substance called **plaque[3]**

IV. Future Outlook

Bioresorbable stents[4]

Most bioresorbable stents are made of poly-lactic acid, a naturally dissolvable material that is used in medical implants such as dissolving sutures. The drawbacks of using polymer include recoil after expansion, stent thickness causing manoeuvrability and crossing issues, difficulty visualizing a non-metallic stent on fluoroscopy and stents not crimping firmly on delivery balloons. However, the advantage is not implanting a permanent metal prosthesis. Since the stent disappears, it eliminates the cause of potential inflammation that can lead to late-stent thrombosis and restenosis. Once the stent dissolves after about two years, it restores the vessel to a natural state of vasoconstriction and vasodilatation. The disappearance of the device also leaves open all options if future interventions are needed.[5]

V. Conclusion

At the moment, the list of potential medical applications for biodegradable metal stents seems limited, but their potential is obvious. Biodegradable metals provide new insights into the biomaterials field for a number of surgical fields, including paediatric, orthopaedic and cardiovascular. These materials may stimulate a revolutionary development of new devices which were not envisaged before. However, the user must be prudent in translating these materials into direct clinical application. A catastrophic effect could result following the implantation of degradable metals issuing from immature technologies[4]

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ADVANTAGES AND LIMITATIONS OF ROBOTIC PROSTATECTOMY — REVIEW AND OUTLOOK

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INTRODUCTION

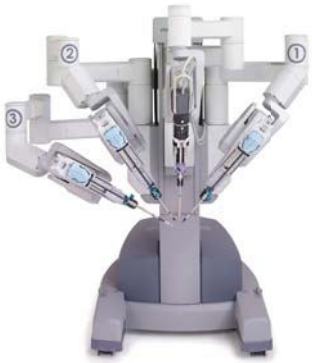

Image 1. Da Vinci system for robotic assisted laparoscopic prostatectomy [1].

Currently, prostate cancer has become the most common cancer developed cancer in men. Consequently, several modalities have been analyzed so as to reduced negative impact after prostatectomy. Traditional open retropubic prostectomy has been notoriously replaced by laparoscopy and robotic radical prostatectomy. Just in United States of America more than 50% of radical prostatectomies are performed through computer assisted laparoscopy with Da Vinci system [3]. The inclusion of assisted robotic systems has brought several benefits that benefit not only medical systems but also patients around the world.

Prostatectomy modalities:

- Radical prostatectomy with retropubic
- Nerve-sparing prostatectomy approach
- Laparoscopic radical prostatectomy
- Robotic-assisted laparoscopic prostatectomy
- Radical prostatectomy with perineal approach.

EQUIPMENT AND TOOLS

Reduction of sexual loss, trauma and pain.

DA VINCI ROBOT

Console components | Surgical | Video

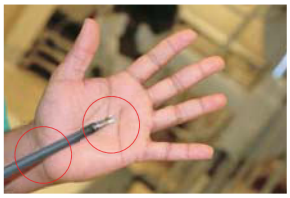

Image 2. Articulation at the wrist in tools [2].

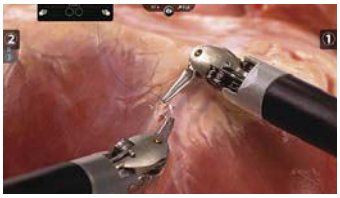

Image 3. Complete motion is translated into tools [4].

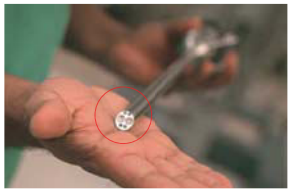

Image 4. Robotic telescope composed by two scopes [2].

Image 5. Fingers´ and wrist´s movement is detected by the control [4].

Da Vinci system is designed under immersive intuitive interface based on intuitive laparoscopic control, stereoscopic immersive vision and multiple sensor configuration. The system allows seven degrees of freedom that makes an excellent suturing performance and tissue manipulation. The system is activated when the surgeon´s head is inside the vision system.

Image 6. Different tool possibilities as scissors, graspers and dissectors [5].

ADVANTAGES AND PROBLEMS

Advantages
Length of stay
Recovery
Incontinence
Erectile dysfunction
Positive margins

Table 1. Advantages in Robotic-assisted laparoscopic prostatectomy [3].

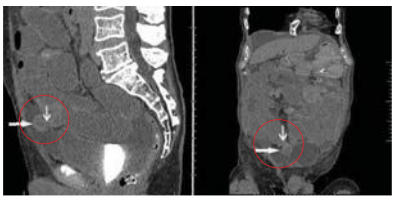

Image 7. Small bowel hernia after extra-peritoneal robotic prostatectomy [2].

Image 8. Da Vinci ergonomics [2].

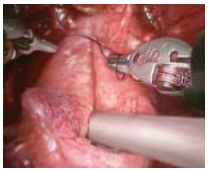

Image 9. High quality visualization[2].

Problems
Intraoperative bleeding
Lymphoceles
Intestinal injuries
Urinary complications
Robotic failures
Impact of the learning curve

Table 2. Problems in Robotic-assisted laparoscopic prostatectomy [6].

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Dose Management of XR procedures — Summary XR dose for selected procedures and ways to reduce that

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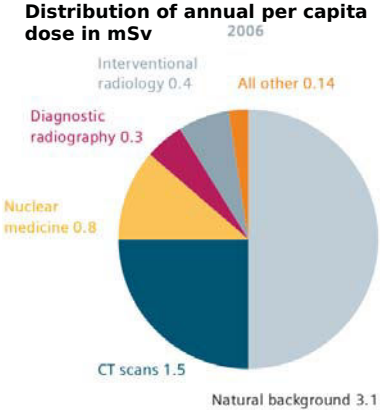
Abstract: Ionizing radiation in medical imaging as well as cancer treatment has become the focus of an intense public and scientific discussion. In both cases there has to be found a balance between harm and benefit. In the USA, the annual exposure to radiation from medical sources has risen from 0.53 mSv to 3.1 mSv over the past three decades. Within this alarming development Computed Tomography (CT) takes a special position because it is the largest contributor to radiation exposure in medicine. Medical radiation exposure by now has reached levels similar to the annual natural background radiation. This development can be observed in all industrialized nations equally with expectations for newly industrialized countries to follow suit. With sufficient training and education for physicians and other medical staff the doses can be efficiently decreased. This work aims to introduce the most important aspects of dose management in relation to several widespread applications of ionizing radiation in medicine.

Introduction

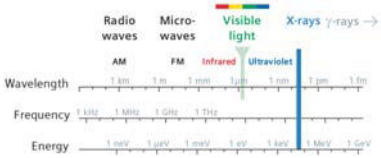
Distribution of annual per capita dose in mSv



Biological effects of ionizing radiation

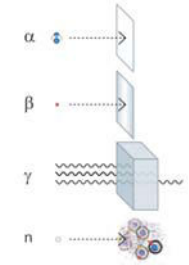
- Ionizing radiation can harm cells in two ways. Directly by ionizing atoms in the DNA molecules or by creating free radicals which are highly reactive and can react directly with DNA molecules.
- All cells can naturally repair damaged DNA within limits yet if exposed to high amounts of radiation beyond a certain threshold the damage becomes too much for the repair mechanisms.
- So called deterministic radiation damage includes changes of the blood count, hair loss, or tissue necrosis.
- Exposure levels of medical diagnostic imaging procedures are typically below the threshold for deterministic radiation damage. In the case we speak of “stochastic” damage.

Energy levels of ionizing radiation



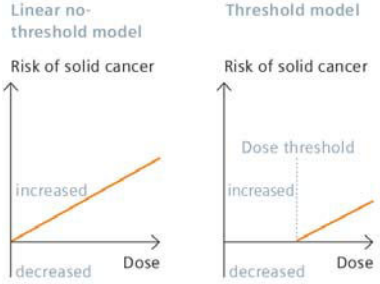
Penetration depth of certain types of radiation

Alpha (α) radiation can already be stopped by a sheet of paper, Gamma (γ) radiation and X-rays are only absorbed by dense materials like lead



Risk assessment and Management

Currently there are 2 main models used to determine the risks of low doses of radiation. The linear, no-threshold model and the threshold model. The linear, no-threshold model predicts that all levels of radiation exposure increase the risk of long term or stochastic damage. The threshold model proposes that anything below a certain level of radiation is safe. Currently the no-threshold model is the most widely accepted.



Effective Dose

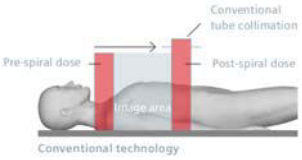
Starting with the total absorbed dose (D) one can calculate an Equivalent dose (H) with an estimated damage factor (w_r) for that type of radiation. $H(Sv) = D(Gy) * w_r$ an additional weighting factor for the sensitivity of different tissues gives the effective dose: $E(Sv) = \sum w_i * H_{tissue}$

Tissue or organ	w_i according to ICRP 60	w_i according to ICRP 103
Gonads	0.20	0.08
Red bone marrow	0.12	0.12
Colon	0.12	0.12
Lungs	0.12	0.12
Stomach	0.12	0.12
Breast	0.05	0.12
Liver	0.05	0.04
Esophagus	0.05	0.04
Thyroid	0.05	0.04
Skin	0.01	0.01
Bone surface	0.01	0.01
Salivary glands	–	0.01
Brain	–	0.01
.....	.....	.....
$\sum w_i$	1.00	1.00

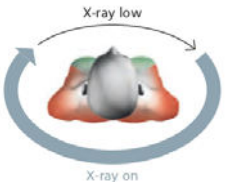
Weighting factors as estimated and published by the International Commission on Radiological Protection

Adaptive Dose Shield – Dynamic Collimator Control

It is routine in spiral CT to do an half-rotation of the gantry before and after each scan. Only part of the data acquired in this “over-ranging” is necessary.



Organ-Based Dose Modulation



Stochastic health risk assessment

Based on cancer incidence rates from a general population, the lifetime baseline risk (LBR) can be calculated. It is the cumulated probability of having a specific cancer over a lifetime. $LBR = \int_{a_{min}}^{a_{max}} m(a,g) S_{aj}(a,g) da$ where $m(a,g)$ is the cancer incidence rate in a chosen population at age (a) and gender (g) and $S_{aj}(a,g)$ the cancer free survival rate. The lower limit is the age at exposure and the upper limit the attained age since exposure.

Summary and Conclusion

Radiation exposure due to X-ray sources such as during Computed tomography can be effectively reduced. Organ-Based Dose Modulation and the Adaptive Dose Shield – Dynamic Collimator Control are just two examples of a number of measures developed by the industry. Other examples such as Real-time anatomic exposure control, ECG-controlled dose modulation for cardiac spiral CT, Flexible ECG-triggered sequential scan or Adjustments of scan parameters dedicated to pediatric CT imaging are other examples.
Computed Tomography is not the only problematic imaging modality out there. There are similar measures for PETCT, SPECT, and conventional X-ray yet the most important are probably effective Dose Monitoring before any scan is even started. Especially children are more vulnerable to long term effects of radiation exposure due to a higher amount of actively dividing cells due to the growth process.

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"Bladder Tumor –Interventional and IGS Therapies"

Systems used, Limitations with Future Outlook

Instruments for Image Guided Procedures
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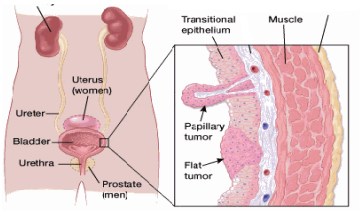
Abstract

Bladder cancer is one of the main cause of cancer related death(7th and 17th among men and women respectively). With early diagnosis and treatment the survival rate can be significantly improved. Currently there are various methods of treatment. The suitability of the treatments depend on the stage of the cancer. .These treatment options are Transurethral Resection of the Bladder Tumor (TURBT), Cystectomy, Intravesical treatments, Chemotherapy and Radiation therapy.

Introduction



Basic Anatomy of Bladder source: http://www.cancer.org/cancer/bladdercancer/

Types of Bladder Tumour

Based on Aggressiveness

Non-invasive: tumors are still in the inner layer of cells

Invasive: cancers grow into the lamina propria or even deeper into the muscle layer.

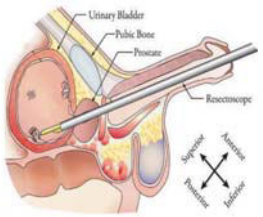
Based on Shape of Tumor

Papillary carcinomas: grow in slender, finger-like projections from the inner surface of the bladder toward the hollow center.

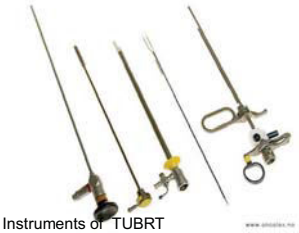
Flat carcinomas: do not grow toward the hollow part of the bladder at all.

Interventional and IGS Systems and Limitations

Transurethral Resection of the Bladder Tumor (TURBT)



TUBRT source: http://www.kanpururologycentre.com/images/facilities/turb.png



Instruments of TUBRT source:http://oncolex.org

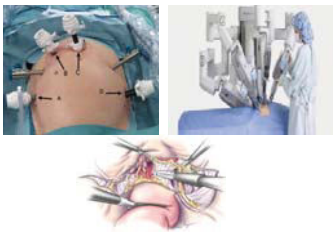
Limitations

- Quality control: all visible and microscopic superficial and invasive tumours must be removed.
- Depends on the experience of the surgeon (institution).
- Tumors could be understaged during evaluation i.e. their penetration can be underestimated.
- Complications after the TURBT.E.g. bleeding and perforation of the bladder
- Conventional white-light cystoscop has low accuracy in the detection of flat lesions.

Future developments

- Dedicated teaching programmes
- New resectoscope design allowing better control of the depth of resection and avoid perforation
- Combination with chemotherapy
- New imaging technologies: for e.g. Fluorescence cystoscopy and Narrow-band imaging

Cystectomy



Laporascopic and Robot assisted Cysectomy Source: [2],[3]

- The partial or complete removal of the bladder
- Used to treat bladder cancer which have grown into the bladder muscle
- Can be open surgery, Laparoscopic or robotically assisted laparoscopic surgery

Considerations and Limitations

Open surgery

- Still considered the gold standard [1]
- Bigger incision meaning higher discomfort and possibly more complications and higher blood loss

Laparoscopic

- Minimally invasive
- Provides encouraging oncologic outcomes mirroring those reported for Open Resection
- Increased operative time with financial costs
- Significant learning curve :

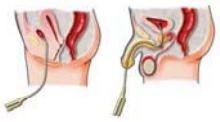
Robot assisted

- Enables complex procedures easily
- Providies three-dimensional (3D) and magnified views

Future developments

- Assessment of long-term for laporascopic oncological results
- Standardization[2] of Laporascopic cystectomy

Intravesical Treatments of Bladder Cancer



Instruments of TUBRT source:http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@cah/@gen/documents/image/cr_116305.jpg

- Uses catheters to admister cytoablative or immunostimulative ajents into bladder
- Usually administered as adjuvant therapy after surgical transurethal resection

Immunostimulative

- Bacillus Calmette-Guerin therapy(BCG)
- Interferon

Cytoablative(Intravesical)chemical therapy

- Mitomycin
- Thiotepa

Limitations

- Mainly affect the cells lining the inside of the bladder
  Used for superficial tumor
- Side effects
- Drug disposition modelling
  Personal variations
- Short drug residence time

Future Developments

- Improving the total drug exposure
- Enhancing the delivery of agents to bladder tissues (e.g., using permeation enhancers)
- Prolonging the exposure (e.g., using bioadhesive)
- Enhancing cell membrane permeability
- Gene therapy, with the goal of either correcting the mutated and malfunctioned genes

Chemotherapy and Radiation therapy

- Administered for advanced stages of bladder cancer
- Could be used in combination
- As a treatment option for people who can not have surgery
- Drug toxicity and radiation dose is the major limiting factor on their application

Summary and Future Outlook

The unique properties and accessibility of urinary bladder render it a fertile ground for evaluating additional novel experimental approaches to regional therapy. Accordingly the following points will be the focus of future developments in the treatment of bladder tumor

- Various intravesical therapies and combinations
- The combination of TURBT with intravesical therapies
- The use of radiation therapy in combination with chemotherapy
- The long term ontcological effectiveness assessment of the effects of robot assisted Laparoscopic surgery
- New innovations in resectoscope design and endoscopic imaging

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