For the Department of Radiotherapy (Medical Director: Professor Dr. med. Dirk Vordermark) and the Department of Gynecology (Medical Director: Professor Dr. med. Christoph Thomssen) of the Medical Faculty of Martin-Luther University, Halle-Wittenberg

External beam radiotherapy for cervical cancer with Cobalt-60 in Ethiopia

—

Adherence to therapy, adverse effects and overall survival of 1009 patients 2008-2012

Dissertation

in fulfilment of the requirements for the academic degree of

Doctor medicinae (Dr. med.)

submitted to the Medical Faculty of the Martin-Luther University Halle-Wittenberg by

Ulrike Mölle

born on 21.01.1989 in Berlin

Assessment committee

1. Prof. Dr. Dirk Vordermark
2. Prof. Dr. Christoph Thomssen
3. Prof. Dr. Rainer Souchon (University Hospital Tübingen)

14.06.2016

15.12.2016

Aus der Universitätsklinik und Poliklinik für Strahlentherapie (Direktor: Prof. Dr. med. Dirk Vordermark) und aus der Universitätsklinik und Poliklinik für Gynäkologie (Direktor: Prof. Dr. med. Christoph Thomssen) der Medizinischen Fakultät der Martin-Luther-Universität Halle-Wittenberg

Radiotherapeutische Behandlung des Zervixkarzinoms mit Cobalt-60 in Äthiopien

—

Therapieadhärenz, Nebenwirkungen und Überleben von 1009 Patientinnen 2008-2012

Dissertation

zur Erlangung des akademischen Grades

Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät der Martin-Luther-Universität Halle-Wittenberg von

Ulrike Mölle

Geboren am 21.01.1989 in Berlin

Gutachter

1. Prof. Dr. Dirk Vordermark
2. Prof. Dr. Christoph Thomssen
3. Prof. Dr. Rainer Souchon (Universitätsklinikum Tübingen)

14.06.2016

15.12.2016

Abstract

Cervical cancer is the second most commonly diagnosed cancer among females in Ethiopia. Data on outcome of radiotherapy for cervical cancer patients in Ethiopia and other parts of sub-Saharan Africa are limited. In Ethiopia, radiotherapy is only available at the University Hospital in Addis Ababa. The purpose of this study is to describe the current practice of radiotherapy for cervical cancer patients at the Radiotherapy Center of Tikur Anbessa Hospital and analyse overall survival of cervical cancer patients according to whether they completed or discontinued radiotherapy.

This unicentric cohort study reports on retrospectively analysed data of all patients diagnosed with cervical cancer by biopsy and treated with radiotherapy 2008-2012 at Tikur Anbessa Hospital, Addis Ababa. Brachytherapy was not available, therefore all patients received external beam radiotherapy by Cobalt-60 according to guidelines based on stage of FIGO. Data on adverse effects and survival were obtained from clinical records and telephone interviews. The multivariate Cox proportional hazards regression was used to estimate hazard ratios. Adjustment was done for total dose of radiotherapy, HIV status, estimated glomerular filtration rate, ECOG score and grade of anemia. Within the framework of this study, the offical translation of the EORTC Quality of Life questionnaires for cervical cancer patients into the Amharic language was conducted.

Out of 1009 cases, 788 patients were scheduled for radiotherapy according to guidelines. Adverse effects were common (e.g., proctitis and incontinence in 29% and 22% respectively). After guideline-conform assignment, patients, who completed radiation treatment had better outcome than those, who discontinued. One-year overall survival after radical radiotherapy (n=180) for FIGO stage IIA-IIIA was 89% and 96% (hazard ratio 1.3, 95% confidence interval 0.5-3.3) for discontinuation ($<$72 Gy) and completion ($\geq$72 Gy) respectively. One-year overall survival after non-radical radiotherapy (n=389) for FIGO stage IIIB and IVA was 71% if discontinued compared to 88% after minimum recommended dose of 44 Gy (hazard ratio 3, 95% confidence interval 1.4-6.7). One-year overall survival after monthly single fractions of 10 Gy for FIGO IVB (n=219) was 14% after 1 and 76% after 2 single fractions (hazard ratio 5.4, 95% confidence interval 1.8-16).

This study provides the first data on outcome of cervical cancer patients after receiving radiotherapy in Ethiopia. Completion of guideline-conform radiotherapy resulted in more favourable OS. This may reflect a true dose-effect or, possibly, a selection of fitter patients, who did not discontinue radiotherapy due to less aggressive tumours. Better supportive care, higher adherence to protocols, radical radiotherapy for patients staged FIGO IIIB and IVA, brachytherapy services, a second radiotherapy machine to secure availability and socioeconomic support would probably add lifetime to the patients. Further research on Quality of Life of cervical cancer patients treated with radiotherapy in Ethiopia is necessary. The respective questionnaires are now available in Amharic language.

Mölle, Ulrike: External beam radiotherapy for cervical cancer with Cobalt-60 in Ethiopia – Adherence to therapy, adverse effects and overall survival of 1009 patients 2008-2012, Halle (Saale), University, Faculty of Medicine, Dissertation (2016), pp. 1-80

Referat

Das Zervixkarzinom ist das am zweithäufigsten diagnostizierte Malignom der Frau in Äthiopien. Bislang existieren keine Daten zu Ergebnissen und Wirksamkeit der Strahlentherapie für Zervixkarzinompatientinnen in Äthiopien und nur wenige Studien dazu aus anderen sub-saharischen Ländern. Zugang zu Radiotherapie besteht in Äthiopien ausschliesslich im Universitätsklinikum Tikur Anbessa in Addis Ababa. Der Zweck dieser Studie ist eine Beschreibung der aktuellen Praxis strahlentherapeutischer Behandlung des Zervixkarzinoms in Äthiopien, sowie die Analyse des Überlebens der Patientinnen nach vollständiger oder frühzeitig abgebrochener Strahlentherapie.

Alle Patientinnen mit histologisch gesichertem Zervvixkarzinom und anschließender Strahlentherapie am Universitätsklinikum Tikur Anbessa 2008 - 2012 wurden in diese unizentrische Kohortenstudie eingeschlossen. Die Frauen wurden in Abwesenheit von Brachytherapie ausschließlich perkutan mit einer Cobalt-60 Einheit entsprechend des FIGO-Stadiums bestrahlt. Daten zu auftretenden Nebenwirkungen und dem Überleben der Patientinnen wurden den Patientenakten und zusätzlichen Telefoninterviews entnommen. Hazard Ratios wurden mithilfe des multivariablen proportionalen Hazardmodell nach Cox ermittelt. Dabei wurde nach der Gesamtdosis der Radiatio, dem HIV-Status, der glomerulären Filtrationsrate, dem ECOG Leistungsstatus und dem Grad der Anämie adjustiert. Im Rahmen dieser Studie wurden die EORTC Lebensqualitätsfragebögen für Zervixkarzinompatientinnen offiziell ins Amharische übersetzt.

Von insgesamt 1009 Patientinnen wurden 788 entsprechend der klinikeigenen Bestrahlungsleitinien einem Bestrahlungsschema zugewiesen. Nebenwirkungen traten häufig auf (z.B. Strahlenproktitis und Inkontinenz in jeweils 29% und 22%). Nach leitliniengemäßer Therapieplanung hatten Patientinnen mit vollständig absolvierter Radiatio bessere Überlebenschancen als Therapieabbrecher. Das 1-Jahres-Überleben nach radikaler Strahlentherapie (n=180) für FIGO IIA-IIIA betrug 89% für Therapieabbrecher ($<$72 Gy) und 96% für Patientinnen nach Bestrahlung mit der vorgesehenen Gesamtdosis ($\geq$72 Gy) (Hazard Ratio: 1.3 95% Konfidenzintervall 0.5-3.3). Entsprechend war das 1-Jahres-Überleben nach nicht-radikaler Radiatio für FIGO IIIB und IVA (n=389) ungünstiger nach Therapieabbruch (71%), als nach Bestrahlung mit der Minimaldosis von 44 Gy (88%) (Hazard Ratio 3, 95% Konfidenzintervall 1.4-6.7). Für die palliativ bestrahlten Patientinnen mit FIGO IVB (n=219) betrug das 1-Jahres-Überleben nach einer Einzelfraktion von 10 Gy 14%, im Vergleich zu 76% nach zwei Einzelfraktionen und insgesamt 20 Gy (Hazard Ratio 5.4, 95% Konfidenzintervall 1.8-16).

Die vorliegende Studie legt die ersten Daten zu Ergebnissen und Wirksamkeit der Strahlentherapie für Zervixkarzinompatientinnen in Äthiopien vor. Nach leitliniengemäß vollständig absolvierter Radiatio zeigten die Patientinnen höhere Überlebenswahrscheinlichkeiten als bei Therapieabbruch. Dies kann sowohl die Dosiswirkung als auch die Selektion von Patientinnen mit ausbleibendem Therapieabbruch bei günstigerer Prognose aufgrund einer weniger aggressiven Tumorbiologie widerspiegeln. Bessere Supportivtherapie, höhere Leitlinienadhärenz, radikale Bestrahlung für Patientinnen mit FIGO-Stadien IIIB und IVA, Brachytherapie, eine weitere Bestrahlungseinheit zur perkutanen Radiatio und sozioöko-nomische Unterstützung der Patientinnen sind grundlegend für eine Verlängerung der Überlebenszeit der Zervixkarzinompatientinnen in Äthiopien. Im Sinne einer Therapieoptimierung ist eine prospektive Untersuchung der Lebensqualität von Frauen mit Zervixkarzinom und Radiatio in Äthiopien grundlegend. Eine Version der jeweiligen Fragebögen in amharischer Sprache steht von nun an zur Verfügung.

Mölle, Ulrike: Radiotherapeutische Behandlung des Zervixkarzinoms mit Cobalt-60 in Äthiopien – Therapieadhärenz, Nebenwirkungen und Überleben von 1009 Patientinnen 2008-2012, Halle (Saale), Univ., Med. Fak., Diss., 80 Seiten, 2016

Contents

List of Abbreviations

AP/PA	anterior-posterior / posterior-anterior
BED	biological effective dose
CCB	concomitant boost (hyperfractionation)
CF	conventional fractionation
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Co-60	Cobalt-60
CTCAE	Common Terminology Criteria for Adverse Events
DAG	directed acyclic graph
EBRT	external beam radiotherapy
eGFR	estimated glomerular filtration rate
e.g.	exempli gratia
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FIGO	The International Federation of Gynecology and Obstetrics
Gy	gray
HDI	Human Development Index
HIV	human immunodeficiency virus
HPV	human papilloma virus
HR	hazard ratio
i.a.	inter alia
ICBT	intracavitary brachytherapy
i.v.	intravenous
Linac	Linear accelerator
MeV	megaelectron-volt
MLC	multileaf collimator
MSAS	minimal sufficient adjustment set
n/a	not applicable
NSAID	nonsteroidal anti-inflammatory drug
p.o.	per os
postOP	after hysterectomy
QLQ-C30	Quality of Life Questionnaire - Core
QLQ-CX24	Cervical Cancer-Specific Quality of Life Questionnaire
QoL	Quality of Life
Rec	Recurrence
RT	radiotherapy
SCC	Squameous Cell Carcinoma
SSD	source-to-skin-distance

TAH	Tikur Anbessa Hospital
TAHRC	Tikur Anbessa Hospital Radiotherapy Center
TD	total dose of radiation in Gy
VIA	visual inspection with acetic acid
vs.	versus
WHO	World Health Organisation
3DCRT	three dimensional conformal radiotherapy
5FU	Fluorouracil
95% CI	95% confidence interval

1 Introduction

This study provides an insight to radiotherapeutic treatment for cervical cancer patients in Ethiopia. The following introductory chapters serve as a theoretical foundation in order to outline the relevance of this study. Therefore, I will firstly demonstrate the global role of cervical cancer. Secondly, the importance of radiotherapy (RT) for cervical cancer and the use of different techniques are explained. This section concludes with a depiction of epidemiology and treatment of cervical cancer in Ethiopia.

1.1 The worldwide burden of cervical cancer

Cancer of the uterine cervix is the leading cause of cancer death among African women [1]. How come that in spite of its preventable and curable properties, this disease still kills more than a quarter of a million women every year [2]? In developed countries cervical cancer gradually becomes a rare disease as data on incidence trends after successful implementation of screening programs suggest [2, 3]. Hence, there is a large disproportion of incidence and mortality rates between countries with higher and lower index of human development (HDI), respectively [4]. In countries with low HDI cervical cancer is the most prevalent among all neoplasms of both sexes [5]. Meanwhile, it is established that virtually all cases of cervical cancer are caused by an infection of certain oncogenic human papillomavirus (HPV) types [7, 8]. Moreover, screening for precancerous lesions caused by HPV prove to be effective [9]. Consequently the large disparity of cervical cancer incidences mainly reflects the lack of preventive measures such as vaccinations and nationwide screening programs for the early detection of precancerous lesions. Accordingly, data on incidence of cervical cancer in the United states prior to the dissemination of Papanicolaou testing (1947-1948) were comparable to those found today in African countries [10]. However, not only prevention is an issue in medically underserved regions - access to adequate therapy of cervical cancer remains insufficient [11]. Cervical cancer tragically serves as a symbol for global health disparity - the limited access to appropriate treatment in Eastern Africa results in an age-standardised mortality rate of 25.3/100,000 and therefore a twelvefold of mortality rates for cervical cancer in Western Europe [12].

Data on survival of cervical cancer patients in sub-Saharan Africa are scarce and of arguable quality [13]. The existing limited data show, that in comparison with survival rates from 2002 of 70% and 66% in the United States and Western Europe respectively, survival of cervical cancer patients in sub-Saharan Africa stays far behind with only 21% [14]. Most likely, not only insufficient access to adequate therapy and late stage at presentation accounts for this large gap in survival probabilities throughout the world. The role of a globally differing quality of treatment may be at least as responsible for the stated disparity. In the following I will take a closer look on the role of different modalities of RT for cervical cancer treatment.

1.2 The role of radiotherapy for treatment of cervical cancer

As shown in Table 1, primary treatment of cervical cancer according to staging by The International Federation of Gynecology and Obstetrics (FIGO; see [46]) consists of either surgery or a combination of RT and chemotherapy [15]. Early cervical cancer (stages of FIGO Ia1, Ia2, Ib1, IIa1) indicates for hysterectomy [16], while stages of FIGO IIb and higher and FIGO Ib2 and IIa2 with risk factors (see Table 1) are treated with primary concurrent chemoradiation [17].

Table 1: Cervical cancer treatment according to stage of FIGO, taken from Colombo et al. [15]

Stage	Treatment	Issue
Ia1	Conisation or simple hysterectomy ± salpingo-oophorectomy and PLND if LVSI	Conservative surgery
Ia2	Conisation / radical trachelectomy or modified total hysterectomy and PLND	Adjuvant RT/CT if risk factors (LVSI, G3, positive resection margins, multiple nodes)
Ib1, IIa	Radical hysterectomy (Wertheim-Meigs operation) and PLND	Adjuvant RT/CT if risk factors (LVSI, G3, positive resection margins, multiple nodes)
Ib2, IIb-IV	Combination CT/RT with cisplatin	NACT to large bulky tumours prior CT/RT

PLND, pelvic lymphadenectomy; LVSI, lymphovascular space invasion; CT, chemotherapy, NACT, neoadjuvant chemotherapy.

Lacking an effective prevention and early detection program, patients with cervical cancer in sub-Saharan Africa tend to present with advanced stages of FIGO [18, 19, 20, 21]. Given these late stages of disease at presentation, RT plays a key role in cervical cancer treatment in sub-Saharan Africa. Almost 60% of all women treated at Mulago Hospital Radiotherapy Center in Uganda 1995-1997 came for cervical cancer therapy [22]. Not only for curative treatment but for palliation as well, RT has proven to be more effective in terms of Quality of Life and cost-effectiveness than analgesia alone or chemotherapy [23]. At the same time, the particular importance of RT for cervical cancer treatment is contrasted by a widely reduced access to treatment in African countries. In 2002, less than one fifth of the needed megavoltage RT machines (cobalt units or linear accelerator) are supplied [23]. Furthermore, 60% of RT supply concentrates in Egypt and South Africa. In 2010 29 African countries did not have a single RT machine available [24].

There are not only considerable quantitative disparities when it comes to distribution of RT services between sub-Saharan countries compared to HDI countries. Moreover, different techniques are used. In the following I will introduce and compare these techniques with regard to irradiation therapy of cervical cancer.

The concept of RT compromises the use of ionising radiation to treat or palliate malignant diseases. However, not only malignant cells but also healthy tissue is damaged by ionising radiation. An optimum cancer therapy would effectively destroy malignant cells while sparing non-cancerous cells. This ideal of sharply targeted irradiation doses can be approached by modern linear accelerators (linacs), which emit either high energy electrons or megavoltage x-rays. Other than that, external beam radiotherapy (EBRT) can be performed with superficial or orthovoltage x-ray machines for treatment of skin cancer or with radioisotope machines that use high energy-emitting radioisotopes. The most widely used radioisotope is Cobalt-60 (Co-60). Being subject to natural decay with a half life of 5.3 years [25], Co-60 units can not be turned off and need to be replaced regularly. Regarding beam penumbra, Co-60 units produce a less sharp beam edge than linacs [26]. Furthermore, radiation dose at 10 cm of depth amounts to only 54% in case of Co-60 units, while radiation dose at skin level varies between 40-50%. EBRT by Co-60, commonly known as telecobalt, consequently causes radiation dermatitis as a very common side effect [26]. Linacs provide a deeper beam penetration, generatig up to 25 MeV compared to 1.25 MeV by Co-60, and are therefore clinically advantageous for larger patients or in

case of deep-seated tumours. Additionally, sharpness in beam avoids unwanted irradiation of nearby organs. Adverse effects are proven to relate directly to dose distribution [27] and therefore Intensity Modulated RT (IMRT) constitutes a viable feature in linacs to decrease radiation associated morbidity [28]. However, in order to increase precision, the handling of linacs became more and more complex due to their computerized control systems and several new features to assure targeted irradiation. Linacs compromise sophisticated features "[...] such as high dose rate modes, multileaf collimation, electron arc therapy, and the dynamic treatment option on the collimators (dynamic wedge), MLC leaves (IMRT), gantry or table while the beam is turned on." [25], p. 56. Additionally the fact that the source of irradiation - x-ray or electron energies - can be selected within one machine contributes to a higher intricacy, which requires a much more skilled technical attention than the handling of telecobalt machines, providing a non-fluctuating source of radiation [29]. Altogether, Co-60 units are cheaper in installation and maintenance, easier to operate, much less dependent on reliable electrical power and less vulnerable to changes in humidity or temperature which makes telecobalt a convincing alternative to linear accelerators in a setting of constrained resources and unstable power supply. For further reading, Van Dyk et al. compiled an excellent overview on strengths and limitations of both treatment modalities [30]. He furthermore emphasizes the advantageous position of Co-60 in treatment of tumours which are situated close to to the patients surface. However, this does not apply to cancer of the uterine cervix, especially if the spatial distance between opposing radiation fields, hence the patient's seperation, is large.

Regardless which technique is used, for best outcome of cervical cancer treatment not only EBRT but the combination of EBRT with Intracavitary Brachytherapy (ICBT) is strongly recommended. First EBRT is used to shrink the cervical tumour into the range of the high-dose portion of the secondly applied ICBT [31]. Altogether the tumour center should receive a total radiation dose of 80-95 gray (Gy) [15, 17]. In spite of the importance of ICBT in treatment of cervical cancer, in merely 20 out of 52 African countries brachytherapy services were available in 2010 [24]. Ethiopia is not among these countries.

1.3 Cervical cancer and radiotherapy in Ethiopia

After Nigeria, Ethiopia is the second most populated African country with over 44 million females [32]. The vast majority of the population (80.6%) lives in rural areas [32], which makes Ethiopia one of the least urbanized countries in the world. Generally, epidemiological data on cervical cancer in African countries is sparse [33, 13]. When publishing information on "Cancer Incidence in Five Continents" in 2013, the World Health Organisation (WHO) included data from 290 cancer registries from 68 countries. However, merely 5 cancer registries were situated in sub-Saharan Africa [34]. Regarding incidence and mortality data in Ethiopia, most figures quoted in the literature are averages from neighbouring countries or hospital-based and therefore biased as most women do not access the hospital care system for financial and logistical reasons. Vice versa, low economic status is a risk factor for cervical cancer and incidence and mortality of cervical cancer is expected to be higher within this unreported group of patients [35].

Ethiopian data on incidence and mortality of cervical cancer are collected by the Addis Ababa City cancer registry since September 2011 [36]. According to their estimates, there are 7095 women newly diagnosed with cervical cancer every year in Ethiopia [37]; 4732 are estimated to die from cervical cancer every year. However, incidence data were calculated on the basis of regional data and no actual

data on mortality were available. Mortality was estimated from national cancer incidence for 2012 and modelled survival. Furthermore, 54.7% of the data on incidence of cervical cancer in Ethiopia originate from the University Hospital Tikur Anbessa [38]. Hence, estimates from the only Ethiopian institution for oncological treatment in an urban setting are destined to represent the whole country, despite its mostly rural profile. Given this fragility of data, underreporting is expected. However, even for the calculated amount of cervical cancer patients, access to adequate oncological treatment remains limited. There is one single public institution specialized on oncology and RT in Ethiopia: the Tikur Anbessa University Hospital (TAH). Among others, the staff comprises the only four radiation oncologists of the whole country. Patients with cervical cancer of all stages are referred to TAH from all over the country, not only, because it solely holds a RT machine. Until 2010, radical hysterectomy, as recommended for early stages of cervical cancer, was exclusively performed in the Department of Gynecology of TAH.

As Table 1 shows, radiation treatment is given as adjuvant therapy to surgery for early stages of FIGO. However, RT gains therapeutic importance being the primary treatment in case of FIGO Ib2 or IIb and higher. Untill the closing date of this study (07.08.2013), RT at TAHRC was performed solely as EBRT by telecobalt without additional ICBT as there were no brachytherapy services available in Ethiopia.

The Radiotherapy Center of Tikur Anbessa Hospital (TAHRC) opened in 1997 as a result of the cooperation between the Ethiopian Government and the International Atomic Energy Agency [39]. According to the oncology registry at TAH, 1300 patients were treated with RT within the first four years. Since then, patient numbers more than quadrupled to up to 1400 patients per year. The Co-60 unit is in daily use from 8 am to 5 pm and is liable to monthly maintenance during which no patients are treated. In 2014, Dr. Eva Kantelhardt, me and several contributors published data on the outcome of a larger sample of cervical cancer patients, who received oncological treatment at TAH [40]. As a result of the limited access to RT and other oncological treatments, we revealed considerable waiting times between registration and the start of radiotherapeutic treatment. Along with these waiting times, stages of FIGO increased. Hence, the demand for specialised cancer treatment in Ethiopia is much higher than the actual supply.

The WHO's calculation for the minimum amount of teletherapy machines necessary for adequate oncological treatment in Ethiopia revealed an actual need for 74 machines [24]. Tragically, one single RT machine is provided for the whole country.

2 Aim of this study

As described in the preceding chapters, cervical cancer patients who present at TAHRC are treated in a setting of limited resources. In general, there are very few data on outcome of cervical cancer patients under comparable circumstances. For all sub-Saharan African countries, there are two studies on survival of radiotherapeutically treated cervical cancer patients to my knowledge, originating from Zimbabwe and Uganda [18, 41]. Bah. et al. published survival rates of cervical cancer patients in the Gambia, who did not receive RT [42].

Recent publications point towards the need for more epidemiological data on non-communicable diseases, including cancer, e.g., from cohort studies [43, 44]. In case of Ethiopia, there is no published information on RT treatment guidelines, neither on outcome of patients treated according to these guidelines. At the same time, aiming to guarantee reliable health care standards, these treatment guidelines need to be transparent and comparable throughout centers [46]. Besides an adequate technical equipment, high process quality is the key requisite for patient safety as it ensures the actual implementation of evidence-based medicine. In terms of oncological RT, underdosing might be as harmful as overdosing as recurrence of the cancerous disease just as radiation toxicities or secondary cancers lead to decreased Quality of Life and even lower survival.

As a response to this lack of data, the main purpose of the present study is to provide first data on RT protocols, their implementation and the resulting outcome in terms of survival of cervical cancer patients in Ethiopia. To understand the setting of the application of these guidelines, I will describe the clinical practice of RT at the TAHRC. Therefore, I will look at the characteristics of the patient's collective on the one hand and the modality of RT and consequently occurring adverse effects on the other hand.

In particular, this study aims to assess, whether guideline-conform RT at TAHRC is effective. Therefore, I will compare the outcome of patients, who completed their RT schedule as recommended with those, who discontinued and received lower doses of radiation. Overall survival serves as the primary endpoint of this study. As overall survival is not only influenced by therapeutic measures, prognostic factors for cervical cancer patients need to be clarified in order to be aware of possible confounding. Appendix 9.2 displays an overview on these prognosis-related characteristics. They are subsequently used to compute directed acyclic graphs shown in Chapter 3.4.1 in order to identify the confounding variables.

Naturally, survival time can only give quantitative information on the outcome of patients after oncological treatment. As an excursus from the data collection and analysis, a viable tool for future research can be presented. That is, within the framework of this study I conducted the translation of Quality of Life (QoL) Questionnaires into Amharic language (see Chapter 3.6)

In summary, the intention of this study is to assess the current practice of RT at TAHRC by means of a survival analysis of cervical cancer patients. The results hopefully give insight to radiotherapeutic treatment in Ethiopia and its effectivity. As a consequence and based on the data and their comparison with international standards, strengths and limitations of RT at TAHRC will be identified (see Chapter 5.1). Subsequently and as a result of the findings, eventual potential for improving the patients' outcome after RT at TAHRC can be pointed out (see Chapter 5.4).

3 Methods

This section provides information on how this study was conducted. A unicentric cohort study design is used in order to assess the current clinical practice of RT for cervical cancer patients at TAHRC 2008-2012 by means of an analysis of overall survival.

Firstly, inclusion criteria for radiotherapeutic treatment in case of cervical cancer are presented. In the following, the mode of data collection is described. In the latter, detailed information on documentation of anamnestical and tumourrelated data is given, such as staging according to FIGO, evaluation of the patient's performance status according to the Eastern Cooperative Oncology Group (ECOG), documentation of adverse effects and the survival status of the patients. Secondly, Chapter 3.3 illustrates the different treatment modalities available at TAHRC, focusing on radiotherapeutic treatment and guidelines for RT according to stage of FIGO. Thirdly, information on the statistical analysis is given. Directed acyclic graphs are used in order to identify adjustable confounders for survival analysis. Fourthly, the ethical approval for the present study will be set out.

The section concludes with an excursus on the first Amheric Quality of Life (QoL) Questionnaires. As QoL is an important indicator for the outcome of patients after receiving oncological treatment, the decision was made to conduct the official translation of these questionnaires into Amharic within the framework of this study. This Chapter may serve as an outlook to future prospective studies.

3.1 Criteria for eligibility of participants

This retrospective unicentric cohort study reports on patients, who were treated with RT for cervical cancer at TAHRC in Addis Ababa, Ethiopia. The study includes all women with histologically verified cancer of the cervix uteri who were diagnosed by biopsy after 10.09.2008 and received RT at the TAHRC before 11.09.2012. All patients included were treated with RT to the pelvis for cervical cancer. Some received primary surgical treatment and some received chemotherapy additionally.

3.2 Information on data collection

3.2.1 Data acquisition from patient files

All patient characteristics, tumour characteristics and information concerning therapy, outcome and follow-up were extracted from the patients' files, where the staff of TAHRC documented the medical history of the patients and information on diagnostic and therapeutic procedures. Language of documentation was English. Dates were recorded according to the Ethiopian calender. However, pathology reports were usually dated according to the Gregorian calender. Conversion of all dates to Gregorian dates was done after data collection.

Patient files contained information on the patient's origin, age, menopausal status, marital status, number of sexual partners, mode of contraception and HIV status. I classified the origin as rural if the patient did not originate from one of the 10 biggest cities in Ethiopia. According to the census data from the Central Statistical Agency from July 2012, their population exceeded 140,000 inhabitants [32]. If patients came from one of these 10 cities, their origin was classified as urban.

Age at time of registration at TAHRC was documented. However, no date of birth was given and within the patient file data on age could vary. If menopausal status was not documented by the physicians, premenopausal status was assumed in case of a patient younger than 30 years, while post-

menopausal status was assumed in case of a patient older than 49 years. Otherwise menopausal status was documented as unknown. Patients were routinely asked for the number of their sexual partners in lifetime. The use of condoms was not inquired. Other contraceptive methods were documented.

Prior to RT, a hemogram and the measurement of serum creatinine served as a routine laboratory test for each patient in order to evaluate eligibility for RT. HIV status was documented if the patient had been screened. After 10.09.2011 every patient registered at TAHRC was screened for HIV on a regular basis. Before 10.09.2011 only patients with a high risk profile (e.g., HIV-positive partner) were tested for HIV. HIV status was measured using the enzyme-linked immunosorbent assay method.

3.2.2 Assessment and documentation of stage of FIGO

Tumours were classified according to the FIGO staging system [46]. The stage of FIGO was documented in the patient's file after clinical examination by at least one of the four radiation oncologists from TAHRC. In cases of discrepancy between examinations, another radiation oncologist was consulted. In case of sonographic detection of hydronephrosis around the time of diagnosis, the FIGO stage was classified as stage IIIb. In case of distant metastasis, diagnosed with abdominal ultrasound or chest X-Ray, the FIGO stage was classified as stage IVb. Patients without findings in routinely performed chest X-ray and abdominal ultrasound were considered "free of distant metastasis". The histological results were documented according to written notes from pathology reports.

The patient's tumour stage at time of booking and start of RT was categorised as "postOP" in case of previous surgical treatment for cervical cancer within 6 months before staging. If surgery for cervical cancer was done before 6 months previous to staging, the patient's tumour was staged as "Recurrence after surgery", regardless of the ongoing presence of the local tumour or an actual recurrence. In case of no surgery and returning cervical cancer after previous RT the tumour was classified as "Recurrence".

The stage of FIGO was documented at three points in time. However, throughout the patient file a large number of differing stages of FIGO was found. TAH is a teaching hospital and both medical students and referring physicians from all over the country collected stages of FIGO. I therefore chose to define the first FIGO stage assessed by an oncologist at TAHRC as viable. A second stage of FIGO was entered into the database, which was collected at the date of booking for RT. This FIGO stage additionally included potential findings of chest X-ray and abdominal ultrasound. The third stage of FIGO entered into the database was assessed at the first day of radiotherapeutic treatment just before the patient started her radiation schedule.

3.2.3 Documentation of patient's performance status according to Eastern Cooperative Oncology Group (ECOG)

As an indicator for Quality of Life (QoL), the patient's performance status was assessed according to the Eastern Cooperative Oncology Group (ECOG) [47]. ECOG scores were surveyed at different times. Three of these were entered into the database. The first ECOG score was recorded before RT started, the second within the first three months after RT and the third at the time of the latest documented follow-up. Consequently, data on the latter two ECOG scores after RT were only given in case follow-up was done. Radiation oncologists usually kept record of the patients' performance status. In case the oncologists of TAHRC did not document an ECOG score, the ECOG score was assessed after interpretation of the combination of the patient's age, her symptoms and further information on her well-being according to the patient's file.

3.2.4 Documentation of adverse effects

Information on adverse effects due to RT was sparse. In case of reporting, adverse effects were documented in the patient files or the treatment records. Grading of adverse effects was done in accordance with the ranking system of "Common toxicity criteria" [48]. Radiation oncologists at TAHRC used the common terms "mild", "moderate", "severe" and "life-threatening" to describe the occurring adverse effect. Thereby mild adverse effects are usually transient and do not require special treatment, moderate adverse effects can be alleviated with simple therapeutic measures and severe adverse effects not only interrupt daily activities of the patient but require therapeutic intervention. Life-threatening adverse effects were not described within this patient collective. However, these serious adverse effects would require immediate hospitalisation.

Incomplete documentation of adverse effects can be suspected, as appearance of, e.g., radiation dermatitis was very common according to the oncologists and documentation would not have had consequences. In Chapter 4.1.5 the limited options for therapeutic management of adverse effects are outlined. Oral follow-ups by telephone, which were carried out systematically by dint of the questionnaire in Appendix 9.4, revealed a notably higher rate of adverse effects than the documentation in the patient files (e.g. urinary incontinence in 32.3% and 18.2% respectively). However, the telephone interviews consist of simple questions concerning the patients' symptoms and possible adverse effects, both of which were self-surveyed by the patient and can not always be clearly separated. To differentiate between symptoms due to the cervical tumour and adverse effects due to RT, the latter had to appear for the first time after start of RT. Clinical signs were documented before and after start of RT. Patients who presented with symptoms, which could be confounded with adverse effects of irradiation before start of RT, were excluded from analysis of toxicity rates, e.g, patients with diarrhea for gastrointestinal infection. In case of a multimodal therapy approach (combination of surgery, RT and chemotherapy) a clear identification of the toxicity causing treatment was limited.

In order to distinguish acute and late adverse effects (see Table 7 and 8), data of the first follow-up done within three months after the last day of RT and data of all follow-ups done thereafter were documented seperately. For the latter, few patients came for several follow-ups. In these cases, the highest occurring grade was documented for each occurring toxicity.

Within the documented adverse effects, subcutaneous fibrosis of the suprapubic tissue, in the following labeled as "suprapubic fibrosis", was reliably documented by radiation oncologists. This naturally led to high rates as shown in Chapter 4.1.4.

In summary, due to the retrospective nature of this analysis and the high number of patients lost to follow-up, the documentation of adverse effects was inconsistent.

3.2.5 Documentation of supportive treatment options

The issue of effective pain management remains an unresolved problem in sub-Saharan Africa [49, 50, 51, 52]. Accordingly, at TAHRC, supportive treatment for cancer patients was generally limited.

Similar to the documentation of adverse effects, the documentation of their therapeutic alleviations was not carried out systematically at TAHRC. Furthermore, only the application of analgesics in general was entered into the database. I did not collect data on doses or frequency of drug administration and I only documented the strongest analgesic ever applied, as detailled information on analgesic treatment did not range within the scope of this study. Additionally, a qualitative interview with one

of the four radiation oncologists at TAHRC was conducted. Chapter 4.1.5 gives an overview of the treatment possibilities for the occurring adverse effects after RT.

3.2.6 Information on survival status after concluded RT

All patients with telephone numbers available were called for information on vital status. Language barrier was reduced as the interviews were conducted by study nurse Tinsae Gelata, whose mother tongue is Oromo. 34.6% of Ethiopians speak Oromo as a mother tongue while 29.3% of the Ethiopian population are native Amharic speakers [53]. However, being the statutory national language, Amharic is widely spoken as a second language. Tinsae Gelata speaks fluent Amharic as well. Information on the date of last contact and survival status was obtained by telephone from the patients or – in case of death – from relatives, who were asked for the date of the patient's death. Date accuracy was limited which is suspectedly due to high illiteracy rates in the rural population of Ethiopia. In 2010 69% of women in rural Ethiopia could not read and write at all and another 11% could only read a part of a sentence [54]. If the patient's death was dated to month and year by the patient's relative I assumed the 15th day of that month to be the date of death and if only the year of death was given by the relatives, I assumed the middle of the year (1st of July) to be the date of death.

If patients or relatives could not be contacted by telephone or in case of no available phone number, the last date of personal contact was taken from the patients' files and patients were censored after.

3.3 Treatment modalities and guidelines at TAH

3.3.1 Indications for radiotherapeutic treatment for cervical cancer

Table 1 already showed, that patients with cervical cancer stages of FIGO Ib2 or IIb-IV are recommended to receive primary RT. At TAHRC, Patients with FIGO $<$ IIb were treated surgically. In case of clear surgical margins and a negative lymph node status, there was no indication for additional RT. Moreover patients with renal failure were not eligible for RT. Other than that, there were no criteria for exclusion of RT.

3.3.2 Planning of RT

All information on treatment modalities, especially radiation treatment, was obtained by oral interviews with both the medical staff and the radiation physicist working at the TAHRC. Documentation of planning and execution of radiation treatment was compiled in forms called "Radiation Treatment Records" (see Appendix 9.1).

Patients were scheduled for planning of RT just before therapy started. First, stage of FIGO was confirmed by examining the patient's uterine cervix vaginally. Second, the optimal beam entry at skin level was marked. Therefore the localisation of the uterine cervix of the patient was externally approached by measuring 3 cm cranially from the symphysis in the body midline. An intradermal ink injection to that spot should ensure equal body positioning for each fraction of RT. Third, the tumour-to-skin-distance for anterior-posterior field technique was calculated by bisecting the sagittal diameter at the marked localisation. For the second radiation phase additional lateral field technique was used. Therefore, the transversal diameter of the patient's hip 3 cm cranially from the symphysis was measured and bisected. During the entire process of RT planning, no body-imaging was used.

Radiation doses were planned according to stage of FIGO (see Chapter 3.3.3). All data on actual radiation doses applied, occurring adverse effects and discontinuation of RT were documented in the above mentioned "Radiation Treatment Records". Reasons for discontinuation of RT were categorized as toxicities, personal/ logistical reasons, clinical worsening, technical reasons or unknown reasons. Cases of informed refusal of continuing RT were subsumed under personal and logistical reasons. In these particular cases, patients signed their dropout against medical advice in the patient file. However, comments in the patient file indicated the fading support for the ongoing RT by the patient's family or the patient's inability to stay in Addis Ababa any longer. The latter may be due to the fact that Ethiopian women shoulder significantly more agricultural and domestic labour than men [55, 56, 57]. Technical reasons for discontinuation apply to any dysfunction of the Co-60 unit. Clinical worsening with contraindication for RT applies to renal failure or uncontrollable hemorrhage. If merely dropout of the patients was documented and no reason was given, discontinuation was categorised as unknown.

3.3.3 RT guidelines according to stage of FIGO at TAHRC

Radiation treatment at TAHRC was done with either curative or palliative intention. As shown in Figure 1, adjuvant, radical and non-radical RT were performed with curative intent. For palliation, single fractions of 8 to 10 Gy were applied. As ICBT was not available for treatment of cervical cancer, patients received EBRT with a source-to-axis-distance of 80-100 cm, which ideally equals the source-to-tumour-distance [25].

Adjuvant, radical and non-radical RT were applied in two phases. In the first phase opposing field technique (anterior-posterior / posterior-anterior) was used and in the second phase four-field box technique was applied. Typically, opposing fields in the first phase were 20 to 22 by 20 to 22 cm in size and included the gross tumour volume and the pelvic lymph nodes. Cranially, the radiation field was limited by the fifth lumbar and the first sacral vertebral segment. The lower field edge was situated 2 to 3 cm below the palpable tumour. Lateral borders of the irradiation field were set to include inguinal lymph nodes. In the second phase of RT, boost series were directed solely at the gross tumour volume. The typical size of an anterior field in the four-field box technique measured 12 by 14 cm.

Adjuvant RT was given to patients after surgery without clear surgical margins or with positive lymph node status and/ or parametrium involvement. Patients received 40 Gy in 20 fractions within 4 to 5 weeks in the first phase. Depending on tumour response, adverse effects and compliance of the patients, a boost dose of 20 to 26 Gy was applied in 10 to 13 fractions within 2 to 3 weeks in the second phase. Dose per fraction was 2 Gy.

In cases of FIGO IIb or IIIa as well as cases FIGO <IIb with contraindication for surgery, primary radical RT was given. The patients received 46 Gy in 23 fractions within 5 to 6 weeks in the first phase and 26 Gy in 13 fractions within 2 to 4 weeks in the second phase. Similar to the adjuvant schedule, dose per fraction amounted to 2 Gy.

Patients with FIGO IIIb or IVa without bilateral hydronephrosis or clinical vesicovaginal fistula received a non-radical RT pattern with a larger dose per fraction: 32 Gy in 8 fractions of 4 Gy within 4 weeks in the first phase followed by a second phase of 18 Gy (6 fractions of 3 Gy each) or 12 Gy (4 fractions of 3 Gy each) within 2 to 3 weeks. At TAHRC this radiation schedule was labeled as "palliative RT" (see Appendix 9.1). However, in case of cervical cancer staged FIGO IIIb curation can be achieved by EBRT in approximately one quarter of the patients [58]. Therefore, I decided to use "non-radical RT" as a more adequate term for a radiation schedule targeting patients with FIGO IIIb

or IVa without bilateral hydronephrosis or clinical fistula.

In cases of FIGO IVa or IIIb with bilateral hydronephrosis, IVa with clinical fistula or FIGO IVb patients received palliative RT, thus single fractions of 10 Gy each. Single fractions were applied at intervals of one months and with a maximum of three single fractions or 28 Gy in total with a third single fraction amounting to 8 Gy. The waiting time for the application of single fraction RT was short (median 5 days) and therefore this concept was used as minimum attempt for patients with lower stages of FIGO who were unable to stay in Addis Ababa for longer periods of time due to their socioeconomic background. This applied to one patient with FIGO IIb (0.4% of all patients who received single fractions), 22 patients with FIGO IIIb (8.0%) and 17 patients with FIGO IVa and no hydronephrosis or clinical fistula (6.2%).

In case of recurrence, palliation was recommended. Nevertheless, palliative single fractions were applied in only 22.4% (n=13) of the cases of recurrence. The majority of these patients received adjuvant (n=22), non-radical (n=17) or radical RT (n=6).

Hemostatic RT (12 Gy in 4 fractions of 3 Gy each) was administered independently of FIGO stage because of massive vaginal bleeding and decline in hematocrit of more than 30% of the initially measured value at time of registration at TAHRC.

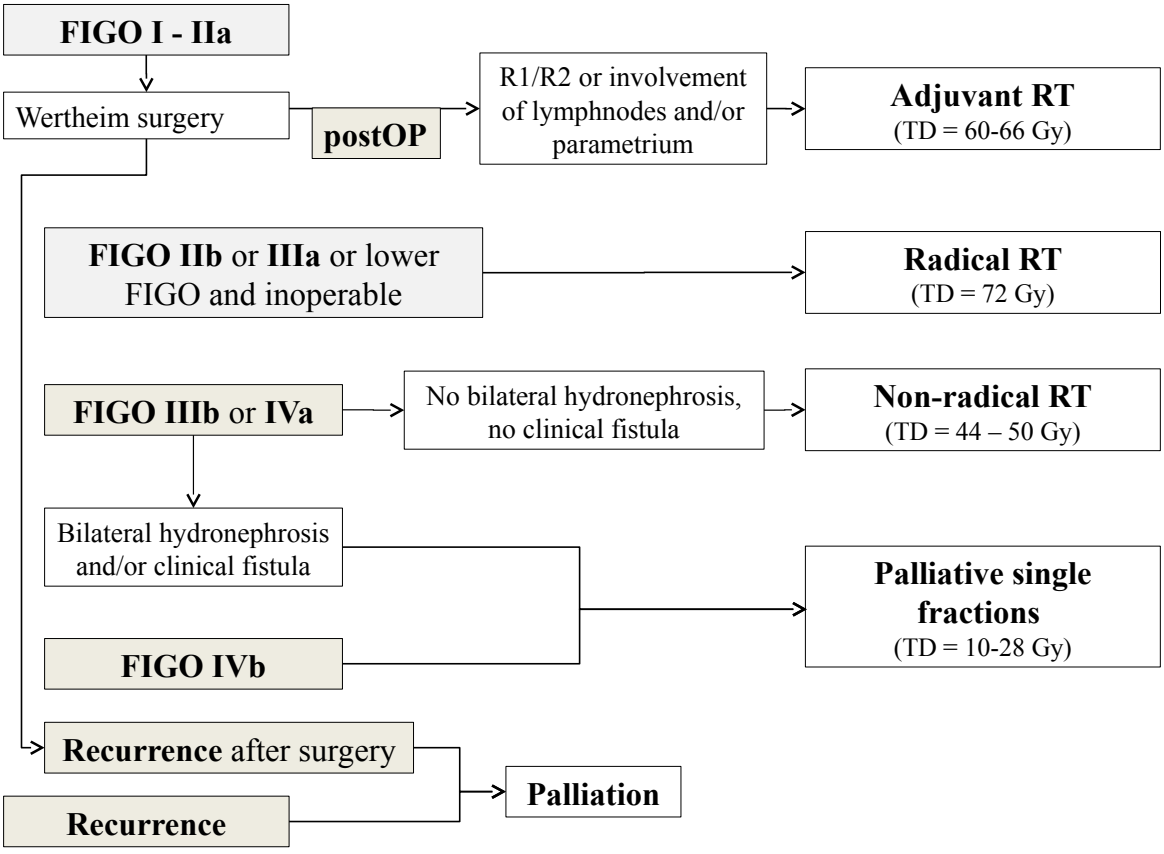


Figure 1: Criteria for therapeutic decision-making at TAHRC, TD = total dose of radiation

3.3.4 Surgery at TAH

Patients with early-stage disease were referred to TAH for surgery as well. The surgical treatment of choice for patients with stages of FIGO Ia2, Ib and IIa is a radical hysterectomy with pelvic lymphadenectomy, thus Wertheim-Meigs operation [16]. TAH was the only hospital in Ethiopia, where radical hysterectomy was performed on a regular basis. For patients, who were operated for cervical cancer elsewhere than at TAH, total hysterectomy was done. That is, no lymphadenectomy was performed. Particularly in case of surgery elsewhere than TAH, operation reports were not documented.

3.3.5 Chemotherapy at TAH

In curative concepts, chemotherapy is recommended as a simultaneous administration with curative RT or rarely neoadjuvant to surgery [15, 59, 60]. In TAHRC, cisplatin was administered. Common doses for patients with FIGO IIb or IIIa were 60 mg/m² for three to six cycles. Patients staged FIGO IIIb or higher usually received a combination of cisplatin (50 mg/m²) and fluorouracil (500 mg/m²) for six cycles. However, patients needed to be fit for chemotherapy [61]. If serum creatinine exceeded 1.4 mg/dl for the first time, the dose of cisplatin was cut in half and chemotherapy was continued. If increase of creatinine did not stagnate, chemotherapy was discontinued.

Within the last decade availability of cisplatin and fluorouracil increased in sub-Saharan countries [11]. However, the financial background of the patients observed for this study can be expected to be limited. Given the monetary costs of chemotherapy for cervical cancer, it is not administered on a regular basis [62, 63].

3.4 Statistical analysis

The primary endpoint of this study is overall survival. Person time equaled the time from the first day of RT to death or to closing date (07.08.2013), whichever came first. Women were right censored at the date of last contact before the closing date. Probabilities of overall survival were estimated using the Kaplan-Meier method. The 95% confidence intervals at year one and two are shown. Kaplan-Meier estimates were compared using the Log Rank test. The Cox proportional hazards model [64] was used to reduce confounding by variables, which will be identified in the following Chapter 3.4.1 by means of directed acyclic graphs. Analyses were conducted using SPSS® Statistics, version 22 (SPSS, Inc., an IBM Company) and SAS® (SAS Inc., Cary, NC, USA), version 9.3. The median follow-up time for patients was 10.1 months. Right censoring was assumed to be unrelated to the risk of distant metastasis. As a remarkable proportion of 79.3% of the total sample of 1009 patients were censored, an additional worst-case analysis was performed. Therefore the assumption was made, that all patients, who were not available for follow-up within 6 months after they were last seen at TAHRC, had died one day after the date of last contact.

3.4.1 Identification of and adjustment for confounders of the impact of RT on overall survival

The prognosis of cervical cancer patients is influenced by a variety of patient-, tumour- and therapy-related factors. An overview of the current state of knowledge on these prognostic factors is displayed in Appendix 9.2. The aim of this study is to make causal inferences about whether completion or discontinuation of guideline-conform RT effects overall survival. Being an observational study, biases

are more likely to occur as patients are not randomized [65]. Lower doses of radiation and thus discontinuation of RT can be due to conditions which effect the outcome of these patients as well. The concept of bias interfering in estimation of causal effects is defined as confounding bias [66].

If one or more of the prognostic factors, shown in Appendix 9.2, does not only have impact on outcome (overall survival), but additionally influences the exposure variable (total dose of radiation received), it potentially changes the causal relation between exposure and outcome variable and is therefore called confounder [67]. The relations between exposure, outcome and covariates can be illustrated by causal diagrams such as directed acyclic graphs (DAGs). DAGs are helpful tools to identify the so called "minimal sufficient adjustment set" (MSAS). That is, DAGs serve to distinguish confounding variables, which have to be controlled by adjustment in order to obtain an unconfounded effect analysis. Since their introduction to the epidemiological literature, Greenland et. al. established certain rules for drawing and evaluating DAGs [68, 69].

Figure 2 displays the DAG for the effect of radiation dose within one assigned RT schedule to overall survival of patients. That dose is a direct indicator for completion and discontinuation of RT respectively, as each schedule is defined by a certain recommended dose of radiation. Mostly due to the lack of reliable data, not all prognostic factors for cervical cancer patients, as shown in Table 22, are included to the DAG. E.g., the extremely low rate of documented comorbidities certainly fails to reliably represent the actual rate of comorbidities. In Ethiopia, access to health care services is extremely limited. There are in average 25 physicians for every million of inhabitants [70]. Hence, contact to the health system is likely to be sparse within the patient collective as well. Underdiagnosing is common, e.g., for Tuberculosis [71]. Beyond that, the socioeconomic background of patients is not sufficiently surveyed, despite its suspected influence on discontinuation of RT. Accordingly, I did not include these data for further calculations. Additionally, in order to present an intelligible graph, I excluded several factors which did not influence the MSAS (see Appendix 9.3 for the extended version).

In the following I will elaborate the causal relations between different variables, referring to evidence in literature. For references of prognostic factors, see Appendix 9.2. As outlined in the same chapter, the burden of comorbidities is very relevant for prognosis. Among all comorbidities, the HIV status was documented most reliably, as awareness for HIV was considerably high. At TAHRC, an HIV screening program for all patients was established in 2011. Before, patients were tested in case of high suspicion (see Chapter 3.2.1). In case of AIDS, as cervical cancer in HIV positive patients is an AIDS-defining disease, QoL and accordingly the ECOG score increases [72, 73, 74]. As reduced erythropoesis is common among HIV-positive patients, HIV status accordingly affects the hemoglobin levels of the patients [75]. Anemia in HIV-patients can be due to other factors, which were not surveyed in this study, e.g. Parvovirus B19-infection [76], antiretroviral therapy [77] and comorbidities such as intestinal parasitosis, which additionally increases the susceptibility to HIV-infection by alteration of T-cell subset counts [78, 79]. For various reasons, HIV-infection is associated with lower adherence to cervical cancer treatment [80]. Hence, HIV-positive patients may tend to discontinue RT.

Generally, the functional status of cancer patients is influenced by age, anemia and other symptoms [81, 82]. In addition, the actual treatment of cervical cancer, thus hysterectomy, RT and chemotherapy impact the physical well-being and activity of the patients, i.a. via appearance of side effects, such as radiation proctitis [83, 84, 85]. Data on adverse effects were incomplete and not reliably documented (see Chapter 3.2.4). As severe adverse effects might prevent patients from travelling to the capital city for follow-up, selection bias can be suspected.

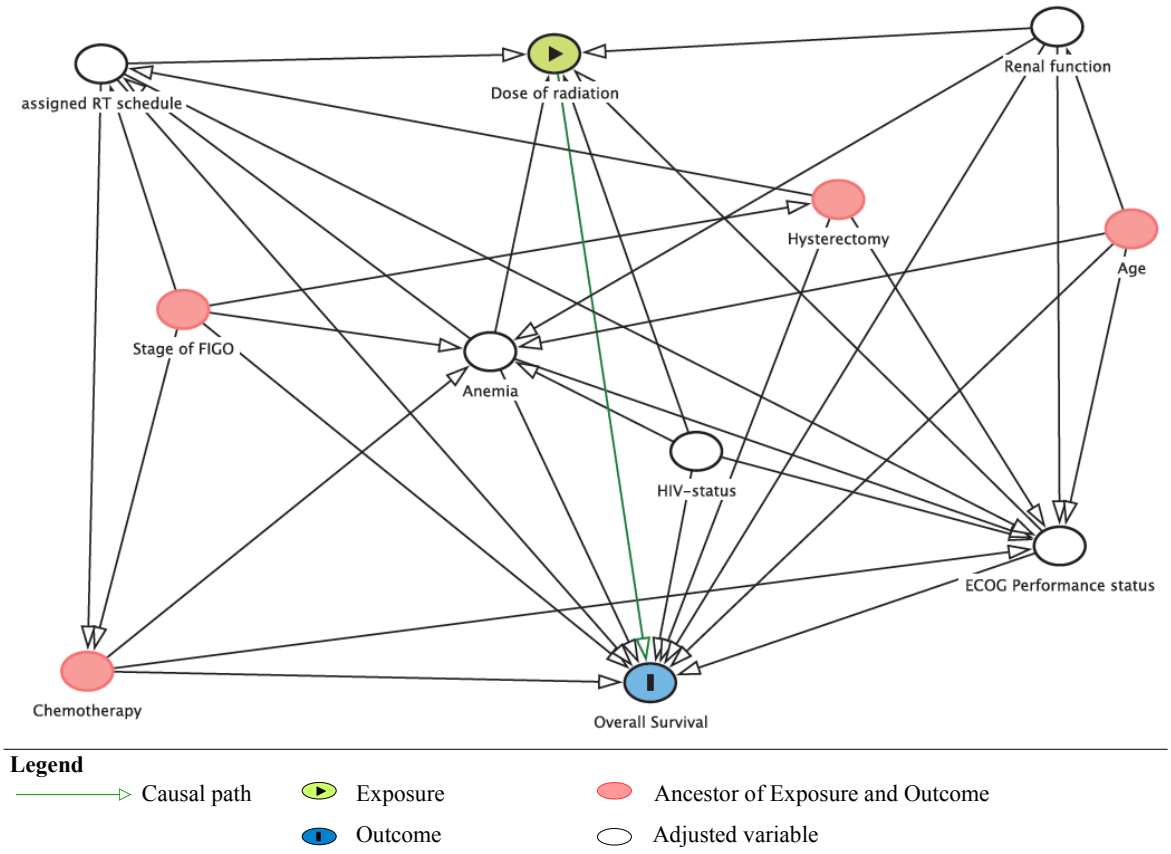


Figure 2: DAG for analysis of impact of radiation dose on overall survival of cervical cancer patients. Control for biasing variables was done.

Hence, adverse effects are not included into the DAG. However, the ECOG score was consistently assessed. Radiation treatment can lead to an increase of ECOG score via occurring side effects. This temporarily precedes the effect of ECOG on radiation dose as, vice versa, worse functional status can cause discontinuation of RT. The DAG shows both effects. First the assignment to a certain RT schedule with its respective recommended dosage affect the ECOG score due to adverse effects, as they appear to be dose-dependent [86]. Then, within one assigned RT schedule, ECOG score affects radiation dose via discontinuation of RT.

RT at TAHRC is given according to guidelines, that is, according to stage of FIGO. There is an adjuvant RT schedule for those patients, who underwent surgery. In that effect, hysterectomy determines the RT schedule the patient is assigned to. Chemotherapy similarly is recommended according to stage of disease and pattern of RT (see Chapter 3.3.5). The only criterion for exclusion of irradiation treatment was renal failure. Reduced renal function is reflected by decrease of the glomerular filtration rate (eGFR), which is best estimated via Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [88]. Ideally, decrease of eGFR over time is measured [89, 90]. However, lacking repeated creatinine measurements, the renal function is estimated by baseline eGFR. Renal failure led to discontinuation of RT, which makes eGFR an influential factor on radiation dose. As the CKD-EPI equation takes age into account, age is not only a prognostic factor itself but influences renal function.

Age prove to be associated with hemoglobin levels [91]. In turn, renal function influences erythro-

poesis as renal tubular damage results in erythropoeitin-deficient anemia [92]. Accordingly, cisplatin based chemotherapy may result in renal tubular damage and thereby produce anemia as a transient adverse effect [93, 94]. Via its additional possible toxicities, such as acute emesis, myelosuppression, oto- and neurotoxicity, the administration of cisplatin reduces QoL of cancer patients and certainly effects ECOG performance status [95, 96, 97]. Besides, decrease of eGFR itself impacts QoL and functional status [98].

The assignment to a certain RT schedule is additionally determined by hemoglobin levels, as there is an option for hemostatic RT, independent of stage of FIGO, in case of "massive vaginal bleeding" (see Chapter 3.3.3). On the other hand, RT was discontinued if bleeding became excessive and did not stagnate.

Figure 2 displays the resulting DAG and shows the identified MSAS. After adjustment for that very MSAS, no biasing pathways remain. For analysis of the effect of radiation dose in case of guideline-conform assignment of RT on estimated overall survival, adjustment for the following confounding variables is appropriate. Respective categories for each factor are shown in square brackets.

- assigned RT schedule [adjuvant, radical, non-radical or single fractions]
- Anemia [grade 0-4 [99]]
- ECOG score [grade 0-4]
- eGFR [chronic kidney disease stages 1-5 [100]]
- HIV status [positive/ negative or unknown]

In order to control for confounding variables, different options exist. Most obviously control can be performed by optimizing the study design. *Restricting the sample* can be a powerful measure to avoid confounding. Admittedly, the reduction of the number of study participants can be unacceptable in terms of comparability of findings with existing studies. In this study, restriction was used by exclusion of patients, who received therapies, which are either unknown in case of recurrence of cervical cancer or, whose uterine cervix was resected (see Chapter 4.2.2). Additionally, patients were excluded from dose-specific survival analysis if they were not assigned to RT according to TAHRC guidelines. Hence, effects of tumour stage would not be mistaken to be effects of RT.

Another method for control of confounding is *matching*. As the remaining patients were all assigned to a radiation schedule according to their stage of FIGO in line with TAHRC guidelines (see Figure 1), the specific radiation schedule directly corresponds with a certain range of stages of FIGO. Consequently, this smaller range of tumour stages remains constant by investigating the subgroup within one RT schedule only. In other words, by choosing this subgroup, I control for the potential impact of other stages of FIGO on outcome.

Other measures to control for confounding based on the study design are described by Greenland et al. [66]. Furthermore, *analytic adjustment* for confounding plays a key role in retrospective analysis. In this regard, the use of regression models is the most common approach to control causal inferences. The Cox proportional hazards model was used for control of confounding in survival analysis (see Chapter 4.2). As confounding by "assigned RT schedule" is controlled by *matching*, that is, a design-based measure, I used the Cox proportional hazards model to control for the remaining confounders (anemia, eGFR, HIV status, ECOG score).

3.5 Ethics

For this study, ethical approval was obtained from the Institutional Review Boards of Addis Ababa University School of Medicine and the Medical Faculty of Martin-Luther University Halle-Wittenberg. The study was conducted without individual informed consent as the study relied on retrospective data, collected as part of routine patient care. For follow-up interviews by telephone, patients or relatives were asked for their oral consent. Patients signed a consent form before participating in pilot testing of the Amharic version of QoL questionnaires described in the following Chapter 3.6.

3.6 Excursus: The first Amharic QoL Questionnaires as a base for future research on outcome of oncological treatment at TAHRC

Background. In this study, overall survival was the main, but merely quantitative indicator for effectiveness of RT at TAHRC. However, evaluating the Quality of Life (QoL) of cancer patients is the appropriate tool to measure the quality of any type of cancer therapy, as cancer in general is associated with psychological distress and reduced QoL.

The common scales to evaluate QoL in patients with cervical cancer include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core (EORTC QLQ-C30) combined with the Cervical Cancer-Specific Questionnaire EORTC QLQ-CX24. At the time of writing, EORTC QLQ-C30 and QLQ-CX24 are available in the following African languages: Afrikaans, Setswana, Xhosa and Zulu. EORTC QLQ-C30 additionally exists in Arabic, Kiswahili, Sotho and Yoruba [101]. However, when this study was conducted, EORTC QLQ-CX24 did not exist in any African language. The vast majority of Ethiopian cancer patients speaks Oromo or Amharic [53]. Therefore, they do not benefit from the English questionnaire.

To permit future studies to evaluate the QoL of the patients who suffer from carcinoma of the cervix uteri, a translation of the two questionnaires EORTC QLQ-C30 and EORTC QLQ-CX24 into Amharic was organised within the scope of this study.

Methods. In line with instructions from the EORTC manual [102], two independent Amharic native speakers translated the English QLQ-C30 and QLQ-CX24 into Amharic. Both versions were reconciled with the help of a third independent Amharic speaker. The reconciled version had to be back-translated into English by two independent English native speakers. Hence, discrepancies were registered and corrected after further reconciliation with the Amharic translators. After discussing all changes with the Translational Coordinator, the resulting interim translation was pilot tested with 11 cervical cancer patients, who came for follow-up to TAHRC at 21st and 22nd of January 2013. A report of the pilot testing was sent to the Translational Coordinator together with the final translations.

Translators and Coordinators of the Translation of EORTC QLQ-C30 and QLQ-CX24 into Amharic. According to the EORTC translational manual, several translators and organisers have to be involved to the translational process to guarantee impartiality and a final version, that is as close to the original as possible [102]. All participants of the translational process are displayed in Table 2. They all worked as volunteers and did not receive any kind of payment.

Results. The translational process was finalized successfully. The final report with all translational versions and justifications for changes in the interim version is available. Few linguistic and cultural

Table 2: Contributors to the official translation of EORTC QLQ-C30 and QLQ-CX24 into Amharic

Role	**Responsible Person**
Translational Coordinator	Dagmara Kulis Brussels (EORTC, Translation Team Leader)
Project manager	Ulrike Mölle Leipzig (medical student)
1st Forward Translator	Aynalem Abraha Woldemariam Addis Ababa (TAH, Radiation Oncologist)
2nd Forward Translator	Zelalem Kebede Addis Ababa (Public Health specialist)
1st Backward Translator	Ralph Lee Addis Ababa (Assistant Professor of Theology at Holy Trinity Theological College)
Reviewer of 1st Backward Translation	Yonas Rohwan Addis Ababa (student at Holy Trinity Theological College)
2nd Backward Translator	Helen Bahru Addis Ababa (Management of Visa affairs at Belgian Embassy)
Interpreter for pilot testing	Tinsae Gelata Addis Ababa (TAH, Oncology Nurse, student of Sociology)

adjustments were necessary (e.g., from “initials” into “first letter of your name, your fathers name and your grandfathers name"). After discussion with all translators and the Translational Coordinator, the content of one question was changed: As only 2.41% of all households in Ethiopia owned televisions in 2002 [103], QLQ-C30 n°20 “watching television” was changed into “listening to the radio”. Apart from these major changes, the translational process went smoothly and the final version was approved by all involved translators. The pilot-phase did not generate a need for additional changes, as patients found the questionnaires to be comprehensible. The complete documentation of the translational process and the pilot-testing was reviewed and approved by the EORTC. Hence, the Amharic translations of the QLQ-C30 and QLQ-CX24 are available for use in clinical practice.

Conclusion. After approval by the EORTC, there is an Amharic version of the EORTC QLQ-C30 and QLQ-CX24 available for future investigation on QoL of cervical cancer patients in Ethiopia. Both questionnaires can be requested at the EORTC. Prior to their use in clinical practice, further tests and retests of the questionnaires are needed to evaluate the internal consistency, the test-retest reliability and the construct validity on a larger patient population. Furthermore, a translation of both questionnaires into Oromo is advisable. Even though Amharic is the statutory national language of Ethiopia, Oromo is spoken by a larger number of people (29% and 35% respectively) [53]. In the long run, further translations into the most common within the 86 living languages in Ethiopia should be planned.

4 Results

This section comprises the major findings from data on 1009 cervical cancer patients, who presented at TAHRC between 2008-2012. First, the formation of the sample will be described. Then the patients' characteristics and the clinical implementation of TAHRC guidelines will be presented. The actual total doses of radiation received are shown for each RT schedule. Furthermore, reasons for discontinuations of RT, adverse effects and patients, who were not treated according to guidelines of TAHRC, will be presented.

This description of the clinical practice of RT at TAHRC is followed by an analysis of overall survival that investigates, if and how the fact of completion or discontinuation of a RT schedule is related to overall survival probability of the patients. Therefore, after an initial presentation of crude overall survival of all 1009 patients, these analyses are conducted for three subsamples. Each subsample comprises patients, who were assigned to their RT schedule according to TAHRC guidelines, who did not receive other therapeutic measures than RT or chemotherapy and who did not suffer from recurrent disease. Hence, survival is shown for patients grouped by the RT schedule they were assigned to due to their stage of FIGO. As the total dose of radiation indicates whether RT was completed or not, comparison of survival between different dose groups was made. I adjusted the analyses for confounding variables identified in Chapter 3.4.1.

4.1 Description of the current practice of RT at TAHRC

4.1.1 Description of the sample population

In the following, the formation of the total of 1009 patients included to this study will be explained.

As displayed in Figure 3, an estimated number of 2300 patients with cancer of the cervix uteri were registered at TAHRC between 10.09.2008 and 10.09.2012. This estimation is based on the TAHRC registration list and, as the list is incomplete, on assessment by Dr. Mathewos, leading oncologist at the TAHRC.

Out of these 2300 patients and another 56 patients, who initially received surgery for cervical cancer and needed adjuvant RT, 1839 patients were seen by a radiation oncologist and RT was planned. A minimum of 165 patients of those, who came for planning, are suspected not to have finished their RT schedule before 10.09.2012 and therefore did not meet the inclusion criteria (see Chapter 3.1). For estimation, the mean period of 166 days between registration and end of first RT phase was used.

The estimated number of patients who received RT was 1400. This estimation was based on assessment of Dr. Mathewos, leading oncologist of TAHRC. Out of those, 2 patients received exclusively RT for distant metastasis and as their cervix uteri was not radiated, they did not meet the inclusion criteria. An approximate number of 389 received RT. However, they were not analysed as their patient files could not be retrieved. Patient files are handwritten and manually stored. Additionally, names vary in spelling and misplacing is common. I am not aware of any other reason for missing files and therefore I do not suspect any associated selection bias.

The study population came down to a total of 1009 patients. For survival analysis of patients, who were assigned to RT according to TAHRC guidelines, this sample will be further narrowed down to three subsamples as explained in Chapter 4.2.2.

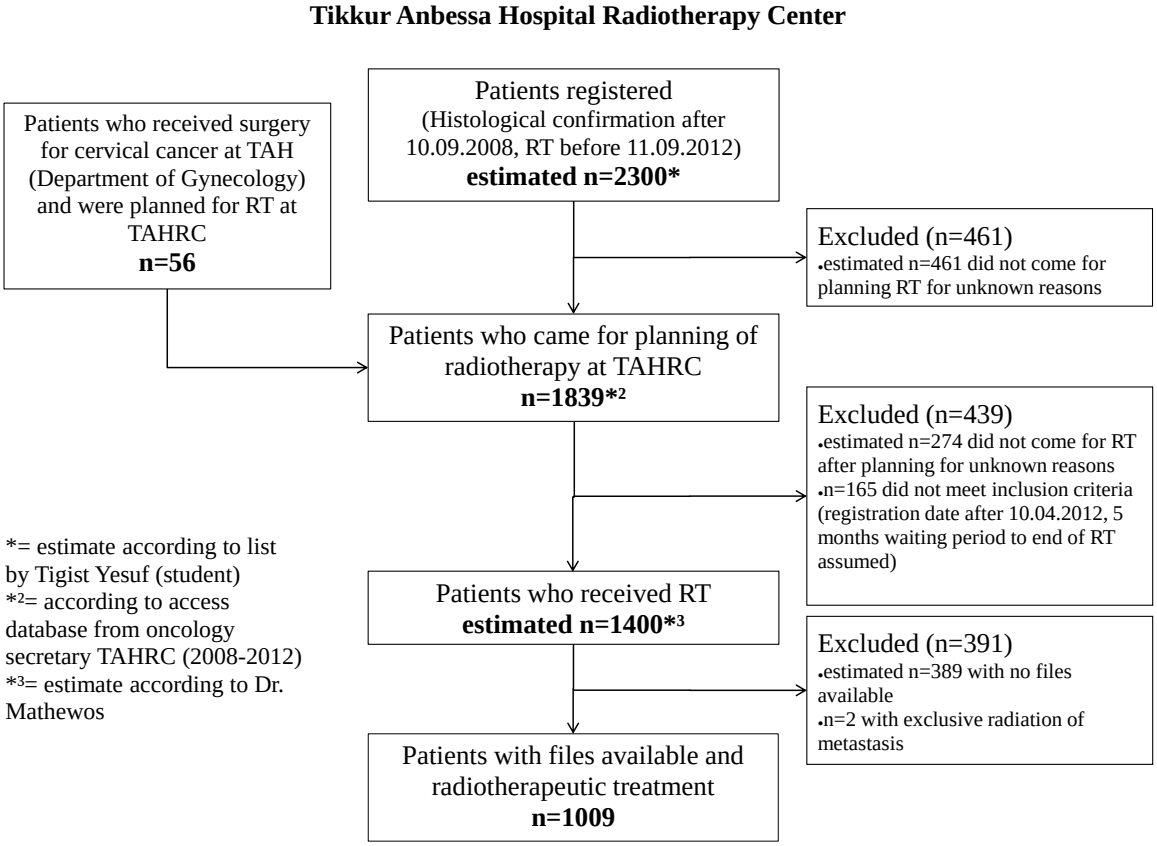


Figure 3: CONSORT flow diagram

4.1.2 Description of patient characteristics

This chapter gives an overview of demographic and disease-specific data from all patients included to this study. See Table 3 for demographic data.

Most patients came from rural areas (56.7%). The women's age varied from 21 to 91. The mean age was 49.1 and accordingly, patients aged 40-49 years constituted the largest group within the cohort. Correspondingly, the majority of patients (78.4%) was postmenopausal. The mean number of children was known for 97.7% of all patients and amounted to 6.1 children, ranging between 0 and 17 children per patient. Two women were pregnant when they registered at TAHRC. One pregnancy was terminated in the 9th week of gestation with the patient's consent for radical RT. The other patient's baby was born by cesarean section after 34+4 weeks of gestation and the patient started her radical RT two weeks after caesarean section.

Many women reported only one sexual partner in their lifetime (52.6%), as well as marriage at the age of 18 years or younger (84.3%). The proportion of women, who used contraceptives at least once in their life, was 28.3%. However, patients were not asked about their use of preservatives on a regular basis. More than a fifth of the patients have ever used the combined oral contraceptive pill. 6.5% of the patients have ever managed their family planning receiving injections of Depot-Medroxyprogesterone-Acetate every 3 months, which represents a more discreet option of contraception [104].

Table 3: Basic demographic data of all 1009 patients at the first medical examination at TAHRC

Characteristics (n=1009)	Number	Proportion (%)
Place of origin		
Rural	572	56.7
Urban (10 biggest cities)	437	43.3
.....of which: Addis Ababa	292	28.9
Age (years)		
<30	26	2.6
30-39	169	16.7
40-49	309	30.6
50-59	275	27.3
≥60	230	22.8
Menopausal status		
Premenopausal	208	20.6
Postmenopausal	791	78.4
Unknown	10	1
Mean number of children: 6.06 +/- 3.141		
Marriage		
With age ≤18 years	851	84.3
After age of 18	60	6
Unmarried	9	0.9
Unknown	89	8.8
Sexual partners (ever)		
None	2	0.2
One	531	52.6
Few (2-3)	147	14.6
Multiple (>3)	225	22.3
Unknown	104	10.3
Contraception		
Oral combined Contraceptives	205	20.3
Depot-Medroxyprogesterone-Acetate (DMPA) Injections	66	6.5
Progestin only Implanon	2	0.2
Intrauterine Device (copper)	4	0.4
Tubal Ligation	9	0.9
None	674	66.8
Unknown	49	4.9
HIV status		
Known positive	98	9.7
Known negative	148	14.7
Not screened / negative	763	75.6

9.7% of all patients were known to be HIV-positive. However, underdiagnosing can be expected. HIV-screening was not performed on a regular basis before 10.09.2011 in TAH and only 156 patients (15.5%) included into this study were registered at TAHRC thereafter. Therefore, 84.5% of all patients were tested on demand and not screened on a regular basis.

Table 4 displays findings regarding the pathology of cervical cancer of all 1009 patients. Patients tended to present with a lightly restricted performance status and with late stages of FIGO at time of booking for RT. Being the second evaluation of FIGO stage after a median 16 days after the first staging, information of chest X-ray and abdominal ultrasound is included. However, during waiting times until the actual start of RT, tumour stages advanced. Patients, who presented with radically

treatable cervical cancer stages of FIGO IIb and IIIa in 36.7% at time of booking, came down to 20.4% at time of starting RT. Consequently the proportion of FIGO stages IIIb and IVa increased from 48.8% at booking date to 64.1% at RT start.

Results of histopathological examination after bioptic probe excision showed squamous cell carcinoma (SCC) in the majority of patients (93.8%). 4.7% of the patients suffered from an adenocarcinoma of the cervix uteri. In case of histological grading, which was merely done in less than one quarter of the patients, most often the tumour cells were moderately differentiated.

Table 4: Disease-specific data of the 1009 patients when first seen by a physician.

Characteristics	Number	Proportion (%)
First assessment of ECOG score		
Fully active (ECOG 0)	5	0.5
Lightly restricted (ECOG 1)	568	56.3
Unable to work (ECOG 2)	310	30.7
Limited selfcare / >50% of the time in bed (ECOG 3)	116	11.5
No selfcare, bedbound (ECOG 4)	10	1
Stage (FIGO) at date of booking for RT		
IIa	10	1
IIb - IIIa	370	36.7
IIIb - IVa	493	48.8
IVb	37	3.7
PostOP	55	5.4
Recurrence after surgery	37	3.7
Recurrence	7	0.7
Histology		
Squameous Cell Carcinoma (SCC)	947	93.8
... Keratinizing	291	28.8
... Non-Keratinizing	334	33.1
... not specified SCC	322	31.9
Adenocarcinoma	47	4.7
Adenosquameous Carcinoma	11	1.1
Small Cell Carcinoma	2	0.2
Unknown/ Unspecified	2	0.2
Grade		
Well differentiated	70	6.9
Moderately differentiated	91	9
Poorly differentiated	59	5.9
Undifferentiated	7	0.7
Not done	782	77.5

4.1.3 The clinical implementation of treatment guidelines at TAH 2008-2012

Oncological treatment of patients with cervical cancer at TAH 2008-2012. Table 5 displays the distribution of all cervical cancer patients, presenting 2008-2012 at TAH, to radiotherapeutic, chemotherapeutic and surgical treatment. As radiotherapeutic treatment was the main criterion for inclusion into the study, all 1009 patients received RT. 4.9% were treated with adjuvant RT after initial surgery for early stages of disease. 27.1% of the patients were radiated with single fractions of 10 Gy with palliative intent.

With regard to chemotherapy, merely 17.3% of all 1009 patients received systemic cytoreduction of their cervical cancer. Supposedly due to the lack of financial means or availability of the drugs,

only 45.5% of the patients who received radical RT, received the recommended concurrent chemotherapy with curative intent [15]. Out of the two patients who received chemotherapy to treat additional neoplasms, one patient received 9 cycles of carboplatinum (450 mg/cycle) to treat her ovarian carcinoma and the other patient received fluoruracil for treatment of gastric cancer with no information on number of cycles or dosage. Both received chemotherapy before RT for cervical cancer started.

In 9.2% (n=93) of all patients cervical cancer was initially treated with surgical resection of the cervix uteri. 49 of these patients were additionally treated with an adjuvant schedule of radiation. The remaining 44 patients received radical (n=11), non-radical (n=20) and palliative RT (n=14) after surgical resection of the uterine cervix was performed. 8 patients received surgery on the uterus, which was not related to cervical cancer: one patient had a caesarean section, two patients received surgery for uterine myoma, two patients were treated for their ovarian carcinoma with subtotal, thus supracervical, and total hysterectomy respectively. For another three patients, whose hysterectomy is known to be unrelated to their cervical cancer, data on the type of surgery performed were missing.

Out of the 93 patients with therapeutic surgery for cervical cancer, 45.2% received the recommended radical hysterectomy, that is Wertheim-Meigs surgery [16]. At the time this study was conducted this procedure was only performed at TAH in Addis Ababa. Besides, there were 4 patients who merely received an exploratory laparotomy. There was no operation report filed. However, most likely the exploratory laparotomy assessed an inoperable stage of cervical cancer without further surgical interventions, as stage of FIGO at start of RT was either IIIb (n=3) or IVb (n=1).

Table 5: Treatment modalities. Proportions relate to all patients included (n=1009).

Characteristics (n=1009 patients)	Number	Proportion (%)
Curative RT		
Radical RT (72 Gy planned)	222	22
Adjuvant RT (60 - 66 Gy planned)	49	4.9
Non-radical RT (44 - 50 Gy planned)	464	46
Palliative RT		
Single Fractions at 10 Gy each (10 - 28 Gy planned)	274	27.1
Chemotherapy		
For stage of FIGO<IIIb		
Concurrent to radical RT (60 mg/m² cisplatin)	101	10.0
Neoadjuvant before start of RT (60 mg/m² cisplatin)	18	1.9
For stage of FIGO≥IIIb		
Adjuvant to non-radical RT (50 mg/m² cisplatin, 500 mg/m² 5FU)	55	5.4
Chemotherapy for other neoplasm	2	0.2
No chemotherapy	833	82.5
Surgery for cervical cancer		
Total hysterectomy	51	5.1
Wertheim-Meigs Surgery	42	4.2
Exploratory laparotomy	4	0.4
Out of which:		
Surgery for cervical cancer with adjuvant RT following		
Total hysterectomy	29	2.9
Wertheim-Meigs surgery	20	2

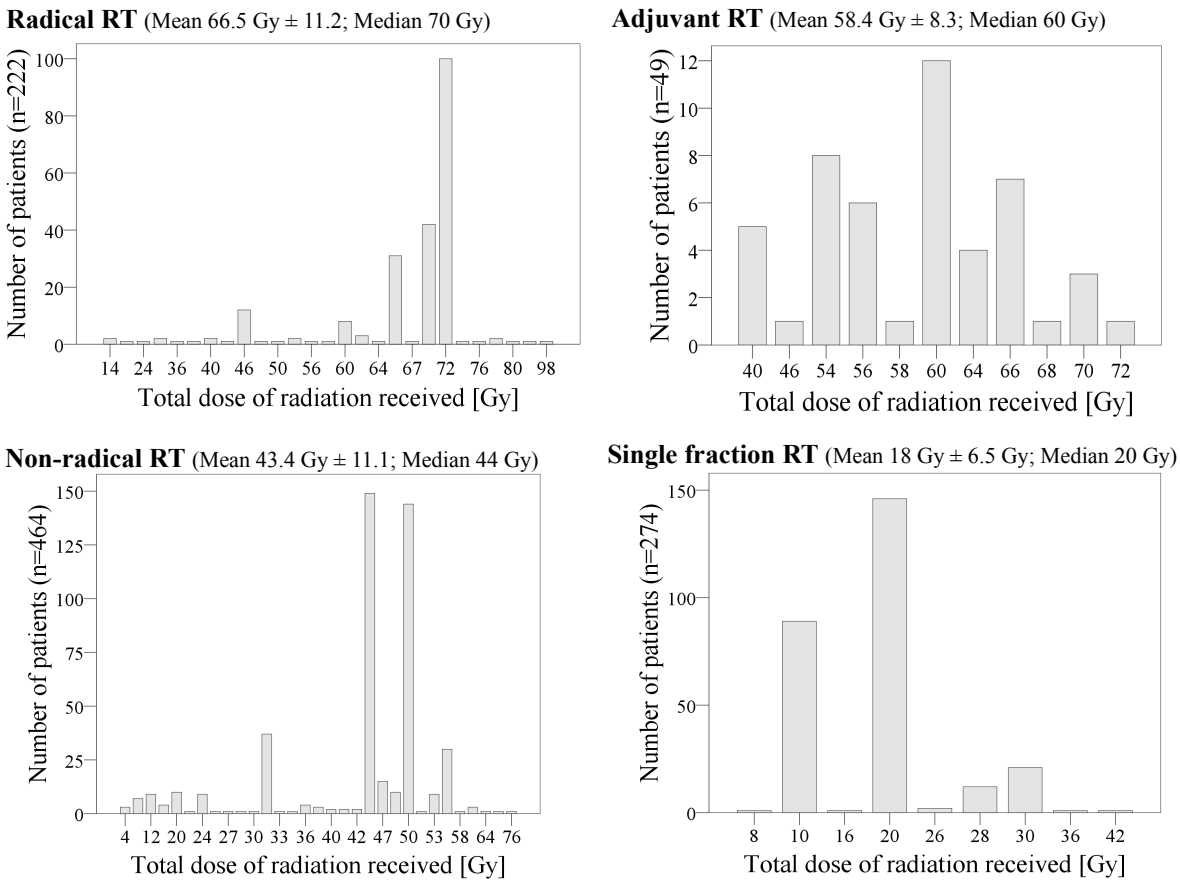


Figure 4: Total dose of radiation received according to RT schedule for all patients treated at TAHRC 2008-2012 (n=1009)

The clinical implementation of RT guidelines. In the following, the total doses of radiation applied for each RT schedule are shown, regardless, whether assignment to the respective RT schedule was guideline-conform or not. The distribution of the applied actual doses of RT is displayed in Figure 4 and may indicate the adherence to TAHRC guidelines in daily clinical practice.

According to TAHRC guidelines (see Chapter 3.3.3) the radical, adjuvant and non-radical radiation RT schedules consist of two phases with a resulting total dose of 72, 60-66 and 44-50 Gy to the patient's uterine cervix respectively. The actual doses applied result in a median 70 Gy for radical, 60 Gy for adjuvant and 44 Gy for non-radical RT. Hence, median total doses approximate the scheduled total doses, ranging at the lower limit of planned total doses. The planned overall treatment times for radical RT were 7-10 weeks, for adjuvant RT 6-8 weeks and for non-radical RT 6-7 weeks. The collected data show overall treatment times ranging within this plan: a median 50, 43 and 37 days for radical, adjuvant and non-radical schedules respectively. Shorter treatment times in case of non-radical RT are due to early discontinuations. Regarding the scheduled total doses, patients, who were planned for non-radical RT, showed the best adherence to TAHRC guidelines: 68.5% out of 464 patients received the intended total dose of 44-50 Gy. For radical RT a proportion of 45% out of 222 patients received 72 Gy and for adjuvant RT 46.9% out of 49 patients received 60-66 Gy. Altogether, 60.0% of patients treated with curative intent (n=735) received guideline-conform doses of irradiation.

Patients, who received lower doses of RT than planned, discontinued RT. However, there was a large proportion of 33.3% out of 222 patients planned for radical RT, who received 66-70 Gy and might have terminated RT earlier than planned for good tumour response. Similarly 32.7% of patients with adjuvant RT who received 46-58 Gy are likely to have dropped out for either good clinical response or RT toxicities.

5.4% of patients with radical RT dropped out after a first phase of 46 Gy. Similarly 10.2% of patients, who received adjuvant RT, and 8% of patients, who received non-radical RT, did not come back for the second phase of RT and received a total dose of radiation of merely 40 and 32 Gy respectively. Out of the patients who were assigned to non-radical RT, 10.1% discontinued even earlier during the first phase of RT. Possible reasons for such discontinuations are presented in the following Chapter.

However, some patients received higher doses of radiation than planned. In case of radical RT, this applied to 7 patients, out of which two patients with total doses of 98 Gy and 87 Gy respectively received a third palliative radiation cycle. Palliation might have been indicated for actual progression of disease or initial misstaging. One patient received a total dose of 80 Gy as a result of 50 Gy by ICBT in Nairobi for FIGO IIb cervical cancer in 2009 and an additional 30 Gy in 15 fractions in 2010 after diagnosis of liver metastasis at TAHRC. Therapeutic decision-making was not documented. Another three patients needed an extra phase for hemostasis. One patient discontinued and restarted her first phase in radical RT and, therefore, received a total dose of 76 Gy.

Regarding palliation, monthly single fractions of 10 Gy each were a feasible measure to alleviate pain or bleeding in late stages of cervical cancer. 55.8% out of the 274 patients treated with single fractions at TAHRC suffered from final stages of FIGO (IVa or IVb) or recurrence at time of RT. A large proportion of 43.1% was staged FIGO IIIb at time of RT and received single fractions for bilateral hydronephrosis or logistic matters as single fractions only require short waiting time (median 5 days) and just one day of stay in Addis Ababa for the treatment. Out of all 274 patients palliated with single fractions, most patients (53.3%) received 2 fractions and a resulting total dose of 20 Gy. 32.5% received one single fraction of 10 Gy and 4.4% received the maximum planned dose of 28 Gy. Patients with higher doses than planned were mostly treated with 3 single fractions of 10 Gy each (7.7%). One patient received a total dose of 42 Gy as a result of an additional hemostatic RT and another patient received 36 Gy due to 4 single fractions (10-10-8-8 Gy). These irregularities can be due to the fact, that single fractions can be applied relatively spontaneously and as a quick response to acute and severe symptoms.

Description of discontinuations of RT schedule. As shown in the preceding Chapter, the radical, adjuvant and non-radical RT schedules were discontinued at different points of time. A proportion of 32.0% of all patients except those, who were palliated with single fractions, received less than the minimum recommended total dose of radiation according to TAHRC guidelines. Discontinuation of RT and its reasons were documented in the patient files only if discontinuation took place during ongoing RT phase. If patients completed their first phase of RT and did not come back for the planned second one, reasons for that were not visible from the patient files. This applies to a total of 54 patients. These patients presumably did not return as a result of the financial and logistical burden of their treatment. Side costs of cervical cancer are considerably high and medical reasons were more likely to be documented in the patient files [62].

Table 6: Reasons for discontinuation of ongoing radiotherapy phase. Proportions relate to n=85.

Reason for discontinuation (n=85)	Number	Proportion (%)
Toxicity of RT	22	25.9
Personal / logistical reasons	9	10.6
Clinical worsening for tumour progression	8	9.4
Toxicity of chemotherapy	3	3.5
Co-60 unit broke down	2	2.4
Unknown	41	48.2

Data on discontinuation of an ongoing radiation phase are available for 85 patients and displayed in Table 6. For 48.2% of these 85 patients reasons for dropout were not mentioned in the patient files (see Table 6). Regarding the known reasons for discontinuation, toxicity of RT caused dropout in half of the cases. 20.5% of the patients with known reason for discontinuation did not come back for completion of RT because of personal or logistical reasons. Direct medical costs of RT are unlikely to be the main reason for discontinuing, as exemption from duty could be granted. For exemption of paying treatment costs, patients needed to prove their indigence by three attestors who confirm the patient's neediness in front of the local government. However, costs caused by the high expenses of staying in the capital Addis Ababa compared to rural sites most patients originated from, are more likely to burden the patients and their families [105, 106].

18.2% of the patients with known reason for discontinuation within one phase of RT had to stop radiation for renal failure or massive bleeding, which was not controllable by RT. Two patients could not receive the planned dose of RT due to operational disorder of the single Co-60 unit in use at TAHRC. After repair their was no restart of RT for these two patients, however.

Table 7: Early adverse effects (n=784 who came for first follow-up after end of RT)

	Diarrhea		Radiation Dermatitis	
Grade	Number	%	Number	%
None	692	88.6	718	91.6
Mild	8	1.0	27	3.4
Moderate	71	9.1	38	4.9
Severe	10	1.3	1	0.1
Detected before start of RT	3		0	

Table 8: Late adverse effects (n=578 who came for follow-up after 3 months after RT)

	Suprapubic Fibrosis		Radiation Proctitis		Incontinence		Fistulae		Vaginal stricture	
Grade	n	%	n	%	n	%	n	%	n	%
None	346	59.9	411	71.1	446	78.3	476	83.4	504	87.5
Mild	81	14	104	18.0	60	10.5	26	4.5	26	4.5
Moderate	114	19.7	58	10.0	61	10.7	64	11.2	40	7.0
Severe	37	6.4	5	0.9	3	0.5	5	0.9	6	1.0
Detected before start of RT					8		7		2	

4.1.4 Description of adverse effects

As outlined in the preceding Chapter, toxicity of RT was the major known reason for discontinuation of RT. Therefore, the occurring adverse effects are presented in the following. Documentation of adverse effects was not done on a regular basis, as mentioned in Chapter 3.2.4. Hence, the actual incidence of adverse effects is expected to be higher.

Table 7 shows early adverse effects, which had to be documented within the first three months after termination of RT. 11.4% of the 784 patients who came for a first follow-up within that period of time, suffered from diarrhea and 8.4% presented with radiation dermatitis. Late adverse effects are shown in Table 8. Data are based on 578 patients, who came for follow-ups after three months passed after their last day of RT. 28.9% out of these suffered from radiation proctitis. Proctitis was severe in 5 of these cases. 21.8% of 570 patients were incontinent after RT, mostly because of vesicovaginal fistula as a result of radiating the pelvis. Suprapubic fibrosis was the most commonly documented late adverse effect, affecting 40.1% of all patients who came for follow-up after three months after RT was terminated. As a consequence of tissue induration by radiation, 12.5% of these patients suffered from vaginal stricture.

Figure 5 shows the relation between total dose of radiation applied and appearance of adverse effects. Therefore, patients were distributed to 4 equally sized groups according to the total dose of radiation received in Gy. A clear increase of incidence of adverse effects along with an increasing dose

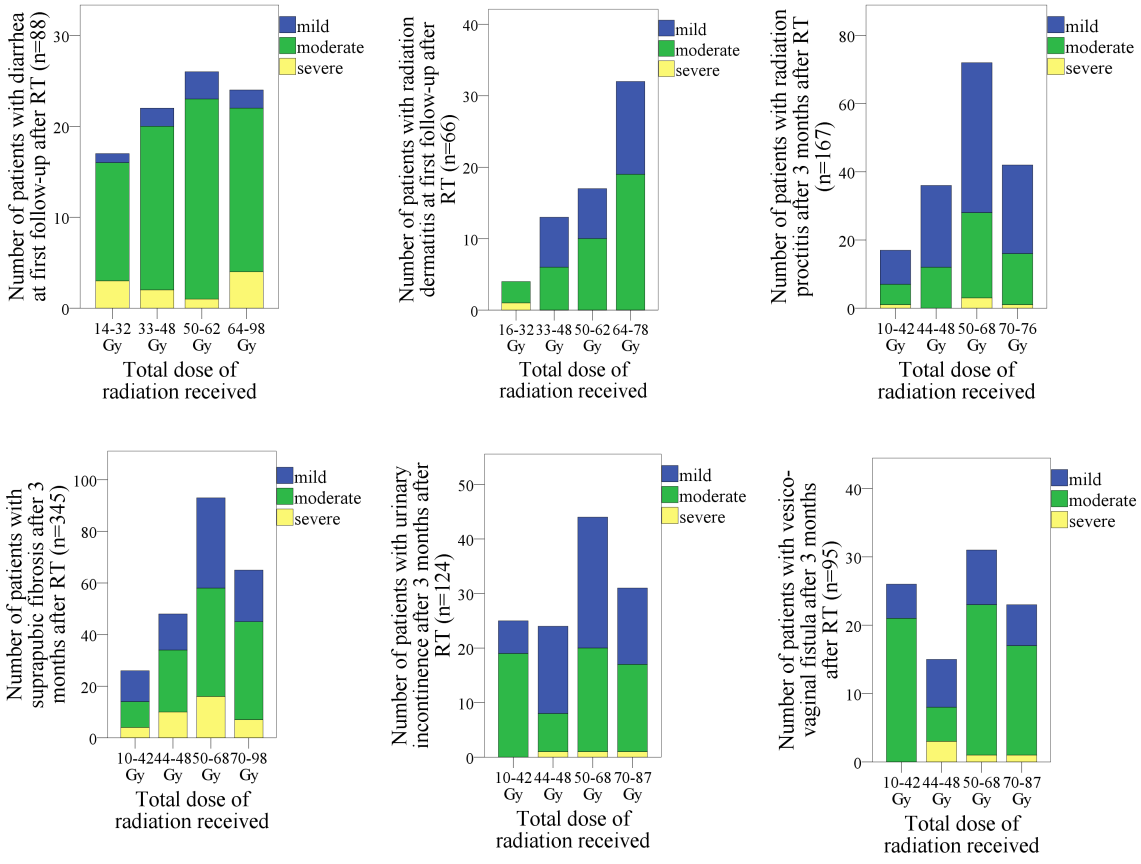


Figure 5: Incidence of early and late adverse effects according to total dose of radiation received

of radiation in Gy could not be verified, except for radiation dermatitis. The higher the total dose of radiation received, the more patients suffered from radiation associated dermatitis. With regard to diarrhea, suprapubic fibrosis and radiation proctitis, a trend towards a dose-effect is shown, as incidence rises along with the first three dose-groups. The fact, that incidences of urinary incontinence and vesicovaginal fistulae was high despite lower doses of RT administered, could be a result of tumour progression as patients receiving lower doses of RT were more likely staged FIGO IIIb and higher. Hence, both symptoms could have partially been mistaken for adverse effects due to RT. However, as explained in Chapter 3.2.4, the quality of data on adverse effects does not allow to draw conclusions about the causal effect of radiation dose on appearance of adverse effects.

4.1.5 Supportive treatment options for pain and adverse effects of RT at TAHRC

Chapter 3.2.5 already points out the insufficient therapeutic setting when it comes to treatment of cancer-associated symptoms, mainly pain, or adverse effects of oncological therapy in sub-Saharan countries. At TAHRC, three analgesics were on dispose: paracetamol per os (p.o.), tramadol p.o. and morphine for intravenous administration (i.v.). For 42.1% of all patients included into this study, no pain medication was documented throughout the whole patient file. 410 patients (40.6%) received tramadol p.o. during the course of their cancer treatment, morphine i.v. was given to 141 (14%) patients and administration of paracetamol p.o. was documented in 33 cases (3.3%). The low number of nonsteroidal anti-inflammatory drug (NSAID) administration may be due to the fact, that only the strongest analgesic applied was documented. Patients, who received tramadol or morphine, were treated according to the WHO analgesic ladder [107].

Only 19.7 % of all patients who received palliative RT received at least one injection of morphine. This low proportion can be due to the fact that orally administered morphine was not on dispose and patients needed to come to TAHRC for injections, generating costs of transport and waiting time.

Treatment options for radiation associated adverse effects are unsatisfying in general [17, 108, 109]. Naturally, the best treatment of adverse effects is their prevention by precise targeting of radiation. As the Co-60 unit at TAHRC does not provide this kind of precision (see Chapter 1.2), a higher demand for treatment of the occurring adverse effects is suspected.

For radiation cystitis antispasmodic drugs such as hyoscine butylbromide p.o. are on dispose. For radiation proctitis antiinflammatory agents with mild steroidal effects are applied. In case of constipation, bisacodyl p.o. is used. In case of CTCAE grade 4 radiation proctitis [99], patients are treated surgically, often resulting in colostomy. For radiation dermatitis, aquaeous creams are used to moisturize as soon as an erythema evolves. 1% hydrocortisone cream is given for relief of pruritus and patients are educated in order to avoid perfumed skin products, deodorants and make-up, just as protecting their skin from wind, sun and extreme temperatures. In case of vesicovaginal fistulae, patients are referred to Addis Ababa Fistula Hospital. Occuring lymphedemas should be alleviated by excercise and compression therapy with elastic bandages. Furthermore, patients are advised to elevate the affected extrimity after travelling or standing for longer periods at a stretch. Radiation diarrhea is usually treated symptomatically with codeine phosphate or loperamide p.o. at TAHRC.

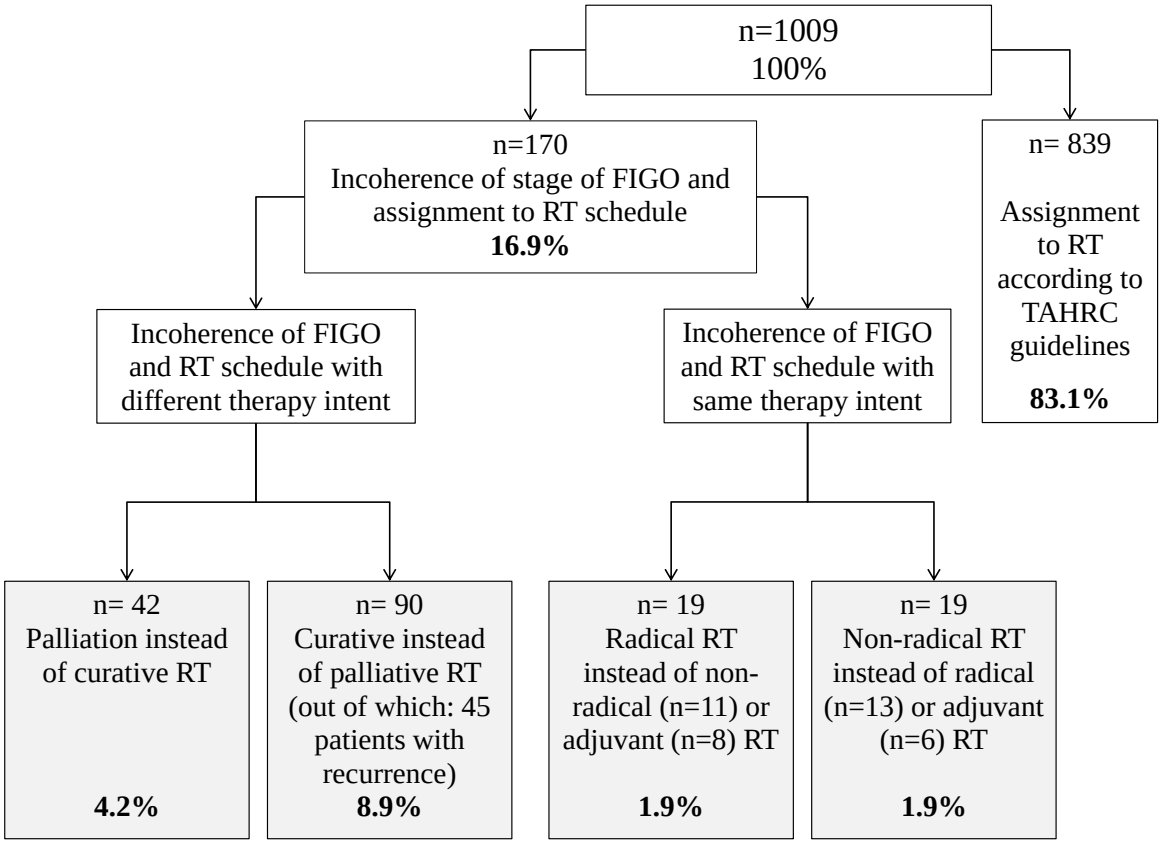


Figure 6: Distribution of patients treated according and not according to TAHRC guidelines

4.1.6 Adherence to TAHRC guidelines in therapeutic decisionmaking

Figure 1 shows the algorithm of radiotherapeutic decisionmaking at TAHRC. However, these guidelines were not realized in 16.9% of all patients as Figure 6 shows. All stages of FIGO mentioned in the following were documented at start of RT.

The indicated therapy intent according to stage of FIGO was missed in 13.1% of all patients. Out of all, 728 patients were staged FIGO IIa-IVa or operated within 6 months before start of RT and did not suffer from hydronephrosis or fistula. Hence, they were designated for curative RT. However, 42 of these patients were palliated with single fraction RT. Out of the 281 patients intended for palliation by single fraction RT, 32% (n=90) were treated with curative schedules (radical, adjuvant or non-radical RT). 40 patients with FIGO stage IVa and one patient with FIGO stage IIIb suffered from fistulae. However, they did not receive single fractions as TAHRC guidelines indicate. One patient staged FIGO IVb, 2 patients with recurrence and 4 patients with recurrence after surgery were treated with radical RT. Non-radical RT was given to 3 patients staged FIGO IVb, 3 patients with recurrence and 14 patients with recurrence after surgery. Furthermore, 22 patients with recurrence after surgery received belated adjuvant RT.

Within the patients, who should receive radical RT (n=210, inoperable FIGO IIa, FIGO IIb and FIGO IIIa), 93.3% were treated accordingly. Out of the 14 patients with misassignment of RT schedules, one patient staged FIGO IIb received palliative single fractions, 3 patients staged FIGO IIb and

10 patients staged FIGO IIIa received non-radical RT. None of them suffered from hydronephrosis or fistulae according to patient files.

Patients with surgery within 6 months before start of RT received the intended adjuvant RT schedule in 62.8% out of the 43 cases. 8 patients received radical RT and 6 patients received non-radical RT after surgery. Two patients were palliated with single fractions.

Patients with stages of FIGO IIIb and IVa were designated to be treated with non-radical RT or in case of bilateral hydronephrosis or fistulae with palliative single fractions. Within the group of patients with FIGO IIIb (n=525) 93.9% were treated accordingly. 10 patients with stage of FIGO IIIb received radical RT and 22 patients with neither hydronephrosis nor fistula received single fraction RT. Out of the 122 patients with FIGO IVa at start of RT, 85.2% were treated according to the mentioned RT algorithm. One patient received radical RT and 17 patients staged FIGO IVa received single fractions, albeit not suffering from neither hydronephrosis nor fistulae.

Patients staged FIGO IVb were palliated with single fraction RT as intended in 92.2% of the 51 cases. Three patients staged FIGO IVb received non-radical RT and one patient was treated with radical RT.

Palliation, thus single fraction RT, was recommended for patients with recurrence of cervical cancer. However, clinical practice varied considerably: only 3 out of 7 patients with recurrence without previous surgery as initial therapy received single fractions. 51 patients were operated for cervical cancer earlier then 6 months before start of RT and staged as recurrence after surgery by definition. In 27.5% (n=14) of these cases, radiotherapeutic palliation by single fractions was done. 43.1% (n=22) received belated adjuvant RT and 4 patients were erroneously treated with radical RT. 27.5% of these 51 patients received non-radical RT.

4.2 Survival analysis

This section displays the estimated survival probabilities for cervical cancer patients after RT at TAHRC. First, overall survival including worst-case-analysis is presented for all patients included in this study. For a more detailed comparison of survival for different stages of FIGO, see Appendix 9.5. In order to investigate, whether TAHRC guidelines are effective in terms of overall survival, the outcome of patients, who discontinued and those, who completed guideline-conform RT, was compared. Therefore, the total sample of 1009 patients was narrowed down to a subsample of 788 patients, who were assigned to RT according to TAHRC guidelines and did neither receive surgical treatment nor previous therapies other than chemotherapy for their cervical cancer. Results of survival analysis for these patients after standardised radiotherapeutic treatment are shown in Chapter 4.2.2. For better evaluation of the effect of total doses on overall survival of patients, adjustment for confounding variables identified in Chapter 3.4.1 was done by dint of multivariate proportional hazards regression model [64].

4.2.1 Estimated overall survival of the whole study sample

Within the whole cohort of 1009 patients, a total of 209 deaths were registered. Another 36 patients were reported dead at the time of telephone interview. However, the date of death remained unknown. Therefore, these patients were entered as alive and censored at the time of last personal appointment documented in the files. 367 patients were lost to follow-up, i.e., there was no current information on these patients' vital status at the time of data collection and the contact by phone call was not

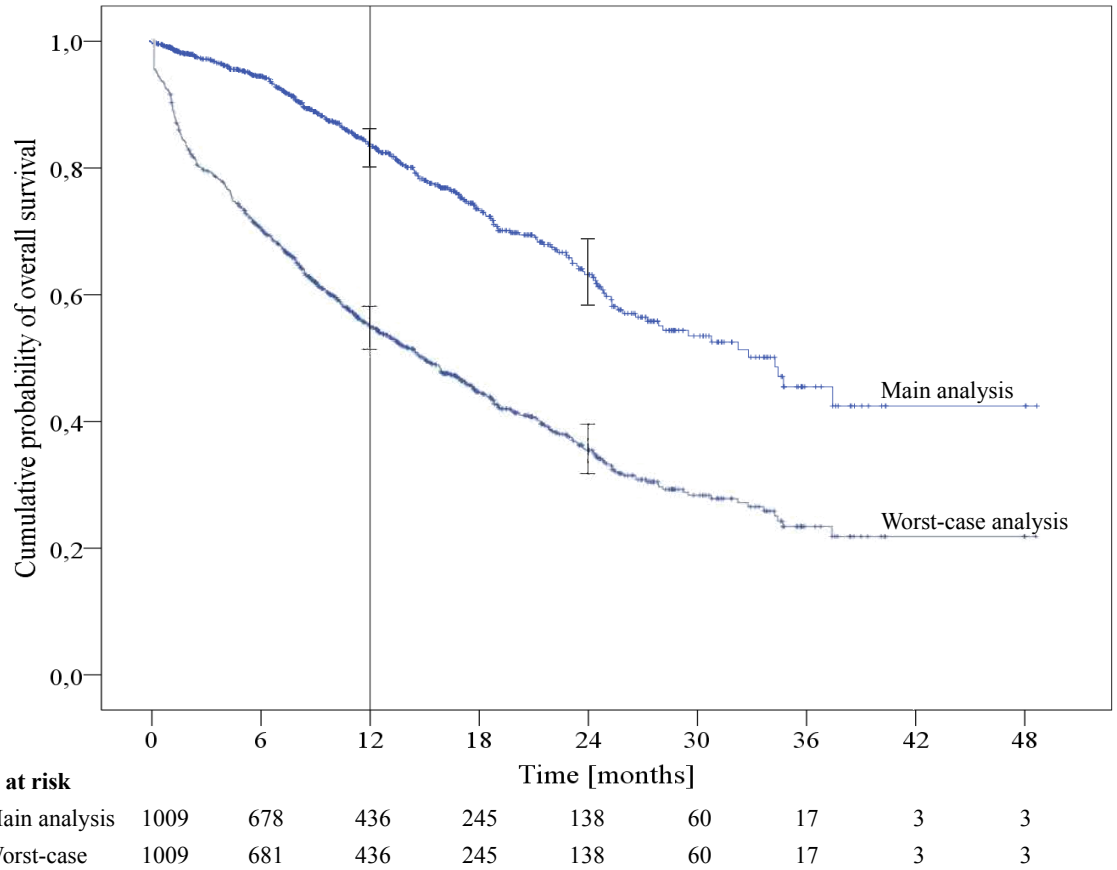


Figure 7: Crude overall survival of all patients after RT at TAHRC 2008-2012. Main-analysis and worst-case analysis are shown with 95% CIs after one and two years.

successful. Notably, at year 4 the number of patients under observation declined to 3. As the vast majority of patients (79.3%, n=800) was censored, a worst-case analysis was performed. The worst-case scenario would be death one day after last contact. It was assumed if the patient could not be contacted by telephone or did not show up in person at TAHRC within 6 months before data collection, as follow-ups were scheduled every 6 months. In worst-case analysis, censoring came down to 42.9% of all patients and the simulated maximum number of occurring deaths was 576.

In Figure 7 the estimated overall survival is shown for the total patient cohort. The estimated 1- and 2-year survival probabilities were 83.4% and 63.2% respectively. Assuming worst-case scenario estimated 1- and 2-year overall survival probabilities declined to 54.8% and 35.6% respectively. The median survival time was 34.3 months, declining to 15 months in worst-case analysis. Table 23 displays the respective 95% confidence intervals (95% CIs).

4.2.2 Dose-effect of radiation on overall survival

Selection of patients with guideline-conform assignment to RT schedule. In order to analyse the influence of the total dose of radiation received on patients' survival, the patient's collective was narrowed down to patients, whose primary therapy for cervical cancer was RT. Accordingly, Figure 8 shows the exclusion of patients in consideration of therapies received.

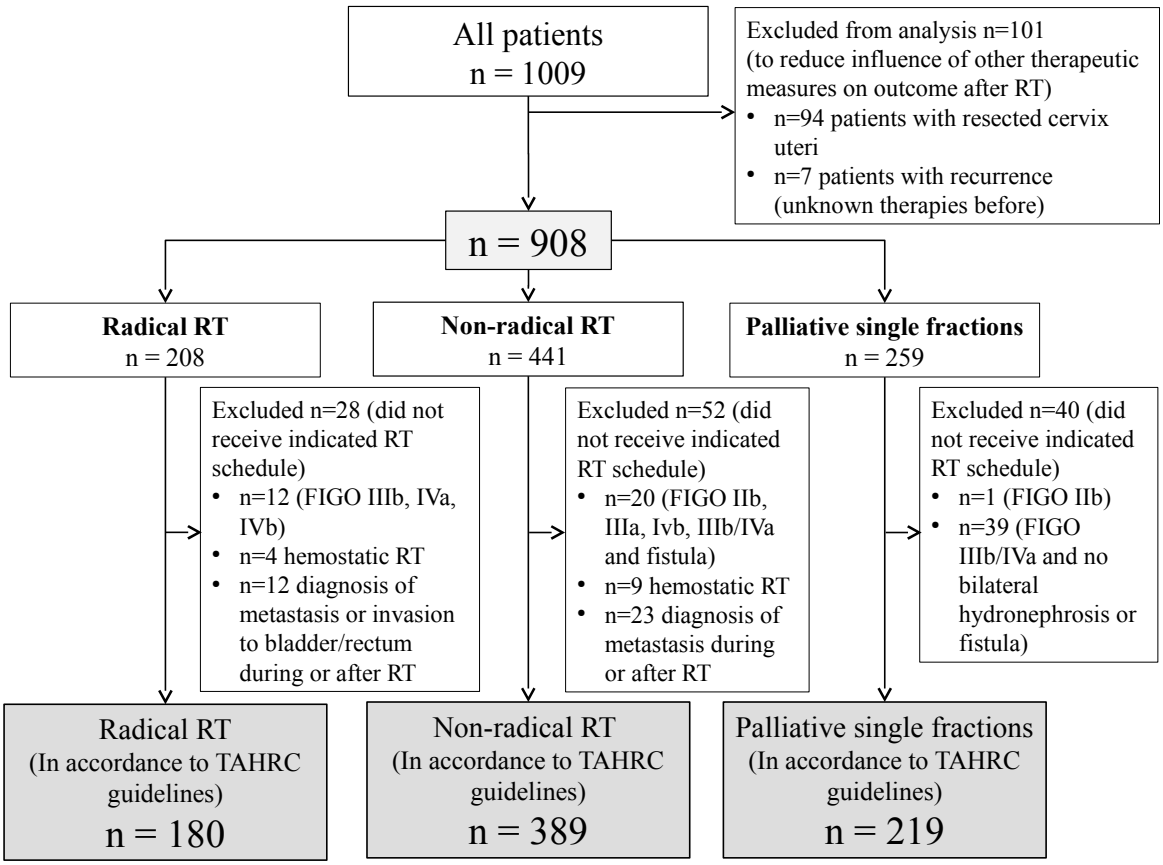


Figure 8: Exclusion of patients for reduction of confounding.

The first group excluded comprises patients, whose uterine cervix was resected for treatment of cervical cancer (or, in one case, for ovarian carcinoma) before start of RT by performing either radical Wertheim-Meigs-surgery or total hysterectomy (n = 94). The initial surgical reduction of the tumour's size affects survival. Hence, influence of the respective radiation dose on survival would be confounded and is not expected to be reliably shown. 51 out of these patients experienced recurrence of cervical cancer after more then 6 months after surgery. The second group excluded were 7 patients with recurrence and no documentation of initial therapy. As unknown therapies can not be controlled for, these patients were excluded from further analysis. Subsequently, the patients' collective is reduced by 101 patients and comes down to n = 908. These patients were treated either with radical RT, non-radical RT or single fractions. All patients, whose RT was planned in contradiction to TAHRC guidelines, were excluded. Reasons for exclusions were stages of FIGO other than those, who indicate the performed RT schedule, or hemostatic RT. The latter was indicated in case of massive vaginal hemorrhage. Hence, tumour progression or underdiagnosing in the first place could be suspected. From patients, who were treated with radical RT, 12 cases were excluded from analysis. These patients presented with stages of FIGO IVa or IVb during or after RT. Hence, initial underdiagnosing can be assumed. The same assumption applies for 23 cases with non-radical RT schedule, where metastasis was found during or after RT.

For analysis of guideline-conform RT, the study cohort came down to a total of 788 patients. Sur-

vival analysis for these patients, grouped by the respective RT schedule, is shown in the following. Estimated overall survival is presented according to the total dose of radiation received. Correspondingly, survival after completion versus (vs.) discontinuation of RT can be compared.

Dose-specific overall survival of patients staged FIGO IIa, IIb and IIIa and treated with radical RT according to TAHRC guidelines. In the following, survival of patients after radical RT according to TAHRC guidelines (n=180) is presented. At start of RT, they presented with a stage of FIGO of IIa (n=3), IIb (n=160) or IIIa (n=17). Their altogether median survival time was 29.5 months. For comparison of survival according to completion or discontinuation of RT schedule patients were grouped according to total dose of radiation received. 87 patients received the total dose of 72 Gy as indicated (see Chapter 3.3.3). 1 patient received 76 Gy and 92 patients discontinued. Given the near-balance size of both groups, comparison between patients who completed their radical RT schedule and those who discontinued was appropriate. In main and worst-case analysis censoring was done in 87.8% and 71.1% respectively of the cases. Calculated dates of death in worst-case simulation resulted in a total of 52 deaths, while 21 deaths were confirmed by relatives and hence classified as certain.

As shown in Figure 9 and Table 9, estimated overall survival, both in main and in worst-case analysis, was more favourable for patients who completed radical RT than for those, who discontinued. Estimated overall survival after one year was considerably high for patients with completed radical RT (96.1% and 90.5% in main and worst-case analysis respectively), while one-year-survival-probabilities of patients who received less than the recommended dose of 72 Gy declined to 88.7% and 75.1% in main and worst-case analysis respectively. In all cases, except for worst-case analysis of the discontinuation group, no median survival time was given (see Table 10). This is due to the fact, that estimated probability of overall survival exceeded 50% in these cases. Worst-case scenario for patients, who discontinued radical RT, showed a median survival of 24.4 months. The 95% CI is not shown as the survival function does not reach 0.45 (p-5), which is necessary for computing standard errors and confidence intervals for the 50th percentile of survival time distribution in the SPSS Kaplan-Meier procedure.

Refutation of null hypothesis (no difference between completing and discontinuing radical RT) by means of Log-Rank-Test was only possible for worst-case analysis (p=0.033). In the following, further comparison accounting for confounding variables is shown.

Table 9: Cumulative probability of overall survival after one and two years after radical RT with 95% CI shown, according to total dose of radiation received.

	Overall survival (95% CI)			
	after one year		**after two years**	
Total dose in Gy	Main analysis	Worst-case analysis	Main analysis	Worst-case analysis
14-70 Gy	88.7 (81.1-96.3)	75.1 (65.5-84.7)	79.9 (67.7-92.1)	57.7 (44.3-71.1)
72 & 76 Gy	96.1 (91.7-100)	90.5 (84.1-96.9)	82.6 (70.6-94.6)	69.4 (55.8-83)

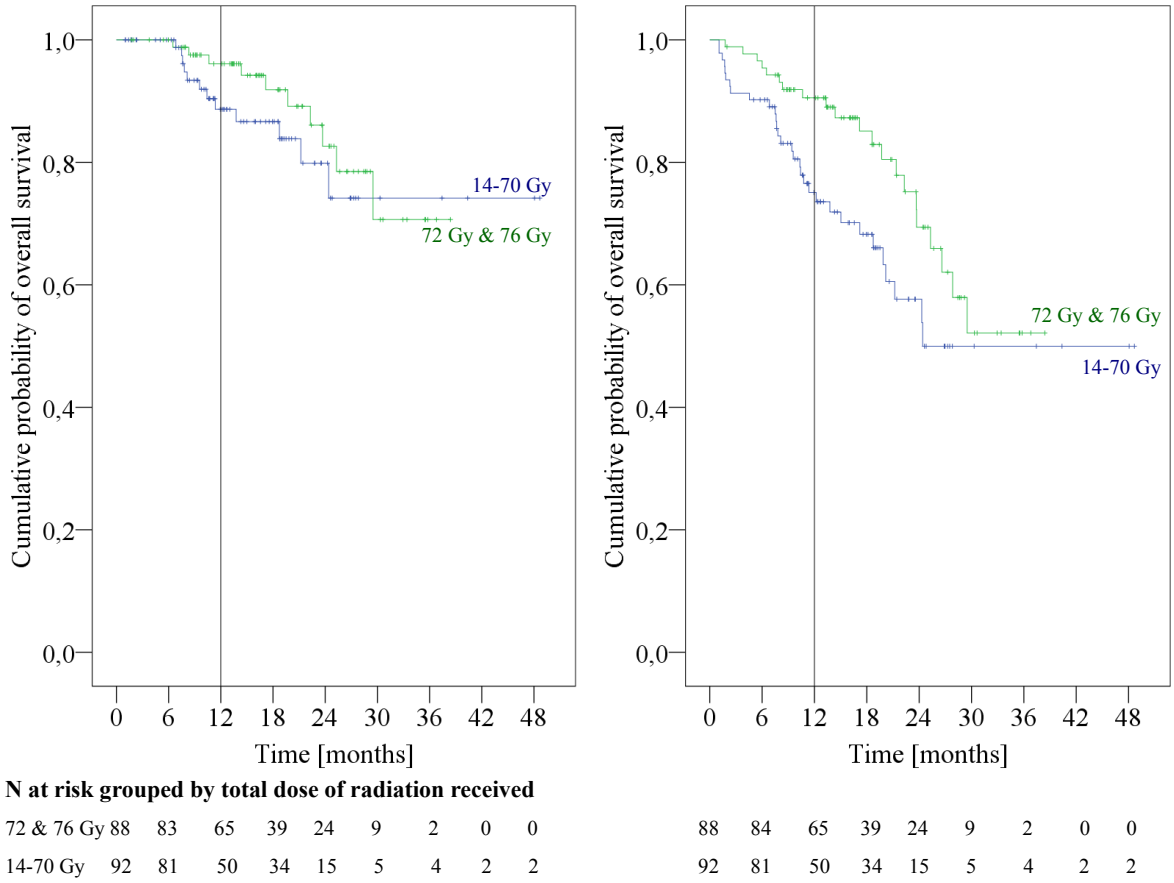


Figure 9: Crude overall survival in main (left) and worst-case analysis (right) after radical RT at TAHRC 2008-2012, grouped by total dose of radiation.

Table 10: Estimated median survival time [months] after start of radical RT, according to total dose of radiation received.

	Estimated median survival time [months]	
Total dose in Gy	Main analysis	Worst-case analysis
14-70 Gy	-	24.4
72 & 76 Gy	-	-

Table 11: Hazard ratios according to total doses of radiation received in main analysis of patients after radical RT (n=180).

Total dose of radiation received	Hazard ratio	CI 95%	p-value
72-76 Gy vs. 14-70 Gy	1.33	0.54 - 3.31	0.54

Table 12: Hazard ratios according to total doses of radiation received in worst-case analysis of patients after radical RT (n=180).

Total dose of radiation received	Hazard ratio	CI 95%	p-value
72-76 Gy vs. 14-70 Gy	1.53	0.85 - 2.77	0.16

According to the MSAS identified in Chapter 3.4.1, adjustment for confounding variables was performed. For analytic adjustment by means of the Cox proportional hazards model, adjustment was done for grade of anemia, HIV status, eGFR and ECOG score before start of RT. Significant prognostic value was only asserted for no anemia vs. grade 1 anemia in worst-case analysis (HR 0.3 (95% CI 0.1-0.7)). Cox regression model of main and worst-case analysis shows no significant difference of overall survival of patients who discontinued and patients who completed their radical RT schedule (see Table 11 and 12). However, Figure 10 shows a trend of higher survival probabilities for patients, who completed their radical RT schedule. Moreover, 95% confidence bounds for hazard ratios (HR) in main and more distinctly in worst-case analysis clearly tend towards values above 1. In worst-case analysis, difference between both groups is more distinct, which can be appreciated both graphically (see Figure 10 on the right) and numerically by means of HRs displayed in Table 12. Note, that the lower 95% confidence bound approaches 1 and, therefore, 1.53 times lower chances of survival can be assumed for patients, who discontinued a radical RT schedule.

To sum up, both in main and in worst-case analysis overall survival for patients who received radical RT tends to be worse in case of discontinuation. However, statistical significance could not be shown.

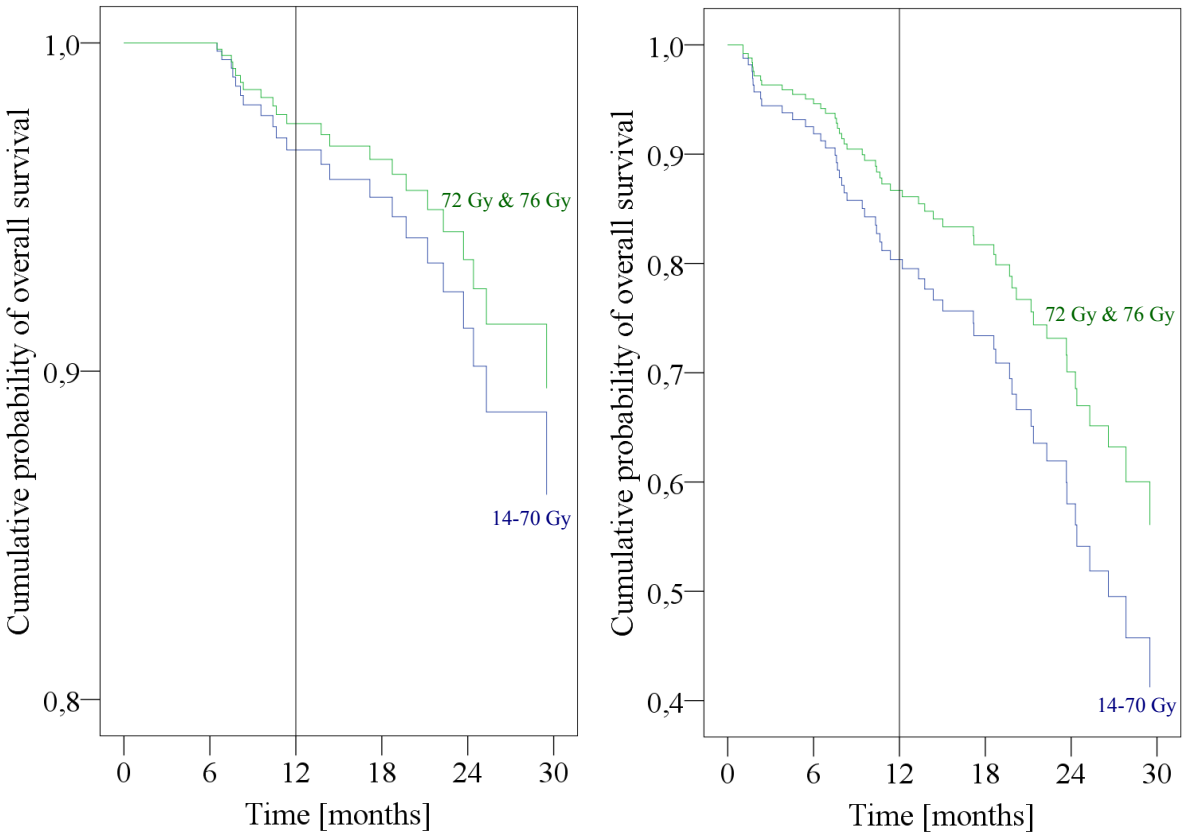


Figure 10: Estimated overall survival in main (left) and worst-case analysis (right) after radical RT at TAHRC 2008-2012 (n=180), grouped by total dose of radiation and adjusted for grade of anemia, HIV status, eGFR and ECOG score.

Dose-specific overall survival of patients staged FIGO IIIb and IVa and treated with non-radical RT according to TAHRC guidelines. For better evaluation of the influence of total radiation dose received, in the following only patients are presented, who were assigned according to guidelines to a non-radical RT schedule as shown in Figure 8. The remaining total of 389 patients comprises 365 patients staged FIGO IIIb and 24 patients staged FIGO IVa. None of them suffers from clinical fistulae. Patients were grouped into 4 groups according to total dose of radiation received. Deviations from planned total doses, as described in Chapter 3.3.3, result from either discontinuations or excessive RT for unreported reasons. These 4 dose groups are not as commensurate as intended, since the vast majority of patients received either 44 or 50 Gy of RT, being the recommended total doses for a non-radical RT schedule. 67 patients discontinued non-radical RT and received a total dose of 4-42 Gy. All 389 patients had an altogether median survival time of 30.8 months (CI 95% 25-36.6) in main analysis and 17.4 months (CI 95% 14.9-19.9) in worst-case analysis. The number of certain deaths for main analysis was 91. In a worst-case scenario, 213 patients deceased. In main analysis 76.6% and in worst-case analysis 45.2% of the cases were censored.

When comparing different total doses applied, Figure 11 and Table 13 show a more favourable estimated overall survival for patients, who completed non-radical RT and received total doses ranging between 44-76 Gy. Those with discontinuation of non-radical RT schedule had lowest probabilities of survival in main analysis (71.1% after one year and 41.8% after two years) as well as in worst-case analysis, where survival probabilities after two years came down to 18.7% only. Median survival time for these patients with a total dose of radiation lower than the minimum total dose of 44 Gy recommended according to TAHRC guidelines was 5.1 months in worst-case analysis (see Table 14). Difference in survival after discontinuing versus completing the minimum recommended total dose of non-radical RT according to Log-Rank-Test is significant both for main (p=0.1%) and for worst-case analysis (p=0.0%).

Within patients, who completed non-radical RT, survival probabilities were similar in main-analysis, showing a slight positive dose-effect. However, in worst-case analysis, estimated overall survival after one (60.8%) and two years (39.6%) tends to be lower for patients, who received 53 Gy and higher doses. In these cases, the planned total dose was exceeded, assumedly for symptom control and underlying aggressive disease. The latter could lead to worse survival. However, the sample number for this case is much smaller than for patients with guideline-conform treatment. Therefore, bias for difference in group size is expected.

Table 13: Cumulative probability of overall survival after one and two years after non-radical RT with 95% CI shown, according to total dose of radiation received.

	Overall survival (95% CI)			
	after one year		**after two years**	
Total dose in Gy	Main analysis	Worst-case analysis	Main analysis	Worst-case analysis
4-42 Gy	71.1 (57.3-84.9)	33.8 (22.2-45.4)	41.8 (22.8-60.8)	18.7 (8.3-29.1)
44-47 Gy	87.7 (81.3-94.1)	65.9 (57.7-74.1)	59.5 (46.5-72.5)	40.4 (29.8-51)
48-50 Gy	86.4 (79.8-93)	66.6 (58.2-75)	67.7 (53.3-82.1)	40.9 (29.3-52.5)
53-76 Gy	89.4 (77.8-100)	60.8 (45-76.6)	69.4 (49.2-89.6)	39.6 (22.8-56.4)

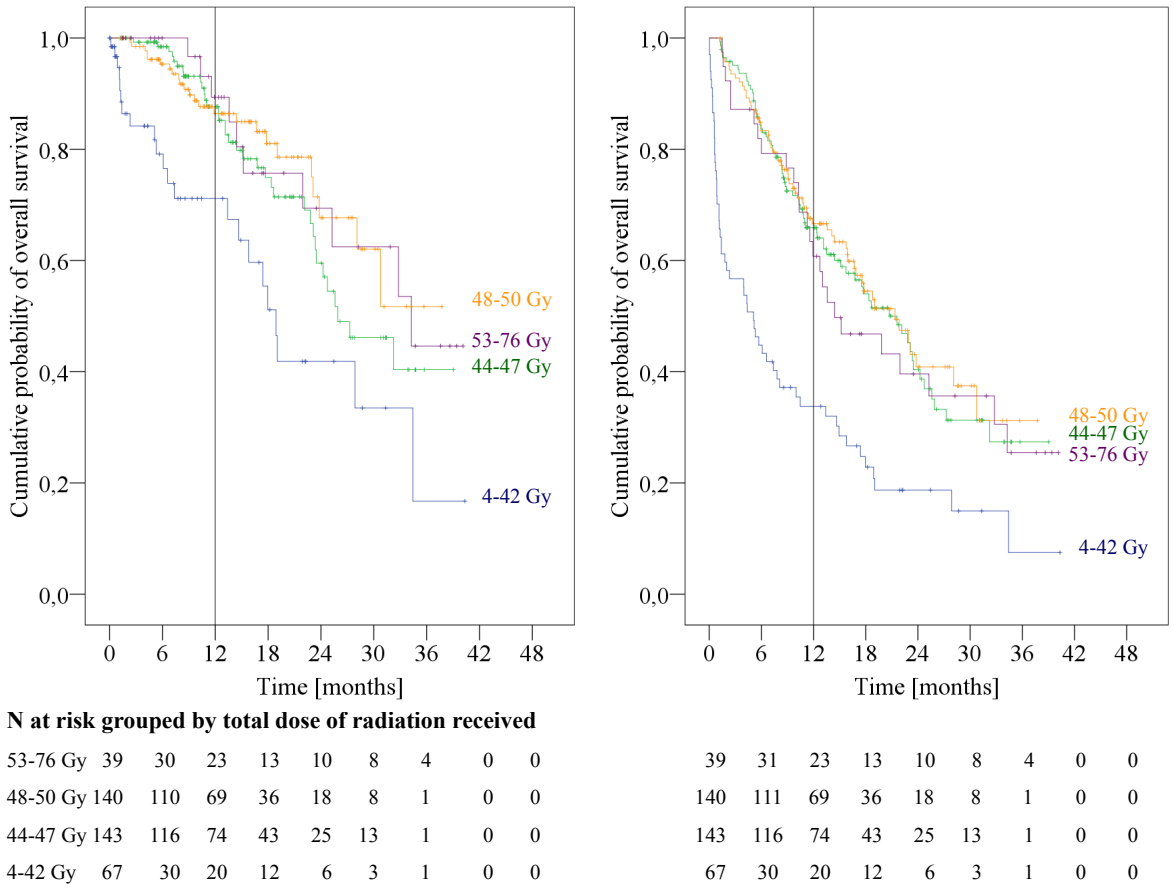


Figure 11: Crude overall survival in main (left) and worst-case analysis (right) after non-radical RT at TAHRC 2008-2012, grouped by total dose of radiation.

Table 14: Estimated median survival time [months, with 95% CI shown] after start of non-radical RT, according to total dose of radiation received.

	Estimated median survival time [months, 95% CI]	
Total dose in Gy	Main analysis	Worst-case analysis
4-42 Gy	18.9 (16.7-21.1)	5.1 (3.1-7.1)
44-47 Gy	25.9 (19.1-32.7)	20.7 (16.1-25.3)
48-50 Gy	-	21.4 (16.9-25.8)
53-76 Gy	34.3 (21.1-47.4)	14.4 (5.4-23.4)

Table 15: Hazard ratios according to total doses of radiation received in main analysis of patients after non-radical RT (n=389).

Total dose of radiation received	Hazard ratio	CI 95%	p-value
4-42 Gy vs. 44-47 Gy	3.03	1.37 - 6.71	0.006
44-47 Gy vs. 48-50 Gy	1.33	0.64 - 2.77	0.44
48-50 Gy vs. 53-76 Gy	0.96	0.44 - 2.09	0.92

Table 16: Hazard ratios according to total doses of radiation received in worst-case analysis of patients after non-radical RT (n=389).

Total dose of radiation received	Hazard ratio	CI 95%	p-value
4-42 Gy vs. 44-47 Gy	2.72	1.65 - 4.5	0.000
44-47 Gy vs. 48-50 Gy	1.04	0.65 - 1.66	0.88
48-50 Gy vs. 53-76 Gy	0.91	0.55 - 1.49	0.72

In the following, estimated overall survival is shown with adjustment for grade of anemia, HIV status, eGFR and ECOG score before start of RT. Significant prognostic value was only asserted for no anemia vs. grade 1 anemia in worst-case analysis (HR 0.4 (95% CI 0.2-0.7)). Figure 12 displays adjusted overall survival curves for main and worst-case analysis. Cox regression model of main and worst-case analysis shows highly significant differences between patients, who discontinued their non-radical radiation schedule and received a total dose of 42 Gy and less and those with completed schedule and additional doses. As shown in Table 15, those with discontinuation had 3.03 times lower survival probabilities in main analysis. In worst-case analysis (see Table 16), chances for survival after discontinuation were 2.72 times lower compared to patients, who received a total dose of 44-47 Gy. Survival of patients with total doses of 44 Gy and more did not differ significantly, although a slight

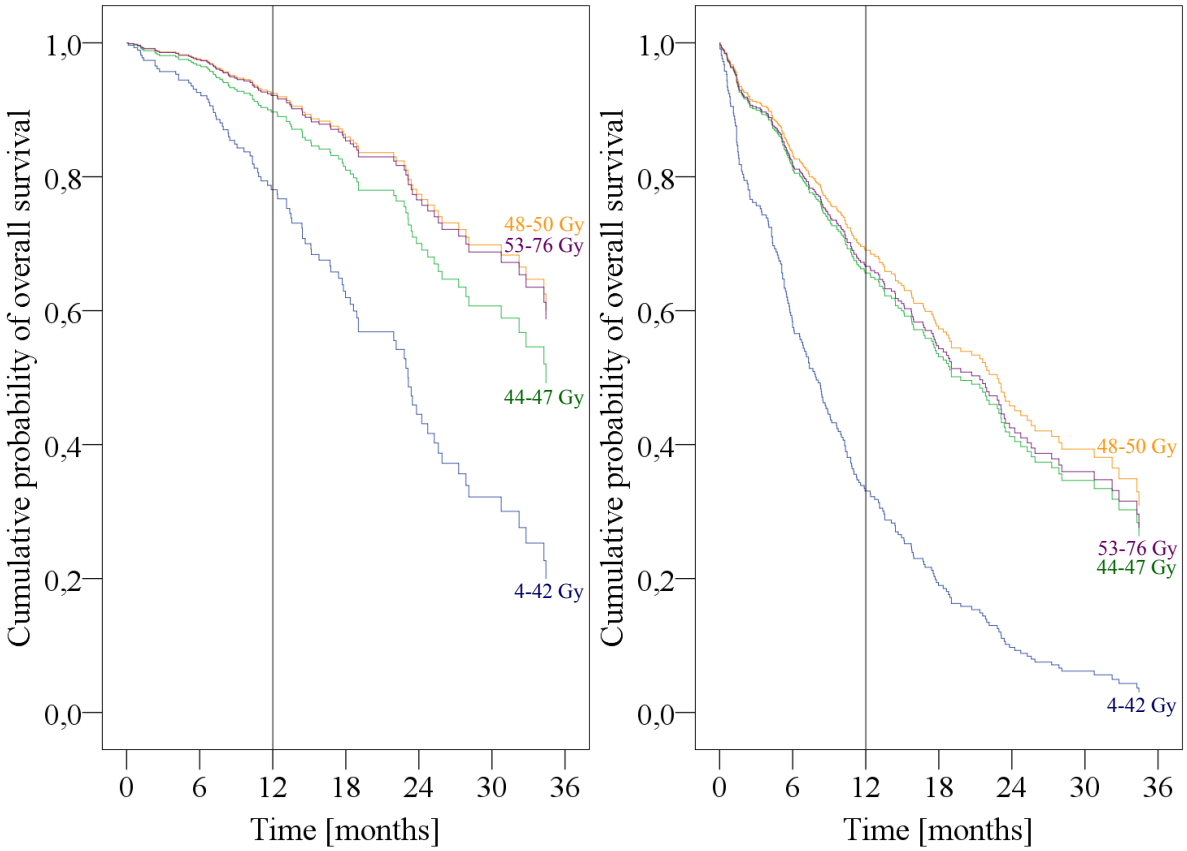


Figure 12: Estimated overall survival in main (left) and worst-case analysis (right) after non-radical RT at TAHRC 2008-2012 (n=389), grouped by total dose of radiation and adjusted for grade of anemia, HIV status, eGFR and ECOG score.

positive dose effect on overall survival can be assumed for patients who received 44-47 Gy and 48-50 Gy respectively. Both groups received total doses of radiation according to TAHRC guidelines. As visible in Figure 12, patients who received additional radiation (53-76 Gy total dose) tend to have no advantage in survival over those patients who received lower doses in main analysis. In worst-case analysis patients with higher doses than recommended have comparable probabilities of survival with those receiving the minimum recommended dose of radiation. Worse or similar overall survival in spite of higher doses of radiation can be due to, e.g., aggressive tumours, that required high dosage.

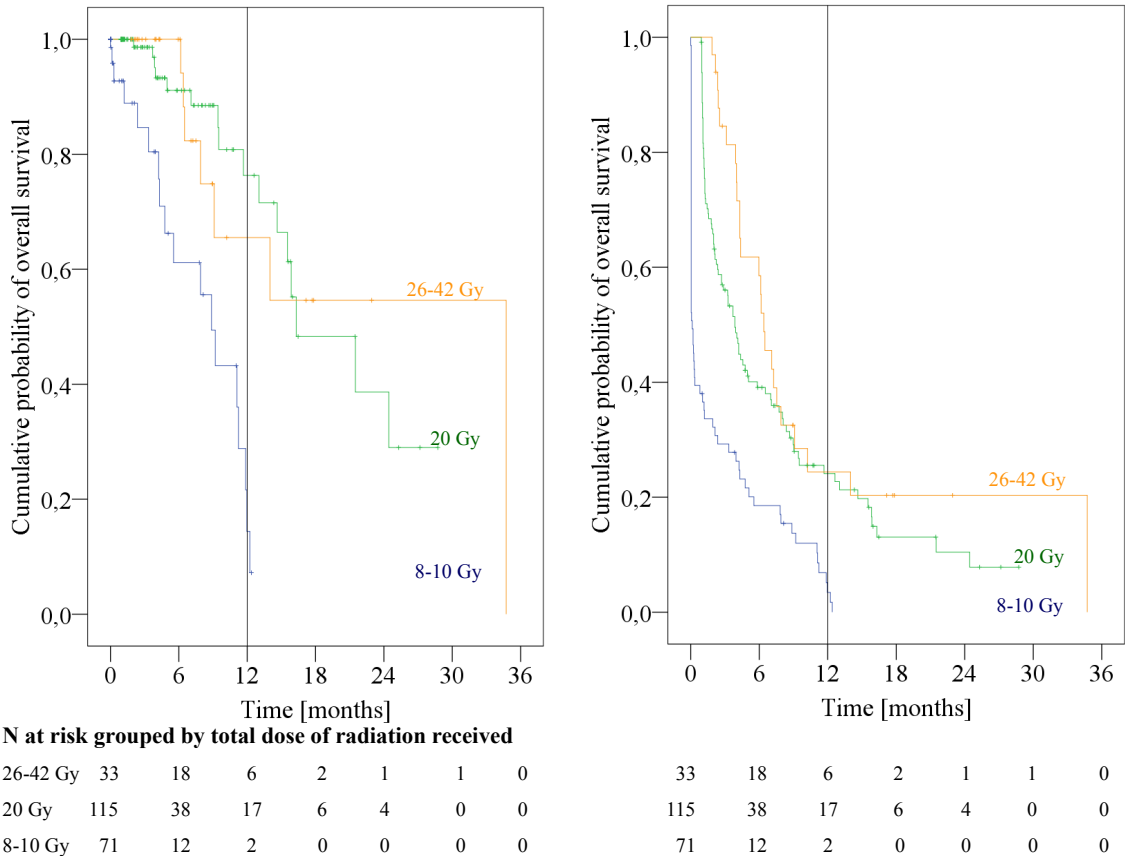
Given these findings, overall survival for patients after non-radical RT is worse in case of discontinuation. Additionally, increased doses of radiation beyond completion of non-radical RT did not have a positive effect on survival.

Dose-specific overall survival of patients staged FIGO IVb or IIIb and IVa and treated with palliative single fraction RT according to TAHRC guidelines. In the following, survival analysis for patients, who received single fractions according to TAHRC guidelines (see 3.3.3), is presented. The total of 219 patients compounds of 96 patients staged FIGO IIIb, 76 patients staged FIGO IVa and 47 patients staged FIGO IVb. Patients with stages of FIGO IIIb or IVa suffered either from bilateral hydronephrosis or vesicovaginal fistula. Hemostatic doses (n=2) were not excluded as single fractions could be used for hemostasis as well, without being labeled as such. Different total doses received result from the number of single fractions applied and were used to group patients into three groups. There is no discontinuation of RT, as the minimum dose of this RT schedule is one single fraction by definition. However, the three resulting groups are not as commensurate as intended, as the vast majority of patients received one or two single fractions and only 33 patients received a higher dose than 20 Gy.

In main analysis, 41 deaths were registered. In contrast, 178 deaths (83.6%) were assumed in calculating the worst-case scenario. Notably in worst case, 95.8% of patients who received one single fraction were assumed to be dead within the time frame of this study. Censoring was done in 81.3% of the patients for main analysis and in 16.4% for worst-case analysis. For the latter, numbers of censored patients varied largely: 4.2% of patients with one single fraction and 24.2% of patients with more than two single fractions were censored. For main analysis variance of censoring rates was smaller.

Table 17: Cumulative probability of overall survival after one and two years after single fraction RT with 95% CI shown, according to total dose of radiation received.

	Overall survival (95% CI)			
	after one year		**after two years**	
Total dose in Gy	Main analysis	Worst-case analysis	Main analysis	Worst-case analysis
8-10 Gy	14.4 (0 - 32.6)	3.4 (0 - 8.2)	0	0
20 Gy	76.3 (61.1-91.5)	24.1 (15.3-32.9)	38.6 (13.6-63.6)	10.4 (2.6-18.2)
26-42 Gy	65.5 (39.5-91.5)	24.4 (8.4-40.4)	54.6 (25.2-79.8)	20.3 (4.9-35.7)



N at risk grouped by total dose of radiation received

26-42 Gy	33	18	6	2	1	1	0
20 Gy	115	38	17	6	4	0	0
8-10 Gy	71	12	2	0	0	0	0

	33	18	6	2	1	1	0
	115	38	17	6	4	0	0
	71	12	2	0	0	0	0

Figure 13: Crude overall survival in main (left) and worst-case analysis (right) after single fraction RT at TAHRC 2008-2012, grouped by total dose of radiation.

Table 18: Estimated median survival time [months, with 95% CI shown] after start of single fraction RT, according to total dose of radiation received.

	Estimated median survival time [months, 95% CI]	
Total dose in Gy	Main analysis	Worst-case analysis
8-10 Gy	8.9 (6.6-11.2)	0.13 (0.08-0.19)
20 Gy	16.3 (8.7-23.8)	3.9 (3-4.7)
26-42 Gy	34.7	6. (5.1-7.7)

The overall median survival time for patients, who were treated with single fraction RT, was 14 (95% CI 10.1-17.9) months in main and 3.3 (95% CI 2.2-4.3) months in worst-case analysis. As shown in Figure 13 and Table 17, estimated overall survival was proximate for both patients with two single fractions and those, who received more than two single fractions, both for main and worst-case analysis. However, patients who received one single fraction with a total dose of 8-10 Gy had lowest survival probabilities after one year (14.4% in main and 3.4% in worst-case analysis). After two years, all patients of this group were dead. Median survival time was only 4 days in worst-case analysis (see Table 18).

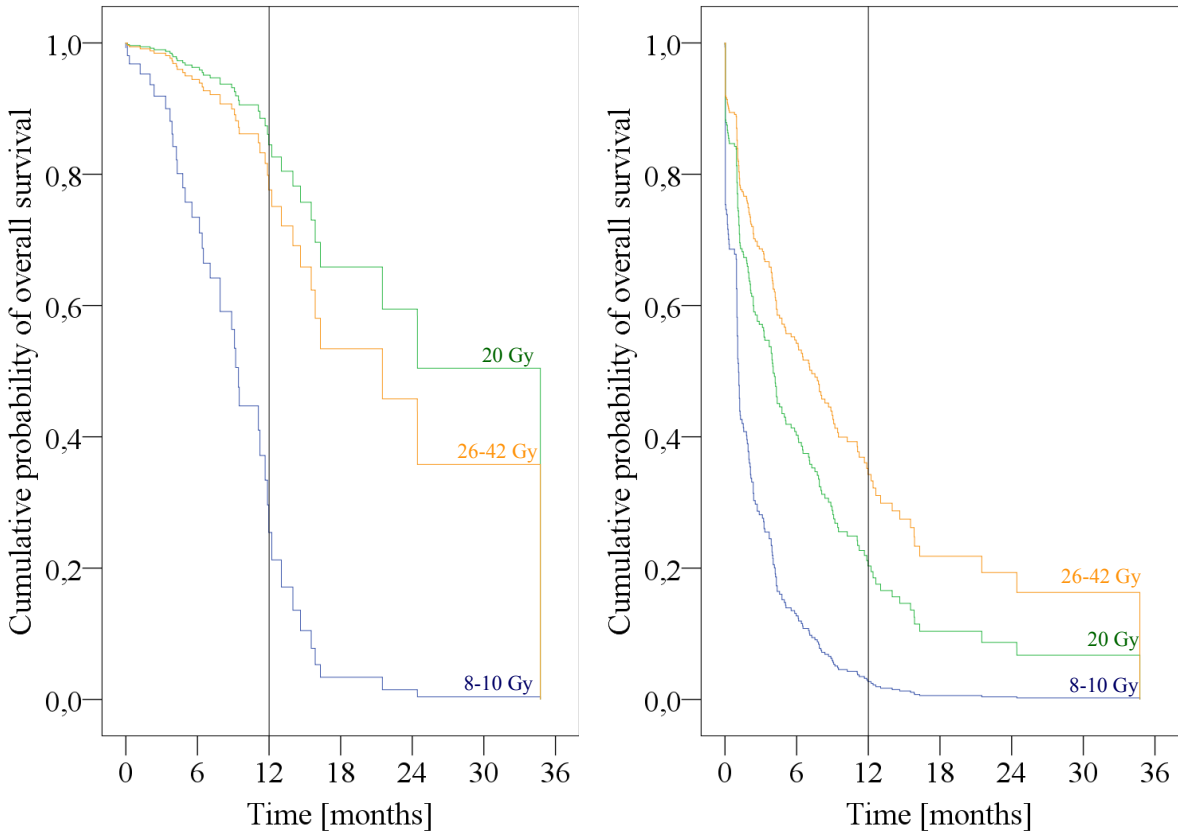


Figure 14: Estimated overall survival in main (left) and worst-case analysis (right) after single fraction RT at TAHRC 2008-2012 (n=219), grouped by total dose of radiation and adjusted for grade of anemia, HIV status, eGFR and ECOG score.

Log-Rank-Test suggests, that difference in estimated overall survival between patients who received one and those who received more single fractions is highly significant (p=0.0% both in main and in worst-case-analysis). Estimated overall survival for patients treated with palliative single fractions is adjusted for grade of anemia, HIV status, eGFR and ECOG score, as illustrated in Figure 14. Significant prognostic value was only asserted for no anemia vs. grade 1 anemia in worst-case analysis (HR 0.5 (95% CI 0.3-1)). Cox regression model of main and worst-case analysis shows a highly significant difference between patients with one single fractions and those, who received more than 10 Gy. After one single fraction, patients had 3.67 and 3.01 times lower survival probabilities in main and worst-case analysis respectively, compared with patients, who received a total dose of 20 Gy (see Tables 19 and 20). There was no significant difference in overall survival between patient groups with 20 Gy and more single fractions. As Figure 14 illustrates, survival of patients after two single fractions tends to be higher than for those with more single fractions in main analysis, while in worst-case analysis the opposite is the case.

Table 19: Hazard ratios according to total doses of radiation received in main analysis of patients after single fraction RT (n=219).

Total dose of radiation received	Hazard ratio	CI 95%	p-value
8-10 Gy vs. 20 Gy	5.41	1.82 - 16.03	0.002
20 Gy vs. 26-42 Gy	0.67	0.23 - 1.93	0.45

Table 20: Hazard ratios according to total doses of radiation received in worst-case analysis of patients after single fraction RT (n=219).

Total dose of radiation received	Hazard ratio	CI 95%	p-value
8-10 Gy vs. 20 Gy	3.37	2.06 - 5.51	0.000
20 Gy vs. 26-42 Gy	1.49	0.93 - 2.37	0.095

5 Discussion

In this section, I will link the main findings of this study to the present state of research with regard to characteristics of the observed study cohort, guidelines and outcome of RT. Furthermore, the strengths and limitations of this study are considered and suggestions for further research on radiotherapeutic treatment of cervical cancer are presented. The chapter concludes with recommendations for optimizing treatment for cervical cancer patients in Ethiopia.

5.1 Findings of this study and links to current research

In the following, I will place the results of this study within the existing research on radiotherapeutic treatment for cervical cancer in a low-resource setting. First, the composition of the observed cohort is shown in contrast to similar studies to evaluate further comparability. Second, the identified TAHRC guidelines are presented in the light of RT practice patterns in other studies with similar facilities. Third, I will compare the collected data on adverse effects to results of other centers. The chapter concludes with a comparison of this study's major findings regarding survival analysis with the results of other studies that use a similar approach.

The study cohort's composition compared to similar studies and the Ethiopian average. The presented cohort of 1009 patients had a median age of 49 years, which is similar to other large cohort studies from India, Brazil and the United States on outcome of cervical cancer patients after RT [110, 111, 112], but lower compared to French, Japanese and German data [113, 114, 115]. Naturally, in a society with merely 17% of its population aged 40 years and older, more women are affected from the chance for early onset of cervical cancer, compared to, e.g., Germany, where the same age group amounts to 58% of the whole population [54, 116]. Additionally, decrease in age at presentation compared to the mentioned studies might be due to high rates of HIV-positive patients within this cohort (10%), as an earlier onset of cervical cancer is common in case of coinfection with HIV [117]. Additionally, HIV-infection is an important risk factor for cervical cancer [123]. Correspondingly, among the patients under observation, a multiple of the Ethiopian average of 1.5% [54] prove to be HIV-positive. Consequently, the implementation of screening for cervical cancer in HIV-positive women launched in Ethiopia [118].

With regard to comparing demographic findings with the Ethiopian average, a higher mean number of children (6.1) was found among the observed patients compared to a total fertility rate of 4.8 children for Ethiopian women [54]. The median age for marriage for Ethiopian women is 16.5 years [54]. In this regard data from the present study reflect the Ethiopian average as the majority of patients married at the age of 18 or younger.

In this study, a comparatively high rate of contraceptive use was noted (28% versus 20% for all Ethiopian women aged 15-49 years [54]), while 79% of the patients observed were postmenopausal and use of condoms was not surveyed. This "high" rate is due to the fact, that based on the patient files, a differentiation between current use or any previous usage of contraceptive methods was not possible. Hence, the comparability to data from the "Ethiopia Demographic and Health Survey 2011" is limited. However, there are notable differences in the pattern of used methods: only 1.5% of all 15-49 year old women in Ethiopia use oral contraceptives, whereas the majority of patients using contraception in this study, reported use of oral contraceptives (20%). On the other hand, only 7% ever used injectables, while the "Ethiopia Demographic and Health Survey 2011" showed a majority of 14% preferring this discrete option for contraception. Hence, injectables might be more popular in a more conservative setting, thus in rural areas, as they require no "partner cooperation or user action at the time of intercourse" [104], p. 900. Accordingly, higher rates for oral contraceptive use in the present study could be due to the fact, that 43% of the included women originated from urban, i.e. less conservative, areas. The mentioned survey, however, refers to the Ethiopian average and subsequently, merely 19% urban origin [32].

Late stages of FIGO were very common, especially at time of RT start, when 64% of all patients presented with FIGO IIIb or IVa. These proportions prove similar to other settings without nation-wide implementation of screening for cervical cancer [18, 19, 20, 21]. Looking at the histopathological type of cervical cancer, a comparatively low rate of 5% adenocarcinoma was found. Data on cervical cancer from, e.g., Germany state a 20% of histologically confirmed adenocarcinoma [119]. The ratio of incidences of adenocarcinoma to SCC increased in the United States and Europe during the last decades, which is most likely due to better prevention of the accessibly located SCC on the one hand and the difficulty of early diagnosis of adenocarcinoma in situ on the other hand, as their location in the cervical canal is less accessible for Papanicolaou smear [120, 121]. I therefore expect the lacking screening options to cause a higher proportion of SCC in Ethiopia.

With regard to the performance status of the patients, 56% of all patients were assessed ECOG 1. However, according to Kim et al. the actual performance status might be worse, as assessment in case of TAHRC was done by medical oncologists, whereas nurses and palliative specialists are shown to report higher ECOG scores [122].

TAHRC guidelines in comparison with RT guidelines for cervical cancer patients in other centers. Within the scope of this study, the RT protocol for treatment of cervical cancer patients and its implementation in clinical practice was presented in order to facilitate comparison to other centers. However, the standard of care set by the "European Society of Medical Oncology" indicates a combination of intensity modulated EBRT and ICBT for adequate irradiation of cervical cancer staged FIGO IB2 or IIb-IVa [15, 123]. Therefore, data on sole EBRT for cervical cancer treatment are scarce and comparison to data from TAHRC is limited.

At TAHRC, radical RT is administered in two phases, while the first one consists of a total dose of

46 Gy to the whole pelvis in opposing field technique and the second phase comprises another 26 Gy to a narrower field size in 4-field-technique. Several authors report a very similar RT pattern, when describing sole EBRT for cervical cancer [58, 114, 124, 125]. However, the only study restricted to patients with FIGO lower than IIIb was conducted by Zi-Zhong et al. 1964-1980. 97 cervical cancer patients staged FIGO IIb received sole EBRT by Co-60 with a total dose of 70 Gy [124]. Compared to the practice at TAHRC, the first phase of RT comprised a larger dose of 60 Gy in 30 fractions, followed by a booster dose of 10 Gy. Within their large unicentric cohort study (n=1069), Logsdon et al. describe an alike RT pattern for cervical cancer patients albeit stage of FIGO IIIb [58]. 50 patents received EBRT by telecobalt with extensive field technique. Total doses were higher than 40-50Gy, each fraction amounting to 2 Gy. In contrast, at TAHRC patients staged FIGO IIIb are assigned to the non-radical RT schedule, receiving fractions of 4 and 3 Gy, a lower total dose of 44-50 Gy and field borders less extensive than for radical RT (see Chapter 3.3.3).

Optimal total doses discussed in literature relate accordingly to the radical schedule at TAHRC; yet these doses are generally recommended for stages of FIGO up to IVa. Zharinov et al. report total doses within the range of 50-70 Gy by EBRT and additional ICBT as effective for the mentioned stages [126]. Studies which report outcome of sole EBRT for cervical cancer without further ICBT for patients staged FIGO IIIb, report total doses of 60-70 Gy [58, 110, 127]. Biswal et al. demonstrate a favorable 5-year survival rate of 58% for patients staged FIGO III (n=145) after a total dose of 80 Gy (EBRT+ICBT) and suggest radical RT for all stages of FIGO up to IVa [128]. Laciano et al. and Perez et al. found no evidence for better survival for FIGO stages I and II comparing total doses of 75 and 85 Gy [129, 130]. In contrast, Eifel et al. found better survival in patients with early staged cervical cancer (FIGO Ib-IIb) and high-dose ICBT [131]. 5-year-survival rates for low- and highdose ICBT were 44% and 60%, respectively. For patients staged FIGO III, however, Lanciano et al. demonstrated a clear benefit from higher dosage of 85 Gy in contrast to 75 Gy [130]. Petereit et al. drew the same conclusion, noting that FIGO IIIb generally indicates for rather higher total doses of radiation compared to RT for lower stages [132]. In contrast at TAHRC, patients with FIGO stages of IIIb are treated with a lower total dose of 44-50 Gy. Indeed, there is no evidence for lower radiation dosage such as the non-radical schedule at TAHRC for patients staged FIGO IIIb or IVa. However, access to RT at TAHRC is limited. The option of a hypofractionation non-radical schedule with a maximum of 14 fractions, thus treatment days, compared to 36 fractions for radical RT, allows for a larger number of patients to be treated.

At TAHRC, stage of FIGO indicates for curative or palliative RT. Patients with disseminated disease or stage of FIGO IIIb / IVa with bilateral hydronephrosis or clinical fistula are assigned to palliative single fractions. Indeed, several authors report rather complex conditions such as high age, patient's refusal for radical RT, low performance status and comorbidities to account for palliative intent. In contrast, Pesee et al. demonstrate considerably high survival rates (52% 5-year survival) for patients staged FIGO IIIb-IVb after receiving a total dose of 86 Gy by EBRT and ICBT and additional thai herbal medicine [133], which might emphasize the need for adequate supportive therapy. However, since the late 1970s, studies prove the effectiveness of monthly single fractions of 10 Gy delivered by Linacs to the pelvis for cessation of bleeding and pain control [134, 135, 136, 137, 138, 139], although serious complications occurred. In case of teletherapy with Cobalt-60, highdosage single fractions should be considered all the more cautiously, especially with regard to obese patients [139]. To avoid late adverse effects of high-dose single fractions, hypofractionation of 5 fractions by 5 Gy each is

suggested by Kim et al., who noted a better control of pain in comparison with 10 Gy single fractions [140]. Interestingly, this fractionation pattern corresponds to a 42-50 Gy schedule in 2 Gy fractions using the linear-quadratic time model, resembling the non-radical schedule at TAHRC [141, 142]. As summarized by Smith et al., there are numerous hypofractionation protocols for palliation of advanced stages of cervical cancer and "the selection of the optimal schedule depends on careful and individualized consideration of each patient's circumstances including extent of disease, life expectancy, performance status and logistical concerns" [143], p. 271.

In summary, the concept of radical RT with a similar fractionation schedule as described in Chapter 3.3.3 is well established in literature. All studies to my knowledge recommend radical RT for all stages of FIGO other than those indicating for palliative intent. There is no evidence for low-dose radiation with total doses of a maximum of 50 Gy in case of FIGO IIIb or IVa and I did not identify any study promoting a comparable RT schedule for these patients. In terms of palliation, single fraction RT is a common approach to effectively alleviate symptoms, such as heavy bleeding and pain. However, in case of life-expectancy of more than 9 months [137], hypofractionation should be considered as a less aggressive schedule for palliation. This applies especially to the fact that RT in Ethiopia will not be delivered by Linacs in near future and adverse effects of single fractions of 10 Gy delivered by Cobalt-60 are expected to be substantial, particularly at skin level [26].

Adverse effects after sole EBRT with Cobalt-60. In this study, toxicities of RT are the major among known reasons for discontinuation of an ongoing RT schedule. A large cohort study of 3273 nasopharyngeal carcinoma patients, who received radiation treatment, drew similar conclusions - almost half of the dropouts discontinued for adverse effects of RT [144]. For comparison of rates of adverse effects with other centers, I only found two other studies from more than 35 years ago, where cervical cancer was similarly treated with sole EBRT by telecobalt without additional ICBT. Both studies lack a detailed presentation of adverse effects of all grades and differ in patient numbers and stages of FIGO represented [124, 125]. Although based on different RT modalities, Table 21 gives a rough overview on rates of adverse effects reported in several studies I found eligible for comparison. The displayed rates of adverse effects are researched to my best knowledge. The presented studies differ in study design, thus patient numbers, stages of FIGO included, degrees of adverse effects reported and modalities of treatment. Consequently, consistent comparability is not feasible.

At TAHRC, acute skin toxicities were documented in 8%. Other studies show a range of 0-17% of all patients observed [125, 145, 146]. Radiation diarrhea as an acute adverse effect occurred in 4-65% [111, 125, 127, 145, 147, 148], whereas I found a low rate of 11%, most probably due to underdiagnosing for patients at TAHRC. Elghamrawi et al. reported bowel dysfunction for 42% out of 57 patients, whereas not only radiation diarrhea was subsumed, but "[...] change in bowel habit, [...]constipation, tenesmus, soiling of clothes and/or flatulence." [147], p. 263. The large proportion of 65% radiation diarrhea reported by Koeck et al. was stated to be mild and did not cause cessation of radiation [125].

Rates for radiation proctitis reported in literature varied between 3-17% [27, 111, 112, 113, 114, 124, 125, 127, 145, 146, 147, 148, 149, 150, 151], which is contrasted by the twofold proportion found within the 578 patients, who came for a late follow-up at TAHRC. Radiation proctitis was registered in almost one third of these patients. However, in 60% of these cases radiation proctitis was not clinically diagnosed but assumed as patients reported bleeding per rectum in telephone interviews. With regard

1st author	Moelle	Zi-Zhong [124]	Koeck [125]	Akine [114]	Ferreira [112]	Patel [150]	Ferrigno [149]	Arulponni [146]	Saibishkumar [145]	Horiot [113]	Barraclough [148]	Matsuura [127]	Perez [27]	Eifel [111]	Elghamrawi [147]	Gondi [151]
Origin of data	Addis Ababa, Ethiopia	Chonqging, China	Newark, USA	Tokyo, Japan	Porto Alegre, Brazil	Chandigarh, India	Campinas, Brazil	Bangalore, India	Chandigarh, India	9 centers, France	Manchester, UK	Hiroshima, Japan	St. Louis, USA	Houston, USA	Cairo, Egypt	Wisconsin, USA
Number of patients	784, 578	97	55	104	109	482	190	99	1069	1383	44	16	1456	1784	57	374
Time range of survey	2008-2012	1964-1980	1957-1964	1962-1979	1980–1997	1986-1989	1989-1995	1998-2005	1996-2001	1970-1981	1996-2004	2002-2009	1959-1993	1960-1989	1996-2005	1989-2009
FIGO stages	IIa-IVb, postOP, Rec	IIb	I-IV	Ia-IVa	IIIb	I-III	Ib-IIIb	Ib-IVa, postOP	I-IVa	Ia-IVb	Ib-IVa	IIb-IVa	Ib-IVa	Ib	IIb	Ib1-IVa
EBRT	Co60	Co60	Co60	Co60	8 MV Linac	Co60	Co60	Co60	61.6 % Co60; 38.4 % 6 MV Linac	30 % 60Co; 70% 25 MV Linac	Linac	Linac, CF or CCB	25 MV Linac	25 MV Linac	6-15 MV Linac	Linac
ICBT	no	no	no	ex	ex	yes	yes	yes	yes (81.5%)	yes (84%)	ex	ex	yes	yes	yes	yes
Median total dose	50 Gy	70 Gy	70-80 Gy	50-81.6 Gy	50-70 Gy	63-110 Gy	80-90 Gy	30-46 Gy plus ICBT	81 Gy	40-50 Gy plus ICBT	55-70 Gy	60-66 Gy	65-95 Gy	35-46 Gy plus ICBT	90Gy	90.6% ≤105 Gy
Dermatitis %	8.4	n/a	0	n/a	n/a	n/a	n/a	17	3.7	5.2	n/a	n/a	n/a	n/a	n/a	n/a
Diarrhea %	11.4	n/a	65	n/a	n/a	n/a	n/a	n/a	5.8	n/a	4.5	43.8	n/a	4.2	42	n/a
Proctitis %	28.9	16.5	5.5	4.8 severe	4.6	13.3	15.3	11	13.4	5.2	6.8	12.5	2.8	5.5	4	11.7
Incontinence %	21.8	2.7*	n/a	n/a	2.8*	n/a	n/a	n/a	n/a	n/a	2.3	n/a	4.1*	2.3*	20	3.7
Fistulae %	16.6	2.7	n/a	n/a	2.8	n/a	n/a	n/a	n/a	n/a	4.5	n/a	4.1	2.3	12.8	n/a
Vaginal stricture %	12.5	n/a	7.3	n/a	n/a	n/a	n/a	n/a	33.9	n/a	25	12.5	2.8	2.1	n/a	28.3
Subcutaneaous fibrosis %	40.1	n/a	7.3	n/a	n/a	n/a	4.2	0	24.3	n/a	n/a	n/a	0.1	n/a	n/a	n/a

Table 21: Adverse effects after EBRT in this study compared to state of data in research. ex = patients were not eligible for ICBT. n/a= not applicable, i.e. no data were given. *= in absence of data on incontinence, I assumed the rate of incontinence to be at least as high as the rate of fistulae.

to urinary incontinence, data in literature ranged from 2 to 20% [27, 111, 112, 113, 124, 147, 148, 151]. Patients included into this study showed a higher rate of 22%. Incontinence was due to fistulae in 17%. In other studies, lower rates of RT-associated fistulae were reported (2-13%) [27, 111, 112, 113, 124, 147, 148]. Reported cases for vaginal stricture tend to be lower than rates, I found in literature (13 % vs. 2-34%) [27, 111, 125, 127, 145, 148, 151]. Vaginal strictures, as a result of an induration of the tissue for irradiation, appear to be associated with higher age and treatment with ICBT [145, 151]. Subcutaneous fibrosis of the suprapubic area was more reliably documented by the staff at TAHRC (see Chapter 3.2.4). A very high proportion of 40% out of 578 patients coming for a late follow-up, suffered from this side effect. Appearance of suprapubic fibrosis appears to be related to Cobalt-60 teletherapy, as Saibishkumar et al. report a rate of 24% out of 1069 patients suffering from this frequent side effect, while rates were higher for patients treated with Cobalt machines [145]. Arulponni et al. report low rates of radiation associated toxicities and a surprising 0% of suprapubic fibrosis within the 99 patients examined, despite telecobalt radiation. The authors explain the absence of suprapubic fibrosis by the fact, that they "did not use external beam therapy as the sole modality in any patient and we used four field treatments in obese patients. This shows that even with the available cobalt machine and brachytherapy, impressive results with acceptable toxicities can be achieved with careful planning especially in younger patients and in women with comorbid conditions."[146], p. 65.

A clear dose-effect relation for appearance of adverse effects was not obvious. This might be due to irregular identification and documentation of radiation associated adverse effects. Particularly patients with disseminated disease and consequently RT with single fractions, thus lower doses, potentially presented rather symptoms of tumour progression such as fistulae and resulting urinary incontinence, than radiation associated adverse effects. On the basis of the collected data, however, distinction of these cases was not feasible. Similarly other studies failed to correlate incidence of adverse effects to dose of radiation [132, 152, 153]. The lack of an established dose threshold for adverse effects in RT for cervical cancer is most likely due to shortcomings in methodological reporting quality on high dose rate brachytherapy in current research [132]. Notwithstanding, other studies did find evidence of higher rates of urological and rectal complications due to increased dose of RT and stage of FIGO to the [27, 114, 125, 152, 154, 155, 156, 157]. Survival decreased in case of major adverse effects, which did not occur below the threshold of a time-dose-fractionation factor of 115 as reported by Akine et al. [114]. The time-dose-fractionation factor is an equation combining data on fractionation pattern, duration of RT and total dose. Other than decreasing radiation dosage, higher source-to-skin-distance (SSD) can be a feasible option to diminish rates of radiation associated complications without lowering survival rates, as noted by Zi Zhong et al. [124].

Data quality of documented adverse effects was insufficient, as explained in Chapter 3.2.4 and 5.2.1. However, resulting rates of documented adverse effects are higher than rates, reported by studies with additional ICBT after initial EBRT. Vaginal strictures excepted from this comparison, as they were less frequent in this study, being a common side effect of ICBT.

Estimated overall survival after EBRT alone delivered by Cobalt-60 teletherapy. In this paragraph, I will place the findings on survival after RT into the current state of research. First, I will compare overall survival rates to the only three existing studies on survival of cervical cancer patients in sub-Saharan Africa. Second, I will relate the results on dose-specific survival data to other studies. Note, that for all intents to compare the present study's findings with those of other studies, bias via

considerable differences in radiation practice can be expected - particularly, since patients included to this study received sole EBRT by telecobalt without further ICBT. As noted, the practice of a low-dose non-radical schedule, which was indicated for 64% of 1009 patients, is peculiar and not described in other studies. Additionally, with a median follow-up time of 10 months in this study, 1- and 2-year survival probabilities are emphasized. In literature, however, mostly 5-year survival probabilities are stated. 5-year survival cannot be estimated for this study, as the maximum observation time was longest observation time was 48.7 months and thus shorter than 5 years.

Survival data of cervical cancer patients in sub-Saharan Africa are retrieved from national or regional based cancer registries. However, there are differences in data quality throughout the reporting cancer registries in sub-Saharan Africa [13]. Moreover, it shall be noted, that the sub-Saharan studies used for data comparison had a broader frame of inclusion than the present study. Particularly, patients were included although in some cases no access to therapy was provided or, early-stage cervical cancer was surgically treated without further RT. As those patients were excluded for this study (n=900, see Figure 3), estimated overall survival rates are expected to be higher than 20-year-old data from the Gambia, Uganda and Zimbabwe, where the only three existing studies on outcome of cervical cancer in sub-Saharan Africa originate.

Looking at the treatment modalities reported by these studies, conditions differed considerably. In Kampala, EBRT by one telecobalt machine and additional brachytherapy was on dispose 1995-1997 [158]. However, only 63 out of 261 patients received RT and out of these, only 25% received both EBRT and ICBT. Surprisingly, an advantage in survival of the 63 patients compared to those without access to RT was only noted for the first year after therapy [41]. In the Gambia, there was no RT facility available at all, whereas in Harare, Zimbabwe, 70% of the patients received both EBRT and ICBT [18]. However, one-year-overall survival was more favourable for patients in Kampala (83%) compared to outcome of patients in Harare (74%) [18, 41]. Lacking any RT facility, one-year-survival in the Gambia was very low (44%), as reported by Bah et al. for 202 cervical cancer patients 1993–1997 [42]. For the present study, a selection of better-prognosis cases is expected, as patients included were able to afford RT and survive the waiting times shown in our first publication on survival of cervical cancer patients at TAH [40]. One-year-survival probabilities for all 1009 patients included into this study range between 83% and 55% for worst-case. As a large proportion was lost to follow-up, survival rates were expected to be situated within the range of main and worst-case analysis. Data from main analysis show slightly better outcome than data from Uganda, clearly better outcome than those from Zimbabwe and twice as favourable survival probabilities compared to data from the Gambia.

After 3 years, survival for radiotherapeutically treated cervical cancer patients in Harare was 46% [18], thus similar to an estimated 46% in main analysis. Looking at data from Uganda, Wabinga et al. did not further differentiate, whether patients received RT or not. Moreover, multivariate analysis did not show a significant difference in 3-year survival of patients with or without RT. 3-year-survival reported from Uganda and the Gambia was low: 35% and 22% respectively. Worst-case analysis for patients at TAHRC resulted in a 3-year-overall-survival rate of 24%. Hence, survival probability in worst-case was only slightly higher than data from the Gambia, where no RT was provided.

As has been noted, the presented survival analysis fits well into the few data existing on survival of cervical cancer patients in sub-Saharan African countries. In fact, the results of the main analysis prove more favourable than data from Uganda, Zimbabwe and the Gambia. However, the calculated survival probabilities in worst-case analysis are comparable to data from the Gambia, where no RT

was administered.

With regard to survival of cervical cancer patients in medium income countries, regardless to their access to RT, 1- and 3-year survival rates in India, China and Thailand were 77% and 58%, 60% and 45%, 59% and 41% respectively [18, 41]. In terms of 1-year-overall-survival, this study's results in main analysis were better, while 3-year-overall-survival was similar to rates in China and Thailand. Compared to high-income countries, stage-dependent survival rates for this study cohort (see Appendix 9.5) were lower after two years than the corresponding stage-dependent survival probabilities after five years in Germany [17]. The CONCORD-2 survey reports on worldwide survival rates for cervical cancer 2005-2009 based on data from cancer registries worldwide [159]. However, information on distribution of FIGO stages in different cancer registries is not given. Better outcome not necessarily results from more sophisticated equipment, as patients in a setting with regular screening for cervical cancer are more likely to present with early stages of FIGO. The mentioned survey states very favourable 5-year survival rates for cervical cancer patients in, e.g., South Korea (77%), and 5-year survival ranging between 60-66% for US-American, German, British and Japanese cervical cancer patients. South African and Algerian registries reported a 5-year survival of 55% for patients registered 2005-2009. Libya reported lower survival of 39% after 5 years [159]. For sub-Saharan countries there are no recent data available, except for unrealistically high survival rates from Nigerian cancer registry Ibadan, which should be interpreted cautiously, as several quality criteria comprising comparability, validity, timeliness and completeness were not met [13]. 5-year survival in The Gambia 1995-1999 was 20%. 5-year survival rates for patients included to this study can not be shown. However, survival rates of patients in this study were lower after 3 years than those after 5 years for all countries stated above apart from Libya and The Gambia. The worst-case analysis for patients at TAHRC results in a 1-year-survival of 55%, which is already lower than 5-year-survival of, e. g., Germany, UK, USA, Japan, South Korea and Algeria.

In the following, I will compare survival rates according to total doses received, i.e. the state of completion of RT schedule. Since most cervical cancer patients throughout literature are treated with RT schedules similar to radical RT at TAHRC, I will mainly relate the outcome of these patients staged FIGO IIa-IIIa to the existent research. For patients staged FIGO IIIb-IVa, I can only compare outcome after low-dose non-radical RT with high-dose schedules in other studies.

The findings of this study suggest best outcome for patients who complete their RT schedule, which resulted in 1- and 2-year-survival rates in main analysis of 96% and 83% respectively for at least 72 Gy in radical RT. Completed non-radical RT, thus 44-50 Gy of radiation resulted in 1- and 2-year-survival of 86-88% and 60-68% for 44-50 Gy in main analysis. Survival for patients receiving lower doses was 3 times worse in non-radical schedule and 1.3 times worse in radical schedule, though the difference in the latter was not significant. However, above the threshold of dose recommendation for non-radical RT, no advantage in survival was shown along with an increased radiation dose. Admittedly, data on tumour progression and socioeconomic background of the patients were not on dispose. Therefore, along with a possible dose-response relation, selection bias can be expected for the conditions of discontinuation on the one hand and excessive RT on the other hand.

The most comparable setting to radical RT at TAHRC was reported by Zi-Zhong et al. for 97 cervical cancer patients exclusively staged FIGO IIb, who received a total dose of 70 Gy EBRT via telecobalt 1964-1980. No ICBT was used and correspondingly 2-year-survival was very proximate to results for patients at TAHRC, who completed radical RT (almost 80% compared to 69% in worst-case

and 83% in main analysis at TAHRC) [124]. Ferrigno et al. presents similar survival rates, although treatment modalities for 190 cervical cancer patients 1989-1995 differed considerably from TAHRC modalities and more than one third of the 190 patients under observation were staged FIGO IIIb. The favourable survival of more than 80% after two years, despite advanced stages of FIGO, is likely to be due to higher doses and additional ICBT (median total doses received: 80-90 Gy). [149].

As mentioned above, most studies, which report on outcome of EBRT for cervical cancer without additional ICBT, present patients who are not eligible for ICBT for anatomical reasons, certain psychiatric comorbidities or because of personal refusal. Hence, these studies suffer from a certain selection bias. Other than the stated report by Zi-Zhong et al., only two studies show outcome after EBRT alone without medical reasons for exclusion of ICBT. More than 30 years ago, both Kakehi and Koeck et al. report comparable outcome for patients, who received EBRT alone and those with additional ICBT. Consequently Koeck et al. came to the conclusion, that EBRT by itself is sufficient without the necessity for intracavitary radiation [125, 160, 161]. Koeck et al. present very high 3-year survival of 69%, although the majority of 55 patients included were staged at least FIGO III. Planned total dose varied from 70-80 Gy and the dose distribution and field size for each phase resembled the radical RT schedule at TAHRC. Survival of these patients was similar to 3-year survival of patients who completed radical RT for lower stages of FIGO in this study (71%). Regarding similar stages of FIGO, patients received non-radical RT at TAHRC and even in case of completion, however, the patients' 3-year survival probability was much less favourable (40-52%) compared to the findings presented by Koeck et al.

Notably, other studies on outcome of cervical cancer patients after EBRT alone, except for the stated data by Zi-Zhong, Kakehi and Koeck et al., present patients who were not eligible for ICBT. Hence, the findings I present in the following are not free from certain selection bias for prognosis-relevant medical comorbidities or aggressive tumour characteristics. 1983, Ulmer et al. report 5-year-survival of 30% for 119 patients with FIGO IIIb after EBRT alone with a total dose of 80 Gy [115]. However, patients with available 5-year follow-up were selected. These results are similar to RT for patients with FIGO IIIb at TAHRC, even though almost half of the doses were applied. For earlier stages of FIGO after sole EBRT of mostly 60-65 Gy, Barraclough et al. report 1- and 2-year-survival rates of 81% and 64% respectively [148]. These rates are similar to patients who underwent complete non-radical RT in the present study. Compared to the UK average, the small cohort observed by Barraclough et al. (n=44) showed clearly lower 5-year-survival rates (58-59% and 49% respectively) [148, 159].

RT was conducted by means of a Linac with prior CT-assisted planning and higher total doses were applied than for non-radical RT at TAHRC. However, survival might have been low due to the lack of ICBT on the one hand and importantly for selection bias on the other hand, as patients were not eligible for ICBT in the first place. The same applies to the second study identified, who includes patients with present contraindications for ICBT. Matsuura et al. report a 3-year-survival of 44%, while Japanese average for 5-year survival 2004-2009 was 66% [127, 159]. Again, survival rates are similar to 3-year survival of patients who received non-radical RT at TAHRC (40-52%), despite the fact, that a more elaborate 3D conformal RT (3DCRT) was performed by a Linac with prior CT-assisted simulation and doses applied were higher than for non-radical schedule: 10 patients received hyperfractionation and a median total dose of 66 Gy; 6 patients received conventional fractionation and a median total dose of 60 Gy. Moreover, 19% of the patients were staged lower than FIGO IIIb.

A dose-response relation for survival of cervical cancer patients is not yet supported by sufficient data in the literature, partially because of methodological shortcomings [130, 132, 152]. However, in case of RT for prostate cancer, there is clear proof for better survival, in case a certain dose threshold (78-80 Gy) is reached [162, 163, 164]. Correspondingly, Beskow et al. demonstrated better survival for cervical cancer patients 1989-1991, who received a biological effective dose (BED) of 94 Gy and higher compared to those with lower BEDs of radiation [153].

Data from TAHRC showed significantly better overall survival for patients, who completed their RT schedule or, in case of single fractions, received two single fractions. This finding may be interpreted as a result of a certain dose effect. Evidently, patients, who complete their schedule received higher total doses than those, who discontinued. At the same time, the admittedly small number of patients, who received higher doses than recommended, did not have more favourable survival than patients treated according to guidelines. Certainly there were causal relationships between variables, which were not measurable in this study, and both outcome and the total dose of radiation. Such factors are, e.g., the patients' financial means to afford supportive therapies in case of adverse reactions to radiation, bonds within their families and, similarly, certain beliefs and family structures in terms of gender equality. The more favourable outcome in case of completion of RT schedule may be interpreted as a result of combining the positive dose-effect and a more beneficial setting, which accounts for higher adherence to therapy [165, 166]. Above all, if patients received higher doses than recommended, it certainly was due to their more radio-resistant tumours. Accordingly, Akine et al. discussed the impossibility "to draw a conclusion that there is no dose-response relationship" in case of 104 patients with FIGO stages IIa-IVb, observed 1962-1979 [114], p. 1616. These patients were not eligible for ICBT and received different RT schedules, all ranging from total doses of 50 to 82 Gy by telecobalt irradiation. Akine et al. report a 5-year overall survival of 17%, but note increased survival probabilities for the so called confirmation group (n=23), who received 50 Gy to the whole pelvis with opposing field technique and a boost of 20 Gy with reduced field size. This pattern resembles radical RT according to TAHRC, although all patients with FIGOs IIa-IVa were treated alike as outlined by Akine et al. Interestingly, for the selected group of patients with stage of FIGO III and IV survival was more favourable if radiation dosage expressed through TDF was lower. In contrast to these data by Akine et al., a larger and younger Brazilian study on RT for cervical cancer patients staged FIGO IIIb (n=202) by Ferreira et al. report a 5-year survival of almost 30% for EBRT alone delivered by a Linac with a total dose of 60 or 70 Gy, compared to significantly lower survival rates for patients, who received EBRT with lower doses. These patients were not eligible for ICBT. Moreover, survival of the patients with higher doses of EBRT alone was not significantly different from survival of patients who received additional ICBT [112].

Still lower survival rates from 1996-2001 for patients excluded from ICBT are reported by Saibishkumar et al. 2-year survival fell below 20% for 146 patients out of which 85% were staged FIGO IIIb. 60-66 Gy were administered and low outcome was explained as result of long treatment times for low adherence [110]. In contrast, survival rates of the present study appear encouraging, as even palliated patients, who received merely two single fractions of 10 Gy, had higher probabilities of overall survival after two years.

Based on the above stated comparisons of patients' survival after RT, the following conclusions can be drawn. First, results in survival analysis from TAHRC rank at the upper edge of older data

on survival of cervical cancer patients in sub-Saharan Africa. However, not all patients included in these studies had access to therapy. In the present study, all patients received RT and better survival was expected. Second, overall survival of the observed sample was similar to data from India, China and Thailand, but clearly less favourable in comparison to survival of cervical cancer patients in high-income countries. Third, when comparing survival of patients after completion of radical RT schedule at TAHRC, results were in line with findings from other authors, who describe similar dose patterns. Fourth, I found strong evidence in literature, that patients with more advanced stages of FIGO may benefit from a radical RT schedule as well. However, some authors report survival rates for treatment with higher doses for patients staged FIGO IIIb or IVa, which were similar to rates after non-radical RT in this study, where patients received around 20 Gy less irradiation. This might be due to the selection of patients, who were not eligible for ICBT for medical reasons. Fifth and with regard to a dose-response-relationship, data from TAHRC do not show advantage in survival for patients, who were assigned to non-radical RT and received higher doses as recommended. However, as Perez et al. noted accurately, therapeutic decisions beyond strict protocols are potentially biased by prognosis-relevant tumour characteristics: "[Radiation] doses were prescribed by physicians based on clinical judgment, with higher doses being given to bulky, more extensive tumours or those that did not show satisfactory tumour regression at the end of the standard prescribed therapy." [129], p. 315. Therefore, it might be wrong to assume a lack of dose-response. Ferreira et al. were able to demonstrate better survival in case of higher dosage. They even report equal outcome after high-dose EBRT compared to the combined EBRT and ICBT [112]. Sixth, findings from TAHRC clearly show better outcome in case of higher adherence to therapy and consequently the completion of a guideline-conform schedule. Lowest survival rates within comparable studies were found in an Indian study, where large treatment durations indicate for low adherence.

5.2 Limitations and strengths of this study

5.2.1 Limitations

The present study suffers from certain limitations, that naturally resemble those of the first study on a similar cohort [40].

First of all, in order to properly evaluate dose-response relations, a prospective study design is indispensable but impossible at the same time. Since evidence based guidelines on good clinical practice for radiotherapeutic treatment of cervical cancer exist, any deviation from these guidelines, other than for an individualized therapy approach, are ethically unacceptable. Consequently, the interpretation of results is limited by the retrospective design of this study. Rather than being randomized to different total doses of radiation, patients received different doses of radiation due to only partially measurable reasons for discontinuation or excessive treatment. The retrospective design of this study additionally implies a less consistent quality of documentation compared to a prospective data collection. If different physicians examined the patient, sometimes different stages of FIGO were assessed. Therefore, I chose to rely only on stages of FIGO assessed by one of the four oncologists employed at TAHRC. Additionally, data on age, number of children, medical records, comorbidities and reasons for discontinuing RT varied within patient files. As complete data on reasons for discontinuation of RT were not on dispose, a fully controlled dose-response relationship for survival analysis was not established. Furthermore, as a lack of a routine check-up, comorbidities other than HIV were not documented on

a regular basis. The same applies to the appearance of mild adverse effects. Moreover, therapeutic measures other than RT were not documented in all cases. This applies to primary therapies such as surgery and chemotherapy. Extensive operation reports were only attached to the patient files, if surgery was done at TAH. Plans for chemotherapy were noted in the patient files, while the actual administrations and reasons for deviations from the inital plan were not consistently reported.

Beyond that, documentation was sparse in case of supportive treatments such as palliative urinary diversions or certain interventions in case of side effects of RT, e.g., colostomies in case of proctitis. Telephone interviews served to additionally retrieve information on adverse effects and vital status (see Appendix 9.4). Naturally, the reliability of data from this source depends on the patients, their relatives, the single interviewer in charge and their interaction. Then again, in reporting data on occurring adverse effects, I did not differentiate, whether data originate from telephone interviews or patient files, despite expected differences in the validity. However, despite low quality in documentation of i.a. adverse effects and other reasons of discontinuations, radiotherapeutic treatment was documented consistently (see Appendix 9.1).

Secondly, I displayed RT guidelines for TAHRC in Chapter 3.3.3. However, there was no written version available at the time this study was conducted. In fact RT guidelines were identified on the basis of interviews with the oncologists at TAHRC. Hence, varying perceptions of these guidelines might result in deviations in RT practice. To improve transparency, quality management and teaching quality at TAHRC, a written handbook for the staff and the numerous medical students serving for short-term is certainly reasonable.

Thirdly, data of approximately 72% of the patients treated at TAHRC 2008-2012 were presented, as nearly 400 files were not retrieved. As Dr. Kantelhardt and me already stated in our first publication in 2014, "files at the Addis Ababa Radiotherapy Center are manual patient files stored according to names and patient number. Files can easily be misplaced manually. Since we selected the files by a name list and illiteracy frequently results in different spellings of names, the individual file might not have been found. We are not aware of any other reason for missing files and therefore we do not suspect a selection bias through this fact." [40], p. 732.

5.2.2 Strengths

In spite of the above stated limitations, this study is the first large cohort study on outcome of cervical cancer patients after RT in Ethiopia and to my knowledge on the African continent. It is also the first study to report in detail on RT schedules, dose-specific survival and adverse effects in a very limited setting. Thereby, important information on radiotherapeutic practice in a setting of low resources is added to the existing literature.

Certainly, the size of the sample marks a big strength of this study. Thanks to the large number of 1009 patients included to this study, confounding was reduced by choosing patient subsamples. Hence, this study reveals representable findings, despite its retrospective nature and the initial bias by patient selection.

Another strength is the uniqueness of this data collection. There are very few published data on oncological treatment of cervical cancer in sub-Saharan Africa and none of them presents RT guidelines and their implementation as extensively as the present study. Moreover, the setting is "unique" because internationally recommended standards can not be implemented due to a lack of resources - there is no ICBT and EBRT is performed by telecobalt. This led to a limited comparability to studies with similar

settings in Chapter 5.1. However, scarcity in published data does not adequately reflect the reality as only 99 out of 160 RT centers in Africa had brachytherapy services available in 2010. Consequently, findings on the outcome of suboptimal radiotherapeutic treatment for cervical cancer are of high interest for countries lacking ICBT.

Besides reporting on the outcome of cervical cancer patients who received RT in Ethiopia, this study additionally provides an important tool for prospective research on the outcome of oncological treatment in Ethiopia. As outlined in Chapter 3.6, the EORTC questionnaires for Quality of Life C30 and CX24 are available in Amharic now.

5.3 Suggestions for further research on radiotherapeutic treatment of cervical cancer at TAHRC

Partially as a result of the limitations of this study, several questions remain open. Hence, I will suggest relevant research questions for further investigation of RT for cervical cancer patients in Ethiopia

Given the retrospective nature of this study, selection bias is inherent. Due to missing information on causes for discontinuations, I was not able to adjust for these conditions in order to extract a clean dose-response relationship. Therefore, I want to point out the need for prospective analysis of outcome after RT. However, assignment to different doses of radiation must not deviate from evidence-based recommendations in order to provide patient safety. There is no evidence for non-radical RT for patients staged FIGO IIIb and IVa without indication for palliation. This can be the vantage point for randomizing patients to radical RT in order to confirm findings regarding the benefit of curative high doses for these patients.

By means of collecting data on adverse effects, the eventual impact of EBRT by telecobalt on Quality of Life (QoL) of cervical cancer patients was investigated. However, rates of adverse effects can only partially reflect the concept of QoL. Particularly, adverse effects are a weak indicator for QoL, as the individual perception of the patients is disregarded and, beyond that, documentation of adverse effects was not sufficient. Ideally, QoL of patients is assessed before and after RT to draw conclusions on the actual impact of RT by telecobalt on the patient's wellbeing. However, at the time this study was conducted, QoL questionnaires EORTC QLQ-C30 and QLQ-CX24 for specific evaluation of QoL of cervical cancer patients were not available in Amharic or another language widely spoken in Ethiopia. Therefore, both questionnaires were officially translated into Amharic within the framework of this study. Chapter 3.6 describes the translational process of creating an Amharic version for QoL questionnaires on generally cancerous diseases and specifically on cervical cancer. Prospective studies using this tool at TAHRC and elsewhere in Ethiopia will not only investigate *if* but also *how* patients survive. Based on findings on QoL before and after RT, my recommendations towards irradiation dosages should be revised.

Another point of interest is the actual reliability of the telecobalt unit at TAHRC in terms of radiation safety and technical reliability. The collected data did not report on number and durations of actual breakdowns. I only found two cases in which RT was discontinued for technical reasons. Nevertheless, more patients can be expected to have delayed RT for breakdowns of the "Theratron Equinox 80" unit. It would be interesting to compare these data to those from Uganda, where a comparable RT device is used [22]. Moreover, these data would further evaluate the need for another Cobalt-60 unit, more RT technicians and available spare parts in detail.

5.4 Recommendations for optimized treatment of cervical cancer patients in Ethiopia

As a consequence of describing the practice of RT at TAHRC and comparing it to treatment patterns described in other studies, certain discrepancies became obvious. The identification of these differences can serve as a vantage point for improvement of oncological treatment in a setting with low resources. In the following, I will draft a number of recommendations based on the comparison of findings in this study to international standards for cervical cancer therapy. These recommendations firstly address the necessity for optimizing the technical background of TAHRC, which surely is related to a matter of financial resources. Secondly, I will look into the potential of improving process quality at TAHRC. Thirdly, the role of a non-radical RT schedule for late stages of FIGO and, fourthly, the importance of prevention programs for cervical cancer will be discussed.

5.4.1 Equipment and technical background for RT at TAHRC

With regard to internationally proposed guidelines [15], RT for cervical cancer at TAHRC is suboptimal for three peculiarities: no ICBT is used and EBRT is performed by telecobalt. Moreover, the generally recommended chemoradiation was only realized in 17 % of all patients. Below I will analyse the imperative and applicability of international standards towards these three shortcomings.

Importance of brachytherapy services for RT for cervical cancer. The advantageous role of ICBT in radiotherapeutic treatment of cervical cancer is clearly stated - in a large patterns of care study by Lanciano 1973 and 1978 et al. 4-year survival with and without ICBT was 70% and 37% respectively [167]. In 1973, Hanks et al. analysed outcome of patients staged FIGO IIIb according to whether they received ICBT or not. The rate of recurrence was 87% after RT without ICBT compared to 63% in case, treatment included ICBT [168]. The recent large cohort study by Han et al. confirmed those findings. Among the included 7359 patients, those with ICBT had significantly higher rates of overall survival (58%) compared to those who did not receive ICBT (46%) [169]. Nevertheless, Ferreira et al. noted, that high dosage EBRT delivered by a Linac might have similar outcome to EBRT and ICBT combined [112]. This finding remains singular and prospective studies are needed to provide stronger evidence. Anyhow, at TAHRC no Linac is available and the same high dosage EBRT by a conventional telecobalt machine as on dispose at TAHRC increases the risk for major complications caused by irradiation. As a consequence, brachytherapy services are a necessary part of radiotherapeutic treatment for cervical cancer and successfully applied in other low-resource-settings [41, 146, 149, 158]. Access to ICBT is necessary at TAHRC.

The role of Linacs in a setting of lower resources - do advantages over telecobalt prevail? Meanwhile, Linacs are perceived as the optimal and most targeted RT modality for deep-seated tumours such as cervical cancer. Notwithstanding, several studies support the use of telecobalt in a setting of lower resources. Hence, discussion for the actual need of a Linac at TAHRC is necessary. Importantly, the following discussion does not solely apply to developing countries, but to cost-effective measures in developed countries as well.

Contrary to the popular opinion, RT by Cobalt-60 still offers excellent treatment results for at least 25% of all cancer patients worldwide requiring RT, as van Dyk and Battista remarked 1996 [30]. This calculation addresses patients, who suffer from tumours situated close to the patients surface or for

patients with a small separation. Albeit deepseated, cancer of the uterine cervix shows viable response to telecobalt treatment in this and numerous other studies as well. Two independent studies from 2001 and 2006 could not show significantly better outcome for cervical cancer patients treated with a Linac, compared to those, who were treated with a telecobalt unit [110, 170]. However, 1985 Hanks et al. correlated the use of Linacs for cervical cancer treatment with a significantly lower rate of recurrences compared to treatment by telecobalt [171]. Given these inconsistent results, uncertainty regarding the advantageous role of Linacs remains. As Van Dyk et al. accurately pointed out, we do not know, whether outcome after RT by Linacs happens to be more favourable either due to the actual machine energy levels or rather due to increased quality of staff and supportive treatment, which is associated with more sophisticated equipment [30]. Only one prospective and randomized trial by Allt exists, which showed better outcome and lower treatment associated morbidities for use of Linacs in cervical cancer therapy [172]. Notwithstanding, the number of included patients was small (n=126) and dating from 1969 the brachytherapy mode used was not recommended anymore in 2003, as noted by Ferrigno et al. [149].

However, "percent depth dose, dose rate, skin dose, and beam penumbra are some of the well-documented limitations of a cobalt unit" [173]. Longer waiting times for lower dose-rates (10 Gy/min and maximum 3.7 Gy/min for Linacs and a fresh Cobalt-unit respectively) contribute to the perception of Co-60 as a suboptimal source of radiation. As a recent response to these limitations, the long since abandoned technical development of Co-60 units is reinitiated. Tomotherapy and IMRT can be performed by telecobalt thanks to the installation of multileaf collimators (MLCs) [174, 175] and motorized wedges [176, 177, 178], which provide dose distributions very similar to Linacs [30]. Joshi et al. compared dosimetric data of, i.a., pelvic RT by telecobalt and a 6MV-Linac and did not find better dose distribution by Linacs. Moreover, the common perception of Co-60 being limited by lower energy can be proven wrong as these inferiorities will vanish after eventual modernisations of Co-60 units with, i.a., MLCs for tomotherapy [179]. The "ViewRay, Inc. Renaissance^{TM}" marks the latest technology for image-guided EBRT with Co-60 [180]. Three Co-60 sources are combined with an MRI in order to track movement of the patient or the tumour in real-time during RT. This provides a degree of accuracy, which certainly rivals the static image-guided technique of Linacs. Moreover, the integration of an MRI into a RT device establishes a technological niche for the use of Co-60, as it is no feasible option for a Linac because both techniques are conflicted. On the one hand the MRI's magnetic field will shut off the Linac and on the other hand Linacs interfere with the MRI's circuitry and thereby damage the quality of imaging. In contrast, the common intersection of magnetic fields of MRI and Co-60 is negligible [181]. Thanks to the use of multiple sources, treatment time decreases considerably. At the time of writing, first clinical results of this advanced technology showed comparable accuracy to IMRT by Linacs [182].

Anyhow, costs for any IMRT technique are high, regardless of the source of radiation. Moreover, due to increased complexity, the sophisticated IMRT techniques are prone to failure in optimizing machine parameters [183, 184]. Consequently, a tendency to make techniques for RT easier to operate should be of interest for both developed and developing countries. Instead of integrating conventional MLCs, which require strict positional tolerances, a binary MLC serves as a less expensive and more robust alternative [185, 186].

When considering Co-60 for RT, radiation safety is an issue not to be ignored. Environmental hazard is present throughout transport, service and at the time of disposal. However, critical events

caused by the use of Co-60 account for a very small proportion compared to other radioactive sources [187].

Given the above considerations, a cost-effective RT center should ideally have both Co-60 units and Linacs available, to treat close-to-the-surface and deep-seated tumours accordingly. However, we should question the feasibility of Linacs in a setting without reliably current electricity and very limited resources in terms of a low number of well trained staff members. At TAHRC, the only RT-providing institution in Ethiopia, there is currently one radiation physicist employed. In spite of these deficits, data from TAHRC show better survival than comparable data from sub-Saharan countries and even more favourable survival in case of guideline-conform RT. In 2003 Ferrigno et al. concluded, "that the use of telecobalt for EBR, with dose up to 50 Gy at whole pelvis delivered by four pelvic fields, previous to brachytherapy, is an acceptable technique for radiation therapy alone in the treatment of patients with cervix cancer and weight up to 89 kg" [149], p. 705. In fact, as outlined in Chapter 4.1.2 and in our previous publication [40], stages of FIGO increase while waiting for the start of RT as a result of the limited access RT. The main challenge for managing cervical cancer in Ethiopia is marked by the fact, that there is a sole Co-60 unit for the whole country. In Africa, Ethiopia shows the second largest gap between offer and demand for RT machines after Nigeria. Judging from the WHO recommendations, there are 73 RT units missing in Ethiopia [24]. This serious quantitative deficit should be addressed first, before insularly enhancing RT quality with complex techniques. The only RT center in the whole country is not accessible for a large proportion of cancer patients from rural areas, who can neither afford the journey to Addis Ababa nor the stay in the capital. Therefore, first and foremost, more RT devices are needed, ideally spread over the country. At the time of writing, there is just one sole Co-60 unit on dispose for treatment, which is constantly decaying with a half life of 5.3 years since 2010 and, therefore, radiating with almost twofold treatment duration compared to a fresh unit.

Not only the actual number of machines available seems inappropriate. As data on radiation safety from a Co-60 unit in a comparable setting in Uganda suggest, spare parts for quick repair in case of breakdown are scarce, too [22]. There are no data on circumstances and duration of breakdowns of the "Theratron Equinox 80" Co-60 unit at TAHRC and the number of patients not treated due to these interruptions in service. However, there were two patients, who did not complete their RT schedule for technical reasons. Therefore, improvement of maintenance services similarly seems to be an important issue at TAHRC. For that matter, enough well trained staff members are just as essential as viable equipment. Not only the number of physicists and radiation technicians is limited at TAHRC. Four certified oncologists are employed at TAHRC. At the same time, they are the only four oncologists all over Ethiopia and hence confronted with an immense work load. In contradiction to the scarcity of specialists in sub-Saharan countries, the time for education until certification is longer than in developed countries [188]. Surely, as a response to the lack of specialists, first, access to and second, efficacy of education should be improved in the long run. Third, the so-called "brain drain" to developed countries is a complex and serious issue and can certainly only be addressed by improving labour conditions on site.

Chemoradiation for cervical cancer patients. An analysis of schedules and actual use of chemotherapy for cervical cancer patients in Ethiopia was not the purpose of this study. Reliable data on guidelines and actual doses applied were not available. However, it was noted, that out of all patients merely

17% received at least one cycle of concurrent or adjuvant chemotherapy. This proportion is considered far to low, given the fact, that chemotherapy is generally proposed to all cervical cancer patients treated with RT [15, 17]. The facts, that a larger proportion of cancer patients in sub-Saharan Africa might not be fit for platin-based chemotherapy [189] and, that adverse effects can be difficult to control [123], do not explain the lack of chemotherapeutic treatment in 83% of all patients observed. I suspect mainly financial and logistical reasons to interfere with clinical indications. Hence, the importance of available and affordable chemotherapy for all cervical patients can not be emphasized enough.

In terms of equipment for improving oncologic treatment in Ethiopia, the urgent need for more RT devices at TAHRC and elsewhere in the country was pointed out. This includes Co-60 units, brachytherapy services and a sufficient amount of spare parts for reliable maintenance services. In the long-run, a specialised RT center with IMRT technique at hand can be viable. In terms of staff members, more oncologists, radiation physicists and radiation technicians are needed in order to reduce waiting times and widen the access to RT for more patients. Furthermore, a broader access to chemotherapy is necessary for all patients, regardless of their financial means.

5.4.2 Process quality

As stated in Chapter 4.1.6, in 17% of all patients included in this study, planning of RT was not guideline-conform for unknown reasons. In case of guideline-conform planning, 35% of the patients assigned to radical or non-radical RT received lower or higher doses than indicated. In case of lower doses, discontinuations were partly patient-related. Nevertheless improvement of process quality at TAHRC is necessary, especially with regard to 132 patients, who were treated erroneously with palliative instead of curative intent or vice versa. However, shortcomings in process quality unfortunately are a common problem all over the world. In an external audit in a new Asian oncology center, suboptimal cancer therapy in terms of clinical practice and guideline-adherence is stated in a warningly high proportion of 52% of 100 randomly assessed patients [190]. Olasinde and Olugbemiro report under- or overdosing of telecobalt in 51% of all patients treated with EBRT 2000-2002 at the ABU Teaching Hospital in Nigeria [191]. However, deviations from standard treatment schedules are by no means a sole issue of developing countries. Furlow reported numerous radiation dosing errors by miscalibration of Linacs and quality control lapses for Australia, France, Canada, the UK and the USA, affecting thousands of patients [192]. Based on a large review by Shafiq et al. on RT-related events through three decades [193], the World Health Organisation published a risk profile for RT, which anew emphasizes the importance of strict adherence to guidelines to reliably provide a safe cancer treatment [183]. Therefore, first and foremost, a written version of RT guidelines available for all staff members at TAHRC is absolutely necessary to improve guideline-conform treatment. Of course, the relevance of and adherence to such guidelines depend on their constant development and reevaluation [194]. Naturally, radiotherapeutic treatment should be based on clinical judgment and tumour response. However, these steps in assessment and therapeutic decision-making should similarly be transparent and comparable throughout centers [46]. In the context of improving transparency regarding TAHRC guidelines, a standardised documentation of discontinuations, adverse effects and therapeutic decisions (e.g., palliation for earlier stages of FIGO than IVb) might be helpful to guarantee reliable health care. Certain needs regarding additional supportive therapies or other irradiation modalities may be revealed, in case a consistent documentation of, e.g., adverse effects according to CTCAE, is available [99].

5.4.3 Radical RT for FIGO IIb-IVa at TAHRC

According to various studies (see Chapter 5.1), radical irradiation schedules are recommended for cervical cancer stages up to FIGO IVa. Palliation can be necessary in earlier stages as well. In these cases, however, indications for therapeutic decisions need to be reproducible. I could not identify a RT pattern comparable to the non-radical schedule at TAHRC throughout the existing research on RT for cervical cancer. Moreover, most patients included in the present study were staged FIGO IIIb, which was shown to respond well to high-dosage EBRT [130, 132]. At TAHRC, a possible advantage of the non-radical schedule is the reduced number of fractions, thus an option, to offer treatment to more patients. To that effect, the limited access to RT needs to be adressed. It is the main obstacle for adequate RT at TAHRC, as explained in Chapter 5.4.1.

In case of RT by telecobalt, adverse effects constitute the limiting factor for increase of total dose. However, the studies I referenced in Table 21 did not show a higher rate of radiation toxicities in case of radical RT with telecobalt for patients staged FIGO IIIb and IVa. Based on comparison with previous studies, I recommend to extend inclusion criteria of radical RT schedule at TAHRC, so that patients staged FIGO IIb-IVa may receive radical RT in absence of indications for palliation. 1- and 2-year survival after radical RT showed good results, confined to patients with better prognosis for early stages of FIGO. Certainly, prospective studies are necessary to substantiate this recommendation.

5.4.4 The role of primary and secondary prevention for cervical cancer

As noted in Chapter 1.1, prevention of cervical cancer is not only possible, but also effective. Focusing on the radiotherapeutic treatment of cervical cancer, studying preventive measures to downstage cervical cancer in Ethiopia was not part of this study. However, most probably due to the lack of screening opportunities, more than half of all patients observed throughout this study presented with late stages of FIGO (IIIb-IVb). Effective prevention for cervical cancer can be performed at the primary level by means of vaccinations and as secondary prevention by screening for cervical cancer. For screening, HPV-testing [195], cytological Papanicolaou testing and visual inspection with acetic acid (VIA) with immediate cryotherapy are at hand [196]. In the latest "WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention" from 2013, the WHO promotes the screen-and-treat-strategy for all women aged 30 years and older [197]. Ideally, patients should be either screened with HPV testing alone or they should receive combination of HPV testing and VIA to effectively reduce false positives [198]. In case of a positive test result, immediate cryotherapy is recommended [197]. As a low-cost approach [199] VIA testing is successfully implemented in, e.g., Malawi and Uganda [200, 201, 202]. However, in Ethiopia VIA is merely provided for HIV-positive women at the time of writing [118]. In order to enforce the dialogue on financing HPV vaccination, Campos et al. recently published calculations proving the cost-effectiveness of both vaccinations against HPV and screening programs for cervical cancer [203]. Along with the implementation of simple screening methods, education on transmission of HPV and signs and symptoms of cervical cancer is necessary. In a recent survey, Getahun et al. showed a relatively low awareness for cervical cancer within women from an urban setting in northwest Ethiopia [204].

After all, prevention and treatment are inseparably linked to each other in a way, that by the time, when early detection programs are initiated, capacities for reasonable treatment of cervical cancer must be available. Conversely, treatment will have better outcome if patients present with earlier stages of FIGO after screening. Rwanda was the first African country to respond to this correla-

tion with a nation-wide cancer control program, including vaccination, early detection and screening for cervical cancer [205]. As Dr. Kantelhardt and me already concluded in our first publication on a similar cohort, generalized implementation of primary and secondary prevention is effective and, therefore, indispensable in order to successfully confront the burden of cervical cancer to Ethiopian women [40]. Fortunately, the Ethiopian Ministry of Health meanwhile promotes guidelines for cervical cancer screening and control [206]. Hopefully, the implementation of these will soon take place.

To sum up, I first and foremost see the urgent need for more RT devices in Ethiopia. In the medium term Co-60 proves to be an adequate option. An acceptable outcome after Co-60 teletherapy can be expected, provided that, firstly, RT is administered according to guidelines and secondly, supportive therapies for better management of RT associated adverse effects are at hand. ICBT services need to be installed and more specialized staff should be employed. In terms of guideline-conform RT, radical RT should be available for patients staged FIGO IIIb and IVa as well. Similarly, chemotherapy must be available and affordable for all patients. Since in the near future, access to RT will be limited to Addis Ababa, patients in need should be supported in order to facilitate their stay in the capital. In the long term, decentralization of RT devices is necessary in order to provide RT for patients all over the country, regardless of their origin and financial background. The prerequisite of a nation-wide screening program, not only for HIV-positive, but for all women aged 30-49 years, is essential.

6 Conclusion

Following the purpose of this study, I described the current radiotherapeutic practice at TAHRC. Therefore, I presented the guidelines for RT with sole EBRT by telecobalt and their clinical implementation by following a total of 1009 patients, diagnosed with cancer of the uterine cervix 2008-2012. At TAHRC, radical, adjuvant, non-radical and single fraction RT is administered with total doses of 72, 60-66, 44-50 and 10-28 Gy respectively. As half of the patients presented with late stages of FIGO, non-radical RT was mostly administered. 17% of all patients were palliated with monthly single fractions of 10 Gy. Assignment to the according RT schedule was not guideline-conform in 17%. There were higher rates of adverse effects than described in existing studies and suspectedly therefore, patients frequently discontinued RT. A minimum of one cycle of chemotherapy was merely administered to 17% of all patients. In spite of this constrained setting, where no brachytherapy services are available, the estimated 1-year overall survival was relatively high (83%) and declined to 55% in worst-case analysis. Outcome was considerably better in case of completed radical RT for patients staged FIGO IIb or IIIa (1-year survival of 96% or 91% in worst case). Both for radical and for non-radical RT, outcome was lower in case of discontinuation. Least favourable survival was noted for patients, who received just one single fraction (1-year survival of 14% or 3% in worst case).

Altogether, overall survival of cervical cancer patients is more favourable compared to similar settings, particularly if patients receive a complete RT schedule according to guidelines. Prior to guideline-conform treatment, however, the mere access to RT remains limited, as TAHRC is the only institution in Ethiopia offering RT. There is an urgent need for not only more RT machines for TAHRC and elsewhere in Ethiopia. Additionally, ICBT has to be implemented in order to improve targeted treatment and reduce Co-60 associated adverse effects. Furthermore, based on the present findings and those from other studies, I suggest radical RT for late stages up to FIGO IVa and propose prospective studies to justify this recommendation. Guidelines for RT need to be transparent to all staff members to avoid misassignments. Chemotherapy and supportive therapies to alleviate adverse effects of RT, need to be available and affordable. Furthermore, more specialised staff needs to be employed to guarantee better treatment results with lower waiting times for cervical cancer patients. In order to downstage cervical cancer from the first instance, the implementation of nation-wide vaccinations and screenings for cervical cancer is necessary. For future research, I suggest to investigate on QoL of cervical cancer patients before and after RT at TAH. From now on, QoL questionnaires are available in Amharic.

The treatment of a potentially curable disease is a basic human right. Global disparities in availability and quality of such a treatment remain a challenging fact. In order to successfully confront these inequities, we need to be aware of them in the first place. This study aimed to facilitate that very awareness and appeals for targeted action. Promoting the first functioning nation-wide cancer-control program in Africa, Rwanda serves as an inspiring example for how this action may look like: “Our experience shows that cancer care can be safely and effectively administered in resource-constrained settings and, with implementation research, care can be continually assessed and improved.”[205].

7 Bibliography

[1] Jemal A, Bray F, Forman D, O'Brien M, Ferlay J, Center M, Parkin DM (2012) Cancer burden in africa and opportunities for prevention. Cancer 118(18):4372–4384.

[2] Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJL, Naghavi M (2011) Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. Lancet 378(9801):1461–1484.

[3] Vizcaino AP, Moreno V, Bosch FX, Muñoz N, Barros-Dios XM, Borras J, Parkin DM (2000) International trends in incidence of cervical cancer: II. squamous-cell carcinoma. Int J Cancer 86(3):429–435.

[4] Lăără E, Day N, Hakama M (1987) Trends in mortality from cervical cancer in the nordic countries: association with organised screening programmes. Lancet 329(8544):1247–1249.

[5] Bray F, Jemal A, Grey N, Ferlay J, Forman D (2012) Global cancer transitions according to the human development index (2008–2030): a population-based study. Lancet Oncol 13(8):790–801.

[6] Bray F, Ren JS, Masuyer E, Ferlay J (2013) Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 132(5):1133–1145.

[7] Muñoz N (2000) Human papillomavirus and cancer: the epidemiological evidence. J Clin Virol 19(1):1–5.

[8] Walboomers JMM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Muñoz N (1999) Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 189(1):12–19.

[9] IARC Working Group (2005) Cervix cancer screening. iarc handbooks of cancer prevention, international agency for research on cancer. WHO, IARC Press.

[10] Dorn HF, Cutler SJ (1955) Morbidity from cancer in the United States. part I. variation in incidence by age, sex, race, marital status and geographic region. Pub Health Service Pub 418(29):1-121

[11] Kingham TP, Alatise OI, Vanderpuye V, Casper C, Abantanga FA, Kamara TB, Olopade OI, Habeebu M, Abdulkareem FB, Denny L (2013): Treatment of cancer in sub-saharan africa. Lancet Oncol 14(4):e158-e167.

[12] Arbyn M, Castellsague X, de Sanjosé S, Bruni L, Saraiya M, Bray F, Ferlay J (2011) Worldwide burden of cervical cancer in 2008. Ann Oncol 22(12):2675–2686.

[13] Crocker-Buque T, Pollock AM (2015) Appraising the quality of sub-saharan african cancer registration systems that contributed to GLOBOCAN 2008: a review of the literature and critical appraisal. J R Soc Med 108(2):57–67.

[14] Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55(2):74–108.

[15] Colombo N, Carinelli S, Colombo A, Marini C, Rollo D, Sessa C (2012) Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 23(7):vii27-32.

[16] Verleye L, Vergote I, Reed N, Ottevanger PB (2009): Quality assurance for radical hysterectomy for cervical cancer: the view of the european organization for research and treatment of cancer - gynecological cancer group (EORTC-GCG). Ann Oncol 20(10):1631-1638

[17] Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF (2014) S3-Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom. Langversion. AWMF (Leitlinienprogramm Onkologie) Available online at http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html, checked on 19/01/2015.

[18] Chokunonga E, Ramanakumar AV, Nyakabau AM, Borok MZ, Chirenje ZM, Sankila R, Parkin DM (2004) Survival of cervix cancer patients in harare, zimbabwe, 1995–1997. Int J Cancer 109(2):274–277.

[19] Sankaranarayanan R, Ferlay J (2006) Worldwide burden of gynaecological cancer: the size of the problem. Best Pract Res Clin Obstet Gynaecol 20(2):207–225.

[20] Rogo KO, Omany J, Onyango JN, Ojwang SB, Stendahl U (1990) Carcinoma of the cervix in the african setting. Int J Gynecol Obstet 33(3):249–255.

[21] Chirenje ZM, Rusakaniko S, Akino V, Mlingo M (2000) A review of cervical cancer patients presenting in harare and parirenyatwa hospitals in 1998. Cent Afr J Med 46(10):264–267.

[22] Mugambe JK, Wegoye P (2000) Pattern and experience with cancers treated with the chinese GWCP80 cobalt unit at mulago hospital, kampala. East Afr Med J 77(10):523-525.

[23] Barton MB, Frommer M, Shafiq J (2006) Role of radiotherapy in cancer control in low-income and middle-income countries. Lancet Oncol 7(7):584–595.

[24] Abdel-Wahab M, Bourque JM, Pynda Y, Iżewska J, Van der Merwe D, Zubizarreta E, Rosenblatt E (2013): Status of radiotherapy resources in africa: an international atomic energy agency analysis. Lancet Oncol 14(4):e168-e175.

[25] Podgorsak ED: Radiation oncology physics. A handbook for teachers and students. Chapter 5: Treatment Machines for External Beam Radiotherapy. IAEA, Vienna, 2005, pp. 123-160.

[26] Ravichandran R (2009) Has the time come for doing away with cobalt-60 teletherapy for cancer treatments. J Med Phys 34(2):63-65.

[27] Perez CA, Grigsby PW, Lockett MA, Chao KC, Williamson J (1999) Radiation therapy morbidity in carcinoma of the uterine cervix: dosimetric and clinical correlation. Int J Radiat Oncol Biol Phys 44(4):855–866.

[28] Portelance L, Chao KC, Grigsby PW, Bennet H, Low D (2001) Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. Int J Radiat Oncol Biol Phys 51(1):261–266.

[29] Blohin NN, Denoix PF, Dvorák V, Easson EC, Gentil F, Aboul Nasr AL, Pack GT: Cancer treatment. Report of a WHO expert committee. WHO Technical Report Series 322, Geneva, 1966, p. 52.

[30] van Dyk J, Battista JJ (1996) Cobalt-60: an old modality, a renewed challenge. Curr Oncol 3:10.

[31] Fletcher GH (1967) Textbook of radiotherapy. Am J Med Sci. 253(4):501.

[32] Federal Demographic Republic of Ethiopia: Population projection values of 2015 at zonal and wereda levels by urban and rural residence and by sex. Population Projection of Ethiopia for All Regions at Wereda Level from 2014 – 2017. CSA, Addis Ababa, 2013, p.60.

[33] Parkin DM, Sitas F, Chirenje M, Stein L, Abratt R, Wabinga H (2008) Part I: cancer in indigenous africans—burden, distribution, and trends. Lancet Oncol 9(7):683–692.

[34] Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova-Foucher E, Swaminathan R, Ferlay J: Cancer incidence in five continents, vol. X [electronic version]. IARC, Lyon, France, 2013. Available online at http://ci5.iarc.fr, checked on 27/01/2015.

[35] Anorlu RI (2008) Cervical cancer: the sub-saharan african perspective. Reprod Health Matters 16(32):41–49.

[36] Addis Ababa Cancer Registry. Available online at http://www.afcrn.org/membership/membership-list/100-addisababa, checked on 06/04/2015.

[37] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F: GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 - Ethiopia (2012) Estimated incidence and prevalence, adult population: female. IARC, Lyon, France, 2013. Available online at http://globocan.iarc.fr/old/summary_table_pop_prev.asp?selection=61231&title=Ethiopia&sex=2&window=1&sort=0&submit=%C2%A0 Execute%C2%A0, checked on 21/01/2015.

[38] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F: GLOBOCAN 2012 v1.0, Data sources and methods. IARC, Lyon, France, 2013. Available online at http://globocan.iarc.fr/Pages/DataSource_and_methods.aspx, checked on 06/04/2015.

[39] Gwoszdecky M, Fleming M (2003) Millions of cancer victims in developing countries lack access to life-saving radiotherapy. IAEA Press Releases 2003/11. Available online at https://www.iaea.org/PrinterFriendly/NewsCenter/PressReleases/2003/prn200311.html, checked on 23/01/2015.

[40] Kantelhardt EJ, Moelle U, Begoihn M, Addissie A, Trocchi P, Yonas B, Hezkiel P, Stang A, Thomssen C, Vordermark D, Gemechu T, Gebrehiwot Y, Wondemagegnehu T, Aynalem A, Mathewos A (2014) Cervical cancer in ethiopia: survival of 1,059 patients who received oncologic therapy. Oncologist 19(7):727–734.

[41] Wabinga H, Ramanakumar AV, Banura C, Luwaga A, Nambooze S, Parkin DM (2003) Survival of cervix cancer patients in kampala, uganda: 1995–1997. Br J Cancer 89(1):65–69.

[42] Bah E, Sam O, Whittle H, Ramanakumar A, Sankaranarayanan R (2011) Cancer survival in the Gambia, 1993–1997. IARC Sci Publ 162:97–100.

[43] Olsen J, Bertollini R, Victora C, Saracci R (2012) Global response to non-communicable diseases—the role of epidemiologists. Int J Epidemiol 41(5):1219–1220.

[44] Holmes MD, Dalal S, Volmink J, Adebamowo CA, Njelekela M, Fawzi WW, Willett WC, Adami HO (2010) Non-communicable diseases in sub-saharan africa: the case for cohort studies. PLoS Medicine 7(5):e1000244.

[46] Sharma V, Gaye PM, Wahab SA, Ndlovu N, Ngoma T, Vanderpuye V, Sowunmi A, Kigula-Mugambe J, Jeremic B (2008): Patterns of practice of palliative radiotherapy in africa, part 1: bone and brain metastases. Int J Radiat Oncol Biol Phys 70(4):1195–1201.

[46] Pecorelli S, Zigliani L, Odicino F (2009): Revised FIGO staging for carcinoma of the cervix. Int J Gynecol Obstet 105(2):107–108.

[47] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982) Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 5(6):649–655.

[48] Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, Gunderson L, McCormick B, Morrisintegral M, Rich T, Shipley W, Curran W (2000) Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys 47(1):13–47.

[49] O'Brien M, Mwangi-Powell F, Adewole IF, Soyannwo O, Amandua J, Ogaja E, Okpeseyi M, Ali Z, Kiwanuka R, Merriman A (2013) Improving access to analgesic drugs for patients with cancer in sub-saharan africa. Lancet Oncol 14(4):e176-e182.

[50] Harding R, Higginson IJ (2005) Palliative care in sub-saharan africa. Lancet 365(9475):1971–1977.

[51] Woldeamanuel YW, Girma B, Teklu AM (2013) Cancer in ethiopia. Lancet Oncol 14(4):289–290.

[52] Harding R, Powell RA, Kiyange F, Downing J, Mwangi-Powell F (2010) Provision of pain- and symptom-relieving drugs for HIV/AIDS in sub-saharan africa. J Pain Symptom Manage 40(3):405–415.

[53] Ethnologue®. Seventeenth Edition. In: Lewis MP, Simons FG, Fennig DC (eds.) (2013): Languages of Africa and Europe. SIL International, Global Publishing, 2013. Available online at http://www.ethnologue.com/country/ET/status, checked on 27/03/2015.

[54] Central Statistical Agency and ICF International: Ethiopia Demographic and Health Survey 2011. CSA and ICF International, Addis Ababa, Ethiopia and Calverton, Maryland, USA, 2012, pp. 40-246.

[55] Kes A, Swaminathan H: Gender and time poverty in sub-Saharan Africa. In: Blackden CM, Wodon Q (eds.): Gender, Time Use, and Poverty in Sub-Saharan Africa. World Bank Publications (73), 2006, pp. 13-38.

[56] Frank E (1999) Gender, agricultural development and food security in Amhara, Ethiopia: The contested identity of women farmers in Ethiopia. United States Agency for International Development, Washington, DC:1-20

[57] UNECA: Women in development: programme proposal for oromiya zone of the amhara region. In: Sustainable agriculture and environmental rehabilitation programme (SAERP). The wereda agriculture and rural development integrated services (WARDIS). Joint production of the Regional Council of the Amhara Regional State and the Economic Commission for Africa, IX:1–58.

[58] Logsdon MD, Eifel PJ (1999) FIGO IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy. Int J Radiat Oncol Biol Phys 43(4):763–775.

[59] Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, Williams CJ (2001) Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet 358(9284):781–786.

[60] Kuroda Y, Murakami N, Morota M, Sekii S, Takahashi K, Inaba K, Mayahara H, Ito Y, Yoshimura R, Sumi M, Kagami Y, Katsumata N, Kasamatsu T, Itami J (2012): Impact of concurrent chemotherapy on definitive radiotherapy for women with FIGO IIIb cervical cancer. In J Radiat Res 53(4):588–593.

[61] Montoya J, Luna HG, Amparo JR, Casasola C, Cristal-Luna G (2014) Renal function of cancer patients "fit" for cisplatin chemotherapy: physician perspective. Gulf J Oncol 1(16):64–72.

[62] Hailu A, Mariam DH (2013) Patient side cost and its predictors for cervical cancer in ethiopia: a cross sectional hospital based study. BMC Cancer 13(1):69.

[63] Yohana E, Kamuhabwa A, Mujinja P (2011) Availability and affordability of anticancer medicines: a case study at ocean road cancer institute in Dar es Salaam, Tanzania. East Afr J Public 8(1):52-57.

[64] Cox DR, Oakes D: Analysis of survival data. CRC Press, 1984, pp. 1-180.

[65] Shrier I, Platt RW (2008) Reducing bias through directed acyclic graphs. BMC Med Res Methodol 8:70.

[66] Greenland S, Morgenstern H (2001) Confounding in health research. Annu Rev Public Health 22:189-212.

[67] Greenland S, Robins JM (1986) Identifiability, exchangeability, and epidemiological confounding. Int J Epidemiol 15(3):413-419.

[68] Greenland S, Pearl J, Robins JM (1999) Causal diagrams for epidemiologic research. Epidemiology 10(1):37-48.

[69] Greenland S (2002) An overview of relations among causal modelling methods. Int J Epidemiol 31(5):1030-1037.

[70] WHO (2009) Global Health Observatory Data Repository. Physicians density (per 1000 population). WHO. Available online at http://apps.who.int/gho/data/node.main.A1444, checked on 27/05/2015.

[71] Terranova M, Padovese V, Fornari U, Morrone A (2008) Clinical and epidemiological study of cutaneous tuberculosis in Northern Ethiopia. Dermatology 217(1):89-93.

[72] Luz E, Marques M, Luz I, Stelitano C, Netto E, Araújo I, Brites C (2013) Survival and prognostic factors for AIDS and non-AIDS patients with non-hodgkin's lymphoma in Bahia, Brazil: a retrospective cohort study. ISRN Hematol 2013:1-7.

[73] Justice AC, Aiken LH, Smith HL, Turner BJ (1996) The role of functional status in predicting inpatient mortality with AIDS: a comparison with current predictors. J Clin Epidemiol 49(2):193–201.

[74] Corn BW, Donahue BR, Rosenstock JG, Hyslop T, Brandon AH, Hegde HH, Cooper JS, Sherr DL, Fisher SA, Berson A, Han H, Abdel-Wahab M, Koprowski CD, Ruffer JE, Curran WJ Jr. (1996) Performance status and age as independent predictors of survival among AIDS patients with primary CNS lymphoma: a multivariate analysis of a multi-institutional experience. Cancer J Sci Am 3(1):52–56.

[75] Doukas MA (1992) Human immunodeficiency virus associated anemia. Med Clin North Am 76(3):699–709.

[76] Frickhofen N, Abkowitz JL, Safford M, Berry JM, Antunez-de-Mayolo J, Astrow A, Cohen R, Halperin I, King L, Mintzer D (1990): Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type 1 (HIV-1): a treatable cause of anemia in AIDS. Ann Intern Med 113(12):926–933.

[77] Parkes-Ratanshi R, Katende D, Levin J, Wakeham K, Heiner G, Kamali A, Lalloo DG (2015) Development of severe anemia and changes in hemoglobin in a cohort of HIV-infected ugandan adults receiving zidovudine-, stavudine-, and tenofovir-containing antiretroviral regimens. J Int Assoc Provid AIDS Care 14(05):455-62.

[78] Mengist HM, Taye B, Tsegaye A (2015) Intestinal parasitosis in relation to CD4+ T cells levels and anemia among HAART initiated and HAART naive pediatric HIV patients in a model ART center in Addis Ababa, Ethiopia. PloS one 10(2):1-14.

[79] Kassu A, Tsegaye A, Wolday D, Petros B, Aklilu M, Sanders EJ, Fontanet AL, Van Baarle D, Hamann D, De Wit TF (2003): Role of incidental and/or cured intestinal parasitic infections on profile of CD4+ and CD8+ T cell subsets and activation status in HIV-1 infected and uninfected adult Ethiopians. Clin Exp Immunol 132(1)113–119.

[80] Ngugi P. 2011. Response and adherence of HIV Positive Women to Cervical Cancer Treatment [Master's Thesis]. Port Elizabeth, South Africa: Nelson Mandela Metropolitan University.

[81] Walsh D, Donnelly S, Rybicki L (2000) The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. Support Care Cancer 8(3):175-179.

[82] Dodd MJ, Miaskowski C, Paul SM (2001) Symptom clusters and their effect on the functional status of patients with cancer. Oncol Nurs Forum 28(3):465–470.

[83] Halkett G, Aoun S, Hayne D, Lund JA, Gruen A, Villa J, Livi L, Arcangeli S, Velikova G, Spry N (2010) EORTC radiation proctitis-specific quality of life module–pretesting in four european countries. Radiother Oncol 97(2):294–300.

[84] Sowa E, Kuhnt S, Hinz A, Schroder C, Deutsch T, Geue K (2014) Postoperative health-related quality of life of cervical cancer patients - a comparison between the Wertheim-Meigs operation and total mesometrial resection (TMMR). Geburtshilfe Frauenheilkd 74(7):670–676.

[85] Froding LP, Ottosen C, Mosgaard BJ, Jensen PT (2015) Quality of life, urogynecological morbidity, and lymphedema after radical vaginal trachelectomy for early-stage cervical cancer. Int J Gynecol Cancer 25(4):699-706.

[86] Foroudi F, Bull CA, Gebski V (2002) Radiation therapy for cervix carcinoma: benefits of individualized dosimetry. Clin Oncol. 14(1):43–49.

[87] Hymes SR, Strom EA, Fife C (2006) Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. J Am Acad Dermatol 54(1):28–46.

[88] Inal BB, Oguz O, Emre T, Usta M, Inal H, Altunoglu E, Topkaya C (2013) Evaluation of MDRD, cockcroft-gault, and CKD-EPI formulas in the estimated glomerular filtration rate. Clin Lab. 60(10):1685–1694.

[89] Bellomo R, Kellum JA, Ronco C: Defining acute renal failure: physiological principles. In: Michael R. Pinsky, Laurent Brochard, Göran Hedenstierna, Massimo Antonelli (eds.): Applied Physiology in Intensive Care Medicine 1. Springer, Berlin, Heidelberg, 2012, pp. 115-119.

[90] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P (2004) Acute renal failure–definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. Crit Care 8(4):R204-R212.

[91] Salive ME, Cornoni-Huntley J, Guralnik JM, Phillips CL, Wallace RB, Ostfeld AM, Cohen HJ (1992) Anemia and hemoglobin levels in older persons: relationship with age, gender, and health status. J Am Geriatr Soc 40(5):489–496.

[92] Isakov E, Froom P, Henig C, Barak M (2014) Anemia and estimated glomerular filtration rates. Ann Clin Lab Sci 44(4):419–424.

[93] Wood PA, Hrushesky WJ (1995) Cisplatin-associated anemia: an erythropoietin deficiency syndrome. J Clin Invest 95(4):1650–1659.

[94] Miller RP, Tadagavadi RK, Ramesh G, Reeves WB (2010) Mechanisms of cisplatin nephrotoxicity. Toxins 2(11):2490–2518.

[95] Davidson S (2011) Treatment for advanced cervical cancer: impact on quality of life. Crit Rev Oncol Hematol 79(1):24–30.

[96] Markman M (2003) Toxicities of the platinum antineoplastic agents. Expert Opin Drug Saf 2(6):597–607.

[97] Accord Healthcare Limited (2014) Package leaflet: information for the user. Cisplatin 1mg/ml Concentrate for Solution for Infusion. Available online at https://www.medicines.org.uk/emc/PIL.25822.latest.pdf, checked on 26/02/2015.

[98] Cruz MC, Andrade C, Urrutia M, Draibe S, Nogueira-Martins LA, Sesso RCC (2011) Quality of life in patients with chronic kidney disease. Clinics 66(6):991–995.

[99] US Department of Health and Human Services: Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. National Cancer Institute, 2010, pp. 3-194.

[100] Eknoyan G, Levin NW (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39(2):S1-266.

[101] Fiskovica E: List of translations available by language – validated modules and C30. EORTC Quality of Life. Available online at http://groups.eortc.be/qol/eortc-qlq-c30, checked on 27/03/2015.

[102] Dewolf L, Koller M, Velikova G, Johnson C, Scott N, Bottomley A: EORTC quality of life group translation procedure. EORTC, Brussels, 2009. Available online at http://groups.eortc.be/qol/sites/default/files/archives/translation_manual_2009.pdf, checked on 27/03/2015.

[103] Nationmaster: Ethiopia Media Facts & Stats. Households with television. Available online at http://www.nationmaster.com/country-info/profiles/Ethiopia/Media, checked on 3/27/2015.

[104] Haider S, Darney PD (2007) Injectable contraception. Clin Obstet Gynecol 50(4):898–906.

[105] Ravallion M, Van de Walle D, Mundial B: Cost-of-Living differences between urban and rural areas in Indonesia. Agriculture and rural development department, The World Bank, pp. 1-25.

[106] Headey D, Nisrane FB, Worku I, Dereje M, Taffesse AS (2012) Urban wage behavior and food price inflation: the case of Ethiopia. IFPRI and EDRI, Ethiopia Strategy Support Program Working Paper 41:1-24.

[107] World Health Organization: Traitement de la douleur cancéreuse. WHO, Geneva, 1987, pp. 5-77

[108] Denton A, Forbes A, Andreyev J, Maher EJ (2002) Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. Cochrane Database Syst Rev (1):CD003455.

[109] Leiper K, Morris AI (2007) Treatment of radiation proctitis. Clin Oncol (R Coll Radiol) 19(9):724–729.

[110] Saibishkumar EP, Patel FD, Sharma SC, Karunanidhi G, Sankar AS, Mallick I (2006) Results of external-beam radiotherapy alone in invasive cancer of the uterine cervix: a retrospective analysis. Clin Oncol 18(1):46–51.

[111] Eifel PJ, Levenback C, Wharton JT, Oswald MJ (1995) Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 32(5):1289–1300.

[112] Ferreira PRF, Braga-Filho A, Barletta A, Ilha LA (1999) Radiation therapy alone in stage III-B cancer of the uterine cervix—a 17-year experience in southern brazil. Int J Radiat Oncol Biol Phys 45(2):441–446.

[113] Horiot JC, Pigneux J, Pourquier H, Schraub S, Achille E, Keiling R, Combes P, Rozan R, Vrousos C, Daly N (1988) Radiotherapy alone in carcinoma of the intact uterine cervix according to G. H. Fletcher guidelines: a french cooperative study of 1383 cases. Int J Radiat Oncol Biol Phys 14(4):605–611.

[114] Akine Y, Hashida I, Kajiura Y, Watai K, Tsukiyama I, Egawa S, Yamada T, Tanemura K, Tsunematsu R, Ohmi K (1986) Carcinoma of the uterine cervix treated with external irradiation alone. Int J Radiat Oncol Biol Phys. 12(9):1611–1616.

[115] Ulmer HU, Frischbier HJ (1983) Treatment of advanced cancers of the cervix uteri with external irradiation alone. Int J Radiat Oncol Biol Phys 9(6):809–812.

[116] Bevölkerung nach Altersgruppen. In: Statistisches Bundesamt (eds.): Statistisches Jahrbuch Deutschland und Internationales 2014. 1. Auflage. Wiesbaden, Deutschland, 2014, pp. 31-33.

[117] Maiman M, Fruchter RG, Serur E, Remy JC, Feuer G, Boyce J (1990): Human immunodeficiency virus infection and cervical neoplasia. Gynecol Oncol 38 (3):377–382.

[118] Price J, Ramin A (2014) Implementation of a cervical cancer screening program linked to HIV care in a primary care clinic in Addis Ababa. APHA 142nd Annual meeting and EXPO.

[119] Robert Koch-Institut und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (2013): Krebs in Deutschland 2009/2010 (9. Ausgabe). Available online at http://www.rki.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2013/krebs_in_deutschland_2013.pdf;jsessionid=46DBF E3D158B3FAC7325A798CA3A803F.2_cid372?__blob=publicationFile, checked on 02/02/2015.

[120] Smith HO, Tiffany MF, Qualls CR, Key CR (2000) The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States - a 24-year population-based study. Gynecol Oncol 78(2):97–105.

[121] Bray F, Carstensen B, Møller H, Zappa M, Žakelj MP, Lawrence G, Hakama M, Weiderpass E (2005) Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev 14(9):2191–2199.

[122] Kim YJ, Hui D, Zhang Y, Chan Park J, Chisholm G, Williams J, Bruera E (2014) Differences in performance status assessment among palliative care specialists, nurses, and medical oncologists. J Pain Symptom Manage 49(6):1050-1058.

[123] Waggoner SE (2003) Cervical cancer. Lancet 361(9376):2217–2225.

[124] Zi-Zhong L, Fang-Zhi H (1989) External cobalt 60 irradiation alone for stage IIB carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 16(2):339–341.

[125] Koeck GP, Jacobson LE, Hillsinger WR (1966) Results of cobalt 60 rotation therapy in carcinoma of the cervix. Am J Roentgenol Radium Ther Nucl Med 96(1):81–91.

[126] Zharinov GM (1984) Relation of the effectiveness of radiotherapy of cervix cancer to the magnitude of the absorbed dose. Med Radiol (Mosk) 29(9):59–62.

[127] Matsuura K, Okabe T, Fujita K, Tanimoto H, Akagi Y, Kagemoto M (2012) Clinical results of external beam radiotherapy alone with a concomitant boost program or with conventional fractionation for cervical cancer patients who did not receive intracavitary brachytherapy. J Radiat Res 53(6):900–905.

[128] Biswal BM, Rath GK, Joshi RC, Mohanti BK, Ganesh T, Singh R (1998) Radiotherapy in locally advanced cancer of the cervix. Med J Malaysia 53(1):30–36.

[129] Perez CA, Grigsby PW, Chao KS, Mutch DG, Lockett MA (1998) Tumor size, irradiation dose, and long-term outcome of carcinoma of uterine cervix. Int J Radiat Oncol Biol Phys 41(2):307–317.

[130] Lanciano RM, Won M, Coia LR, Hanks GE (1991) Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: a final report of the 1973 and 1978 patterns of care studies. Int J Radiat Oncol Biol Phys 20(4):667–676.

[131] Eifel PJ, Thoms WW, Smith TL, Morris M, Oswald MJ (1994) The relationship between brachytherapy dose and outcome in patients with bulky endocervical tumours treated with radiation alone. Int J Radiat Oncol Biol Phys 28(1):113–118.

[132] Petereit DG, Pearcey R (1999) Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: is there an optimal fractionation schedule? Int J Radiat Oncol Biol Phys 43(2):359–366.

[133] Pesee M, Kirdpon W, Puapairoj A, Kirdpon S, Prathnadi P (2013) Palliative treatment of advanced cervical cancer with radiotherapy and thai herbal medicine as supportive remedy - analysis of survival. Asian Pac J Cancer Prev 14(3):1593–1596.

[134] Hodson DI, Krepart GV (1983) Once-monthly radiotherapy for the palliation of pelvic gynecological malignancy. Gynecol Oncol 16(1):112–116.

[135] Halle JS, Rosenman JG, Varia MA, Fowler WC, Walton LA, Currie JL (1986) 1000 cGy single dose palliation for advanced carcinoma of the cervix or endometrium. Int J Radiat Oncol Biol Phys 12(11):1947–1950.

[136] Chafe W, Fowler WC, Currie JL, Davis ML, Walton LA, Montana G (1984) Single-fraction palliative pelvic radiation therapy in gynecologic oncology: 1,000 rads. Am J Obstet Gynecol 148(5):701–705.

[137] Onsrud M, Hagen B, Strickert T (2001) 10-Gy single-fraction pelvic irradiation for palliation and life prolongation in patients with cancer of the cervix and corpus uteri. Gynecol Oncol 82(1):167–171.

[138] Mishra SK, Laskar S, Muckaden MA, Mohindra P, Shrivastava SK, Dinshaw KA (2005) Monthly palliative pelvic radiotherapy in advanced carcinoma of uterine cervix. J Cancer Res Ther 1(4):208–212.

[139] Boulware RJ, Caderao JB, Delclos L, Wharton JT, Peters LJ (1979) Whole pelvis megavoltage irradiation with single doses of 1000 rad to palliate advanced gynecologic cancers. Int J Radiat Oncol Biol Phys 5(3):333–338.

[140] Kim DH, Lee JH, Ki YK, Nam JH, Kim WT, Jeon HS, Park D, Kim DW (2013): Short-course palliative radiotherapy for uterine cervical cancer. Radiat Oncol J 31(4):216–221.

[141] SRC Trial Group (1997) Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 336(14):980–987.

[142] Fowler JF (1989) The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 62(740):679–694.

[143] Smith SC, Koh WJ (2001) Palliative radiation therapy for gynaecological malignancies. Best Pract Res Clin Obstet Gynaecol 15(2):265–278.

[144] Chen YP, Tsang NM, Tseng CK, Lin SY (2000) Causes of interruption of radiotherapy in nasopharyngeal carcinoma patients in Taiwan. Jpn J Clin Oncol 30(5):230–234.

[145] Saibishkumar EP, Patel FD, Sharma SC (2006) Evaluation of late toxicities of patients with carcinoma of the cervix treated with radical radiotherapy: an audit from India. In Clin Oncol (R Coll Radiol) 18(1):30–37.

[146] Arulponni TR, Janaki MG, Nirmala S, Ramesh BS, Rishi KS, Kirthi K (2010) Carcinoma cervix treated with radiotherapy - our experience with emphasis on our concerns. J Obstet Gynecol India 60(1):61–65.

[147] Elghamrawi KA, Haggag MH, Habib EE (2011) Treatment complications among long-term survivors of cervical cancer: treated by surgery or radiotherapy. Oncol Rev 5(4):261–266.

[148] Barraclough LH, Swindell R, Livsey JE, Hunter RD, Davidson SE (2008) External beam boost for cancer of the cervix uteri when intracavitary therapy cannot be performed. Int J Radiat Oncol Biol Phys 71(3):772–778.

[149] Ferrigno R, Campos de Oliveira Faria SL, Weltman E, Salvajoli JV, Segreto RA, Pastore A, Nadalin W (2003) Radiotherapy alone in the treatment of uterine cervix cancer with telecobalt and low-dose-rate brachytherapy: retrospective analysis of results and variables. Int J Radiat Oncol Biol Phys 55(3):695–706.

[150] Patel FD, Sharma SC, Negi PS, Ghoshal S, Gupta BD (1994) Low dose rate vs. high dose rate brachytherapy in the treatment of carcinoma of the uterine cervix: a clinical trial. Int J Radiat Oncol Biol Phys 28(2):335–341.

[151] Gondi V, Bentzen SM, Sklenar KL, Dunn EF, Petereit DG, Tannehill SP, Straub M, Bradley KA (2012): Severe late toxicities following concomitant chemoradiotherapy compared to radiotherapy alone in cervical cancer: an inter-era analysis. Int J Radiat Oncol Biol Phys 84(4):973–982.

[152] Swamy K, Supe S, Kumar MU, Viswanathan N, Anantha N (1991) The time dose fractionation (TDF) relationship in the radiotherapy of carcinoma of the cervix. Strahlenther Onkol 167(10):603–607.

[153] Beskow C, Ågren-Cronqvist AK, Lewensohn R, Toma-Dasu I (2012) Biological effective dose evaluation and assessment of rectal and bladder complications for cervical cancer treated with radiotherapy and surgery. J Contemp Brachytherapy 4(4):205-212.

[154] Yudelev M, Kuten A, Tatcher M, Rubinov R, Karmeli R, Cohen Y, Robinson E (1986) Correlations of dose and time-dose-fractionation factors (TDF) with treatment results and side effects in cancer of the uterine cervix. Gynecol Oncol 23(3):310–315.

[155] Orton CG, Wolf-Rosenblum S (1986) Dose dependence of complication rates in cervix cancer radiotherapy. Int J Radiat Oncol Biol Phys 12(1):37–44.

[156] Ogino I, Kitamura T, Okamoto N, Yamasita K, Aikawa Y, Okajima H, Matsubara S (1995) Late rectal complication following high dose rate intracavitary brachytherapy in cancer of the cervix. Int J Radiat Oncol Biol Phys 31(4):725–734.

[157] Takeshi K, Katsuyuki K, Yoshiaki T, Teppei S, Tadayoshi M, Akira M, Katsumi M (1998) Definitive radiotherapy combined with high-dose-rate brachytherapy for stage III carcinoma of the uterine cervix: retrospective analysis of prognostic factors concerning patient characteristics and treatment parameters. Int J Radiat Oncol Biol Phys 41(2):319–327.

[158] Levin CV, El Gueddari B, Meghzifene A (1999) Radiation therapy in Africa: distribution and equipment. Radiother Oncol 52(1):79–83.

[159] Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo de Silva G, Chen WQ, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP (2015): Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 385(9972):977–1010.

[160] Kakehi M (1975): Radiotherapy of the carcinoma of the uterine cervix by the external irradiation using conformation technique (author's transl). Nihon Igaku Hoshasen Gakkai Zasshi 35(1):16–27.

[161] Koeck GP, Hillsinger WR (1971) Dosage tolerance of pelvic structures with cobalt 60 rotation radiation therapy. Am J Roentgenol Radium Ther Nucl Med 111(2):260–268.

[162] Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, von Eschenbach AC, Kuban DA, Rosen I (2002) Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 53(5):1097–1105.

[163] Eade TN, Hanlon AL, Horwitz EM, Buyyounouski MK, Hanks GE, Pollack A (2007) What dose of external-beam radiation is high enough for prostate cancer? Int J Radiat Oncol Biol Phys 68(3):682–689.

[164] Pollack A, Hanlon A, Horwitz EM, Feigenberg S, Uzzo RG, Price RA (2003) Radiation therapy dose escalation for prostate cancer: a rationale for IMRT. World J Urol 21(4):200-208.

[165] DiMatteo MR (2004) Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care 42(3):200–209.

[166] Hugtenburg JG, Timmers L, Elders PJ, Vervloet M, van Dijk L (2013): Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. Patient Prefer Adherence 7:675–682.

[167] Lanciano RM, Pajak TF, Martz K, Hanks GE (1993) The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: a patterns-of-care study. Int J Radiat Oncol Biol Phys 25(3):391–397.

[168] Hanks GE, Herring DF, Kramer S (1983) Patterns of care outcome studies. Results of the national practice in cancer of the cervix. Cancer 51(5):959–967.

[169] Han K, Milosevic M, Fyles A, Pintilie M, Viswanathan AN (2013) Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys 87(1):111–119.

[170] Holcomb K, Gabbur N, Tucker T, Matthews RP, Lee YC, Abulafia O (2001) 60Cobalt vs. linear accelerator in the treatment of locally advanced cervix carcinoma: a comparison of survival and recurrence patterns. Eur J Gynaecol Oncol 22(1):16–19.

[171] Hanks GE, Diamond JJ, Kramer S (1985) The need for complex technology in radiation oncology. Correlations of facility characteristics and structure with outcome. Cancer 55(9 Suppl):2198–2201.

[172] Allt WEC (1969) Supervoltage radiation treatment in advanced cancer of the uterine cervix: a preliminary report. Can Med Assoc J 100:792–797.

[173] Rawlinson J (1989) The choice of equipment for external beam radiotherapy. Proceedings of the IAEA seminar on organization and training of radiotherapy in Africa, Cairo, 11-15 December.

[174] Singh IRR, Ravindran BP, Ayyangar KM (2006) Design and development of motorized multileaf collimator for telecobalt unit. Technol Cancer Res Treat 5(6):597–605.

[175] Fox C, Romeijn HE, Lynch B, Men C, Aleman DM, Dempsey JF (2008) Comparative analysis of 60Co intensity-modulated radiation therapy. Phys Med Biol 53(12):3175–3188.

[176] Kumar R, Kar DC, Sharma SD, Mayya YS (2012) Design, implementation and validation of a motorized wedge filter for a telecobalt machine (Bhabhatron-II). Physica Medica 28(1):54–60.

[177] Kinhikar RA, Sharma S, Upreti R, Tambe CM, Deshpande DD (2007) Characterizing and configuring motorized wedge for a new generation telecobalt machine in a treatment planning system. J Med Phys 32(1):29-33.

[178] Kinhikar RA, Patkar S, Tambe CM, Deshpande DD (2007) On the transit dose from motorized wedge treatment in Equinox-80 telecobalt unit. J Cancer Res Ther 3(3):140–142.

[179] Joshi CP, Dhanesar S, Darko J, Kerr A, Vidyasagar PB, Schreiner LJ (2009) Practical and clinical considerations in cobalt-60 tomotherapy. J Med Phys 34 (3):137–140.

[180] Mutic S, Dempsey JF (2014) The ViewRay system: magnetic resonance-guided and controlled radiotherapy. Semin Radiat Oncol 24(3):196–199.

[181] Dempsey J, Dionne B, Fitzsimmons J, Haghigat A, Li J, Low D, Mutic S, Palta J, Romeijn H, Sjoden G (2006) WE-E-ValA-06: a real-time MRI guided external beam radiotherapy delivery system. Med Phys 33(6):2254.

[182] Wooten HO, Rodriguez V, Green O, Kashani R, Santanam L, Tanderup K, Mutic S, Li HH (2015) Benchmark IMRT evaluation of a Co-60 MRI-guided radiation therapy system. Radiother Oncol 114(3):402–405.

[183] World Health Organization: Radiotherapy risk profile. Technical Manual. WHO, Geneva, 2008, pp. 4-45.

[184] Cadman PF, Paliwal BR, Orton CG (2010) Co-60 tomotherapy is the treatment modality of choice for developing countries in transition toward IMRT. Med Phys 37(12):6113-6115.

[185] Lissner S, Schubert K, Klüter S, Oetzel D, Debus J (2013) A method for testing the performance and the accuracy of the binary MLC used in helical tomotherapy. Z Med Phys 23(2):153–161.

[186] Lu W (2008) Real-time motion-adaptive delivery (MAD) using binary MLC: I. static beam (topotherapy) delivery. II. rotational beam (tomotherapy) delivery. Phys Med Biol 53(22):6491–6511.

[187] Database of radiological incidents and related events. Available online at http://www.johnstonsarchive.net/nuclear/radevents/, updated on 20/01/2014, checked on 26/03/2015.

[188] Parikh P (2006) Developing countries oncology survey (DC-OS) report 2006, phase 1. European Society for Medical Oncology (ESMO):3–11. Available online at http://www.esmo.org/content/download/8399/170349/file/DC_Survey_Report_Istanbul.pdf, checked on 14/03/2015.

[189] McArdle O, Kigula-Mugambe JB (2007) Contraindications to cisplatin based chemoradiotherapy in the treatment of cervical cancer in Sub-Saharan Africa. Radiother Oncol 83(1):94–96.

[190] Shakespeare TP, Back MF, Lu JJ, Lee KM, Mukherjee RK (2006) External audit of clinical practice and medical decision making in a new Asian oncology center: results and implications for both developing and developed nations. Int J Radiat Oncol Biol Phys 64(3):941–947.

[191] Olasinde TA, Olugbemiro AA (2010) Over and under exposures of radiotherapy patients at the ABU teaching hospital, Zaria, Nigeria: case reports. Nig Q J Hosp Med 21(2):145–148.

[192] Furlow B (2009) Radiotherapy errors spark investigations and reform. Lancet Oncol 10(1):11–12.

[193] Shafiq J, Barton M, Noble D, Lemer C, Donaldson LJ (2009) An international review of patient safety measures in radiotherapy practice. Radiother Oncol 92(1):15–21.

[194] Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J (1999) Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. BMJ 318(7182):527-530.

[195] Flores Y, Bishai D, Lazcano E, Shah K, Lörincz A, Hernández M, Salmerón J (2003): Improving cervical cancer screening in Mexico: results from the Morelos HPV study. Salud pública Méx 45:388–398.

[196] Denny L (2015) Control of cancer of the cervix in low- and middle-income countries. Ann Surg Oncol 22(3):728–733.

[197] World Health Organization: WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. WHO, Geneva, 2013, pp. 1-19. Available online at http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf, checked on 16/05/2015.

[198] Blumenthal PD, Gaffikin L, Chirenje ZM, McGrath J, Womack S, Shah K (2001) Adjunctive testing for cervical cancer in low resource settings with visual inspection, HPV, and the Pap smear. Int J Gynecol Obstet 72(1):47–53.

[199] Mvundura M, Tsu V (2014) Estimating the costs of cervical cancer screening in high-burden Sub-Saharan African countries. Int J Gynecol Obstet 126(2):151–155.

[200] African Population and Health Research Center, International Agency for Research on Cancer, World Health Organization: Prevention of cervical cancer through screening using visual inspection with acetic acid (VIA) and treatment with cryotherapy. A demonstration project in six African countries: Malawi, Madagascar, Nigeria, Uganda, the United Republic of Tanzania, and Zambia. WHO, Geneva, 2012, pp. 5-27.

[201] Maseko FC, Chirwa ML, Muula AS (2014) Client satisfaction with cervical cancer screening in Malawi. BMC Health Serv Res 14:420.

[202] Hosseinipour M, Ndalama B, Rosenberg NE, Kamanga G, Mapanje C, Phiri S, Miller WC, Martinson F, Hoffman I (2013) P6.010 Implementation of VIA for cervical cancer screening in a sexually transmitted infection clinic in Lilongwe, Malawi. Sex Transm Infect 89:A372-A373.

[203] Campos NG, Kim JJ, Castle PE, Ortendahl JD, O'Shea M, Diaz M, Goldie SJ (2012) Health and economic impact of HPV 16/18 vaccination and cervical cancer screening in Eastern Africa. Int J Cancer 130(11):2672–2684.

[204] Getahun F, Mazengia F, Abuhay M Birhanu Z (2013) Comprehensive knowledge about cervical cancer is low among women in Northwest Ethiopia. BMC cancer 13:2.

[205] Shulman LN, Mpunga T, Tapela N, Wagner CM, Fadelu T, Binagwaho A (2014) Bringing cancer care to the poor: experiences from Rwanda. Nat Rev Cancer 14(12):815–821.

[206] Ministry of Health, Federal Republic of Ethiopia: Guidelines for Cervical Cancer Prevention and Control in Ethiopia. Ministry of Health, Addis Abeba, 2015.

[207] Caro JJ, Salas M, Ward A, Goss G (2001) Anemia as an independent prognostic factor for survival in patients with cancer. Cancer 91 (12):2214–2221.

[208] Kapp DS, Fischer D, Gutierrez E, Kohorn EI, Schwartz PE (1983) Pretreatment prognostic factors in carcinoma of the uterine cervix: a multivariable analysis of the effect of age, stage, histology and blood counts on survival. Int J Radiat Oncol Biol Phys 9(4):445–455.

[209] Brooks SE, Chen TT, Ghosh A, Mullins CD, Gardner JF, Baquet CR (2000) Cervical cancer outcomes analysis: impact of age, race, and comorbid illness on hospitalizations for invasive carcinoma of the cervix. Gynecol Oncol 79(1):107–115.

[210] Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R (2009) EUROCARE-4. Survival of cancer patients diagnosed in 1995–1999. Results and commentary. Eur J Cancer 45(6):931–991.

[211] Maiman M, Fruchter RG, Guy L, Cuthill S, Levine P, Serur E (1993) Human immunodeficiency virus infection and invasive cervical carcinoma. Cancer 71(2):402–406.

[212] Iff S, Craig JC, Turner R, Chapman JR, Wang JJ, Mitchell P, Wong G (2014) Reduced estimated GFR and cancer mortality. Am J Kidney Dis 63(1):23–30.

[213] Munagala R, Rai SN, Ganesharajah S, Bala N, Gupta RC (2010) Clinicopathological, but not socio-demographic factors affect the prognosis in cervical carcinoma. Oncol Rep 24(2):511–520.

[214] Tsai CS, Lai CH, Wang CC, Chang JT, Chang TC, Tseng CJ, Hong JH (1999) The prognostic factors for patients with early cervical cancer treated by radical hysterectomy and postoperative radiotherapy. Gynecol Oncol 75(3):328–333.

[215] Xia X, Xu H, Wang Z, Liu R, Hu T, Li S (2014) Analysis of prognostic factors affecting the outcome of stage IB-IIB cervical cancer treated by radical hysterectomy and pelvic lymphadenectomy. Am J Clin Oncol 14(6):1–5.

[216] Miller TR, Grigsby PW (2002) Measurement of tumour volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy. Int J Radiat Oncol Biol Phys 53(2):353–359.

[217] Pradhan TS, Duan H, Katsoulakis E, Salame G, Lee YC, Abulafia O (2011) Hydronephrosis as a prognostic indicator of survival in advanced cervix cancer. Int J Gynecol Cancer 21(6):1091–1096.

[218] Patel K, Foster NR, Kumar A, Grudem M, Longenbach S, Bakkum-Gamez J, Haddock M, Dowdy S, Jatoi A (2015) Hydronephrosis in patients with cervical cancer: an assessment of morbidity and survival. Support Care Cancer 23(5):1303–1309.

[219] Cui L, Shi Y, Zhang GN (2015) Perineural invasion as a prognostic factor for cervical cancer: a systematic review and meta-analysis. Arch Gynecol Obstet 292(1):13-9.

[220] Singh N, Arif S (2004) Histopathologic parameters of prognosis in cervical cancer - a review. Int J Gynecol Cancer 14(5):741–750.

[221] Lee SW, Nam JH, Kim DY, Kim JH, Kim KR, Kim YM, Kim YT (2010) Unfavorable prognosis of small cell neuroendocrine carcinoma of the uterine cervix: a retrospective matched case-control study. Int J Gynecol Cancer 20(3):411–416.

[222] Viswanathan AN, Deavers MT, Jhingran A, Ramirez PT, Levenback C, Eifel PJ (2004) Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence. Gynecol Oncol 93(1):27–33.

[223] Grisaru D, Covens A, Chapman B, Shaw P, Colgan T, Murphy J, DePetrillo D, Lickrish G, Laframboise S, Rosen B (2001) Does histology influence prognosis in patients with early-stage cervical carcinoma? Cancer 92(12):2999–3004.

[224] Creasman WT, Kohler MF (2004) Is lymph vascular space involvement an independent prognostic factor in early cervical cancer? Gynecol Oncol 92(2):525–529.

[225] Perez CA, Grigsby PW, Castro-Vita H, Lockett MA (1995) Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. Int J Radiat Oncol Biol Phys 32(5):1275–1288.

[226] Diaz J, Yu D, Micaily B, Ferriss JS, Hernandez E (2014) Radiation therapy with concurrent chemotherapy for locally advanced cervical carcinoma: outcome analysis with emphasis on the impact of treatment duration on outcome. Obstet Gynecol Int 2014:214351.

[227] Girinsky T, Rey A, Roche B, Haie C, Gerbaulet A, Randrianarivello H, Chassagne D (1993) Overall treatment time in advanced cervical carcinomas: a critical parameter in treatment outcome. Int J Radiat Oncol Biol Phys 27(5):1051–1056.

[228] Petereit DG, Sarkaria JN, Chappell R, Fowler JF, Hartmann TJ, Kinsella TJ, Stitt JA, Thomadsen BR, Buchler DA (1995) The adverse effect of treatment prolongation in cervical carcinoma. Int J Radiat Oncol Biol Phys 32(5):1301–1307.

[229] Toita T, Kakinohana Y, Ogawa K, Adachi G, Moromizato H, Nagai Y, Maehama T, Sakumoto K, Kanazawa K, Murayama S (2003) Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: analysis of dose and fractionation schedule. Int J Radiat Oncol Biol Phys 56(5):1344–1353.

8 Thesis statements

1. More than half of the patients under observation presented with late stages of FIGO (≥IIIb). As yet, no generalized primary and secondary prevention for cervical cancer is implemented in Ethiopia.

2. Stages of FIGO generally increase during waiting time for start of RT. In order to secure on time access to treatment, a second RT machine and a larger number of qualified staff members is needed.

3. Overall survival of 1009 cervical cancer patients presenting at TAHRC 2008-2012 (83% and 63% after 1 and 2 years) was similar to other low-resource settings and lower compared to high-income countries.

4. EBRT by Co-60 for cervical cancer patients according to guidelines of TAHRC is effective. Patients, who completed their RT schedule, had significantly better chances for survival than those, who discontinued.

5. Higher dosage schedules might give more benefit to patients staged FIGO IIIb or IVa. Throughout the existing research, the benefit of high-dose radical RT for these patients was pointed out. As the respective patients form the largest group within the sample, the need for a second RT unit is reemphasized in order to provide the larger number of fractions necessary for curative treatment.

6. Rates of adverse effects at TAHRC were higher than comparable studies reported. This may be partly due to the lack of ICBT and the limited access to supportive treatment.

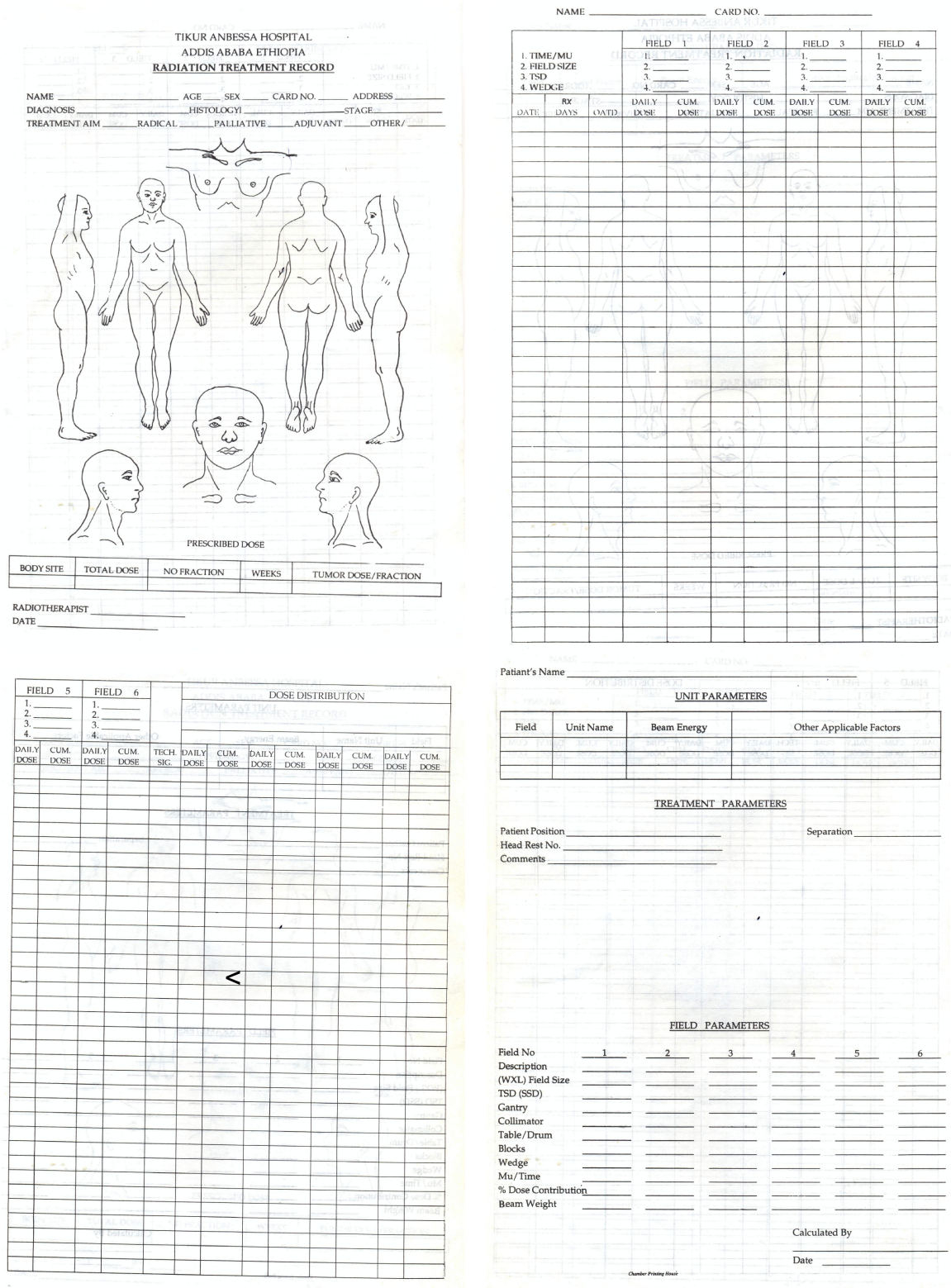
7. The adherence to the existing protocols should be improved. In 17% of all cases, it was not possible to assign patients to RT schedules according to guidelines. In case of guideline-conform planning, 35% of patients assigned to radical or non-radical RT, received lower or higher doses than indicated. Standardised protocols and the meticulous documentation of therapeutic decisions, discontinuations and adverse effects will increase reliability of health care. Better supportive care and financial or logistical support for patients in need may increase the rate of patients, who complete their assigned RT schedule.

8. Concomittant or adjuvant chemotherapy, as recommended by international guidelines, is realized in a very low proportion of all patients (17%). Access to and affordabiliy of chemotherapy is necessary in order to optimize treatment of cervical cancer patients.

9. After presenting data on overall survival of cervical cancer patients, I suggest prospective research on Quality of Life of patients before and after RT. The respective QoL questionnaires are available now in Amharic language.

9 Appendix

9.1 Radiation Treatment Record



TIKUR ANBESSA HOSPITAL
ADDIS ABABA ETHIOPIA
RADIATION TREATMENT RECORD

NAME _____ AGE ___ SEX ___ CARD NO. ___ ADDRESS _____
DIAGNOSIS _____ HISTOLOGY! _____ STAGE _____
TREATMENT AIM _____ RADICAL _____ PALLIATIVE _____ ADJUVANT _____ OTHER/ _____

PRESCRIBED DOSE

BODY SITE	TOTAL DOSE	NO FRACTION	WEEKS	TUMOR DOSE/FRACTION

RADIOTHERAPIST _____
DATE _____

NAME _____ CARD NO. _____

1. TIME/MU 2. FIELD SIZE 3. TSD 4. WEDGE			FIELD 1 1. _____ 2. _____ 3. _____ 4. _____		FIELD 2 1. _____ 2. _____ 3. _____ 4. _____		FIELD 3 1. _____ 2. _____ 3. _____ 4. _____		FIELD 4 1. _____ 2. _____ 3. _____ 4. _____	
DATE	Rx DAYS	OATD	DAILY DOSE	CUM. DOSE	DAILY DOSE	CUM. DOSE	DAILY DOSE	CUM. DOSE	DAILY DOSE	CUM. DOSE

FIELD 5 1. _____ 2. _____ 3. _____ 4. _____		FIELD 6 1. _____ 2. _____ 3. _____ 4. _____			DOSE DISTRIBUTION							
DAILY DOSE	CUM. DOSE	DAILY DOSE	CUM. DOSE	TECH. SIG.	DAILY DOSE	CUM. DOSE	DAILY DOSE	CUM. DOSE	DAILY DOSE	CUM. DOSE	DAILY DOSE	CUM. DOSE

Patiant's Name _____

UNIT PARAMETERS

Field	Unit Name	Beam Energy	Other Applicable Factors

TREATMENT PARAMETERS

Patient Position _____ Separation _____
Head Rest No. _____
Comments _____

FIELD PARAMETERS

Field No	1	2	3	4	5	6
Description						
(WXL) Field Size						
TSD (SSD)						
Gantry						
Collimator						
Table/Drum						
Blocks						
Wedge						
Mu/Time						
% Dose Contribution						
Beam Weight						

Calculated By _____
Date _____

Figure 15: Radiation treatment record for documentation of RT at TAHRC

9.2 Prognostic factors for cervical cancer patients

The primary endpoint of this study is overall survival. Naturally, not only therapeutic measures as RT effect overall survival. Table 22 displays several prognostic factors for cervical cancer patients. Among the patient-related factors, an increase in age, grade of anemia, ECOG performance status and the rate of comorbidities, especially infection with human immunodeficiency virus (HIV), result in lower overall survival probability. Additionally, a diminished renal function measured by a decrease of eGFR increases cancer mortality. The influence of socioeconomic factors on overall survival of cervical cancer patients is not yet clearly established. Two studies report controversial outcome [209, 213].

Table 22: Prognostic factors for cervical cancer patients

	Host-related prognostic factors	Tumour-related prognostic factors	Treatment-related prognostic factors
Adverse prognostic effect	**Anemia** [207, 208] **ECOG performance status** [130] **Comorbidity** [209, 210, 208] **HIV status** [211] **Age** [210, 208, 130]	**Stage of FIGO** [208, 123] **Tumour size** [216, 123, 129] **Parametrial involvement** [214, 215] **Obstructive uropathy** [218, 217] **Pelvine / paraaortal lymph node metastasis** [214, 215, 123] **Perineural invasion** [219] **Histology** (adenosquaemous vs. neuroendocrine small cell carcinomas) [220, 221, 222, 223]	**Overall treatment time of RT** [225, 226, 167, 227, 228]
Favourable prognostic effect	**Renal function** [212]		**Total dose of radiation** [86, 129, 153, 229] **Adjuvant RT for patients with FIGO Ib-IIb** [214, 215] **Concomitant chemotherapy** [15**?** , 59] **Surgical hysterectomy as primary treatment for FIGO Ia-IIa** [214]
Contraversial discussion in literature	**Socioeconomic factors** [213, 209]	**Histological grading** [220] **Lymphovascular space invasion** [224]	**Resection margins after surgery** [220]

With regard to characteristics of the tumour, numerous studies show the negative influence of increase in stage of FIGO on overall survival of cervical cancer patients. Additionally, albeit not part of the FIGO staging system, involvement of lymph nodes is a strong indicator for worse prognosis. However, histology of the cervical tumour does not relate to survival, except for neuroendocrine small cell tumours and adenosquamous carcinoma, which both have significantly worse outcome than the more common squamous cell carcinoma and adenocarcinoma. Histological grading seems to influence outcome of cervical cancer patients. However, the practice of grading is not consistent throughout centers and, therefore, no distinct effect could be shown yet.

Treatment by definition effects prognosis. However, the evidence base for a positive effect of free resection margins after hysterectomy is poor. Moreover, even in case of free resection margins, adjuvant RT does increase overall survival probabilities in certain situations [214]. For all patients staged FIGO Ib2 or IIb and higher, carefully balanced EBRT plus high dose ICBT together with concomitant platinbased chemotherapy outrun hysterectomy alone in terms of positive effect on overall survival. For the existing variety of RT modalities, no consistent stage-specific dose-recommendations exist. Yet, numerous studies state the negative effect of a prolonged radiation treatment. This implies avoidance of unnecessary treatment breaks and a maximum duration of radiotherapeutic treatment of 52 - 56 days [226, 227, 228].

9.3 Extended version of DAG for the effect of RT dose on overall survival

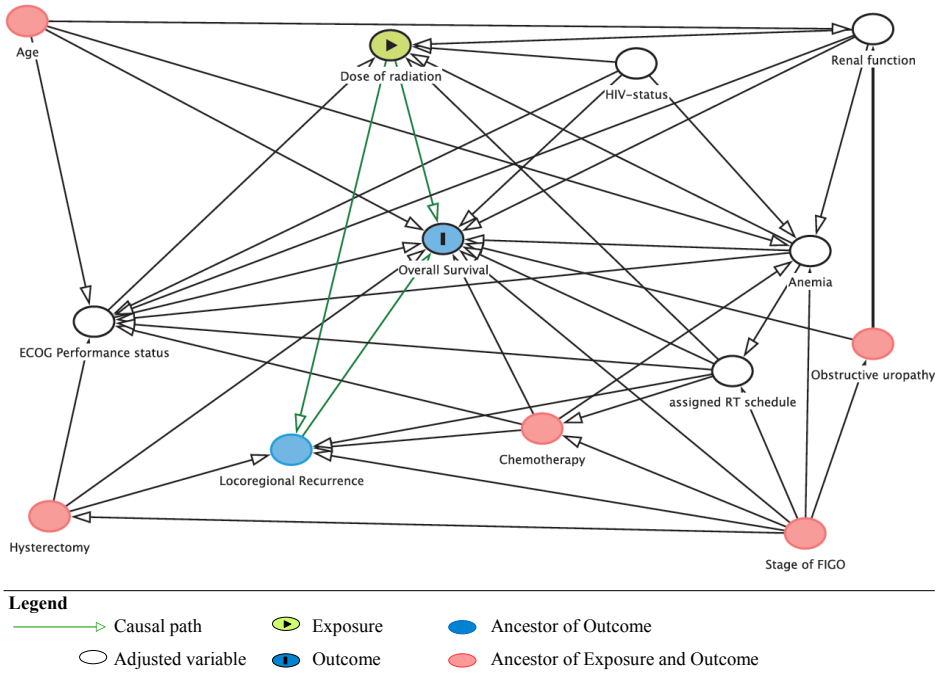


Figure 16: Extended DAG for analysis of impact of radiation dose on overall survival of cervical cancer patients. MSAS is shown.

9.4 Questionnaire for telephone follow-up

Patient numbre							
Patient ID							
Patient name							
Date phonecall						Ethiopian ☐	Gregorian ☐
Date death						Ethiopian ☐	Gregorian ☐
Cause of death	alive	Local Tumor		Metastasis		Not due to tumor	999
Date of symptoms/adverse effects						Ethiopian ☐	Gregorian ☐
Adverse effects *Ask for the appearance of each side effect and only ask for the intensity if you find it possible. For simple appearance of f.e. lymphedema or skin problems, mark '2 moderate'. Try to use the information voluntarily given by the patient effectively.*							
Inflamed Rectum (Proctitis)	none	**1** rectal discomfort	**2** rectal bleeding	**3** incontinence (Colostoma?)		**4** life threat	**999**
Diarrhea (stools>baseline!)	none	**1** <4 stools/d	**2** 4-6 stools/d	**3** >=7 stools/d, incontinence		**4** life threat	**999**
Urinary Problems	none	**1** mild: urgency/ frequency↑	**2** ↑↑+ bloody urine	**3** ↑↑↑ surgical intervention necessary		**4** life threat	**999**
Incontinence (Fistula?)	none	**1** occasional (+cough)	**2** spontaeneous	**3** intervention! selfcare↓			**999**
Passage of urine / stool through the vagina	none	1 mild	2 moderate	3 severe			999
lymphedema (leg swelling?)	none	**1** trace of thickening	**2** marked discoloration	**3** severe selfcare↓			**999**
Fatigue/tired?	none	**1** relieved by rest	**2** not relieved by rest	**3** selfcare↓			**999**
any skin problems in the radiated area? (itching, swelling)	none	**1** mild	**2** modera te	**3** severe	**4** life threatening		**999**
Comments or any other side effects the patient noticed after radiation:							
Symptoms *Ask for the appearance of each side effect and try to find out ist intensity with the help of the grading scale below. Try to use the information voluntarily given by the patient effectively.*							
Vaginal bleeding	none	**1** postcoital	**2** brownish	**3** spontaneous	**4** life threat		**999**
Discharge	none	1 mild	2 moderate	3 severe	4 life threat		999
constipation	none	1 mild	2 moderate	3 severe	4 life threat		999
Pelvic pain	none	**1** mild	**2** moderate	**3** severe			**999**
Comments or any other symptoms the patient noticed after radiation:							
ECOG	**0** fully active	**1** lightly restricted	**2** unable to work	**3** limited selfcare, >50% in bed	**4** bedbound, no selfcare	**5** dead	**999**

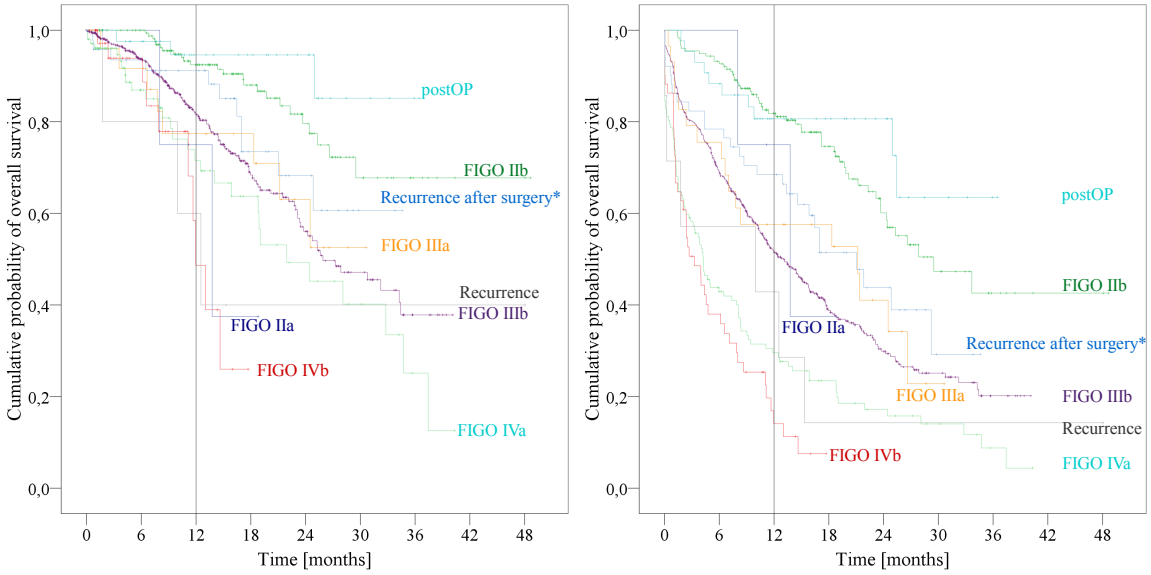
Patient numbre							
Patient ID							
Patient name							
Date phonecall						Ethiopian ☐	Gregorian ☐
Date death						Ethiopian ☐	Gregorian ☐
Cause of death	alive	Local Tumor		Metastasis		Not due to tumor	999
Date of symptoms/adverse effects						Ethiopian ☐	Gregorian ☐
Adverse effects *Ask for the appearance of each side effect and only ask for the intensity if you find it possible. For simple appearance of f.e. lymphedema or skin problems, mark '2 moderate'. Try to use the information voluntarily given by the patient effectively.*							
Inflamed Rectum (Proctitis)	none	**1** rectal discomfort	**2** rectal bleeding	**3** incontinence (Colostoma?)		**4** life threat	**999**
Diarrhea (stools>baseline!)	none	**1** <4 stools/d	**2** 4-6 stools/d	**3** >=7 stools/d, incontinence		**4** life threat	**999**
Urinary Problems	none	**1** mild: urgency/ frequency↑	**2** ↑↑+ bloody urine	**3** ↑↑↑ surgical intervention necessary		**4** life threat	**999**
Incontinence (Fistula?)	none	**1** occasional (+cough)	**2** spontaeneous	**3** intervention! selfcare↓			**999**
Passage of urine / stool through the vagina	none	1 mild	2 moderate	3 severe			999
lymphedema (leg swelling?)	none	**1** trace of thickening	**2** marked discoloration	**3** severe selfcare↓			**999**
Fatigue/tired?	none	**1** relieved by rest	**2** not relieved by rest	**3** selfcare↓			**999**
any skin problems in the radiated area? (itching, swelling)	none	**1** mild	**2** modera te	**3** severe	**4** life threatening		**999**
Comments or any other side effects the patient noticed after radiation:							
Symptoms *Ask for the appearance of each side effect and try to find out ist intensity with the help of the grading scale below. Try to use the information voluntarily given by the patient effectively.*							
Vaginal bleeding	none	**1** postcoital	**2** brownish	**3** spontaneous	**4** life threat		**999**
Discharge	none	1 mild	2 moderate	3 severe	4 life threat		999
constipation	none	1 mild	2 moderate	3 severe	4 life threat		999
Pelvic pain	none	**1** mild	**2** moderate	**3** severe			**999**
Comments or any other symptoms the patient noticed after radiation:							
ECOG	**0** fully active	**1** lightly restricted	**2** unable to work	**3** limited selfcare, >50% in bed	**4** bedbound, no selfcare	**5** dead	**999**

Figure 17: Questionnaire for telephone follow-up, conducted by study nurse in Amharic and Oromo.

9.5 Estimated overall survival according to stage of FIGO

Table 23: Cumulative probability of overall survival after one and two years with 95% CI and estimated median survival time for all patients and different stages of FIGO.

	Overall survival (95% CI)				Estimated median survival time [months, 95% CI]	
	after one year		after two years			
	Main analysis	Worst-case analysis	Main analysis	Worst-case analysis	Main analysis	Worst-case analysis
all patients	83.4 (80.6-86.2)	54.9 (51.7-58.1)	63.2 (58.2-68.2)	35.6 (31.8-39.4)	34.3 (28.9-39.7)	15 (13.1-16.8)
postOP	94 (87.2-100)	80.7 (68.3-93.1)	94.6 (87.2-100)	80.7 (68.3-93.1)	-	-
Recurrence after surgery	91.2 (82.8-99.6)	68.5 (55.5-81.5)	68.2 (50.2-86.2)	43.8 (27.6-60)	-	21
FIGO IIa	75 (31.6-100)	75 (31.6-100)	37.5 (0-94.7)	37.5 (0-94.7)	13.8	13.8
FIGO IIb	92.5 (88.1-96.9)	81.9 (75.9-87.9)	79.6 (70.4-88.8)	60.1 (50.1-70.1)	-	29.5
FIGO IIIa	77.4 (59.4-95.4)	57.6 (39-76.2)	63.1 (39.5-86.7)	41 (20-62)	-	21.2
FIGO IIIb	81.6 (77.4-85.8)	51.7 (47.1-56.3)	56.1 (48.5-63.7)	29.9 (24.7-35.1)	25.9	13
FIGO IVa	71.6 (59.2-84)	29.6 (21-38.2)	49.3 (32.5-66.1)	17.2 (9.6-24.8)	21.9	4.2
FIGO IVb	48.7 (19.7-77.7)	14.1 (3.3-24.9)	-	-	12	3.3
Recurrence	60 (16.2-100)	42.9 (5.5-80.3)	40 (0-83.8)	14.3 (0-40.7)	12.5	10



N at risk grouped by stage of FIGO

PostOP	43	37	23	19	13	4	1	0	0
FIGO IIb	177	162	113	70	38	15	6	2	2
RecOP*	51	40	34	16	10	2	0	0	0
FIGO IIIa	29	21	15	12	6	1	0	0	0
Recurrence	7	4	3	1	1	1	1	1	1
FIGO IIIb	525	346	210	107	5	30	7	0	0
FIGO IIa	4	4	2	1	0	0	0	0	0
FIGO IVb	51	18	5	0	0	0	0	0	0
FIGO IVa	122	46	31	19	12	7	2	0	0

	43	37	23	19	13	4	1	0	0
	177	163	113	70	38	15	6	2	2
	4	4	2	1	0	0	0	0	0
	51	40	34	16	10	2	0	0	0
	29	21	15	12	6	1	0	0	0
	525	348	210	107	58	30	7	0	0
	7	4	3	1	1	1	1	1	1
	122	46	31	19	12	7	2	0	0
	51	18	5	0	0	0	0	0	0

Figure 18: Crude overall survival of all patients after RT at TAHRC 2008-2012 in main (left) and worst-case (right) analysis, grouped by stage of FIGO.

Curriculum vitae

Ulrike Mölle

born 21.01.1989 in Berlin

Work Experience

Since April 2017	Medical doctor in training for Otolaryngology, St. Georg Hospital, Leipzig
Nov 2016 – Mar 2017	Medical doctor in training for Internal Medicine, St. Georg Hospital, Leipzig

Education

Dec 2015 – Apr 2016	Internship Otolaryngology (University Hospital, Leipzig)
Sep – Dec 2015	Internship Internal Medicine (Borna)
May – Sep 2015	Internship General Surgery (Sursee, Switzerland)
2011 – 2012	Medical studies at University of Granada, Spain
2008 – 2016	Medical studies at University of Leipzig
2007	Highschool degree at Sächsisches Landesgymnasium St. Afra, Meißen

Research

Dec 2016	Public defense of dissertation
2012-2013	Data collection in Addis Ababa, Ethiopia

Publication

Kantelhardt, E. J.; Moelle, U.; Begoihn, M.; Addissie, A.; Trocchi, P.; Yonas, B. et al. (2014): Cervical Cancer in Ethiopia: Survival of 1,059 Patients Who Received Oncologic Therapy. In Oncologist. 19 (7), pp. 727–734.

Public presentations on radiotherapy for cervical cancer in Ethiopia

2016	DTG (Conference of the German Tropical Medicine society), Bonn
2015	AORTIC (10th International Conference on Cancer in Africa), Morocco
2014	DGGG (Conference of the German Society for Gynecology and Obstetrics), Munich

Language skills

Mother tongue	German
Mastery	English
Effective Operational Proficiency	Spanish
Upper intemediate	French
Basic skills	Amharic, Hebrew, Latin, Arabic

Declaration of originality

1. I declare that I have not completed or initiated a doctorate procedure at any other university.

2. *Declaration concerning the truth of information given*

   I declare that all information given is accurate and complete. The thesis has not been used previously at this or any other university in order to achieve an academic degree.

3. *Declaration under Oath*

   I declare under oath that this thesis is my own work entirely and has been written without any help from other people. I met all regulations of good scientific practice and I used only the sources mentioned and included all the citations correctly both in word or content. The data this study is based on, were collected at TAHRC in Addis Ababa by Matthias Begoihn and myself. The number of patient files entered into the database was equally shared among us.

Place and date

Ulrike Mölle
Signature

Acknowledgement

First and foremost, I would like to thank my supervisor Dr. Eva-Johanna Kantelhardt at the Martin-Luther University Halle-Wittenberg, for scientific guidance and reliable, immediate advice especially during my stay in Ethiopia. Thanks to her experiences and her social network in Addis Ababa, the data collection went smoothly. I was lucky to have a supervisor with a truly inspiring dedication beyond research on gynecologic cancers in a low-resource setting and towards an actual improvement of the reality of women's lifes in Ethiopia. Her commitment is encouraging.

Then, I would like to thank Matthias Begoihn with whom I collected the data of the 1009 patients we observed for this study. We shared housing, food, early morning and late night transport issues in Addis Ababa and motivated each other, whenever complications arose.

I owe my gratitude to Prof. Dr. Vordermark and Prof. Dr. Thomssen at Martin-Luther University Halle-Wittenberg. Both supervised my work and provided well-thought and inspiring impulses, which notably facilitated the process of conception and data analysis for this dissertation. I especially want to express my gratitute towards Prof. Dr. Vordermark as he proofread this work and drew my attention to improvable sections of this dissertation. Dr. Pietro Trocchi at Martin-Luther University Halle-Wittenberg added helpful advice - I am very thankful for his collaboration.

This thesis would not have been possible without the commitment of numerous staff members at TAHRC. Above all, I am very grateful to the oncologists Dr. Aynalem and Dr. Mathewos, who introduced me to the daily practice of RT planning at TAHRC and both of whom patiently answered my innumerable questions. I would like to thank Dr. Tausjo, Dr. Wondemagegnehu and Dr. Bogale for supporting this study by clarifying numerous uncertainties towards RT at TAHRC. I am very glad for the opportunity to share an office in the cancer registry of TAHRC with Mr. Timotewos Genebo, Mr. Solomon Asmare and Mrs. Ayalnesh Bekele. Not only for daily logistical and moral support, especially by Mr. Timotewos, which was far beyond his responsibilities, but also for a very pleasant working atmosphere. Importantly, we would not have been able to collect any patient data without the help of the record keepers at TAHRC: Mrs. Mulu and Mr. Neme. The study nurse Mrs. Tinsae Gelatae provided essential information on follow-up of the patients by calling them or their relatives by phone, proving a high level of empathy in such sensitive situations. I additionally want to thank her, as she conducted the pilot testing of the Amharic versions of QoL QLQ C30 and CX24 as my Amharic was not sufficient for this matter. I am very grateful for all translators involved into the translational process to create an Amharic version of these questionnaires, all of whom participated voluntarily and without payment: Dr. Aynalem, Dr. Zelalem, Dr. Lee, Mr. Rohwan and Mrs. Bahru.

Dr. Paul C. Bauer and Jakob H. Malsy meticulously proofread my work. I owe my gratitude to both of them. Furthermore, I would like to thank AG FIDE e.V. for sponsoring my flight to and from Ethiopia and inviting me to present my results at their conference.

Eventually, I would love to send warm thanks to Etagegne, the lady I shared a house in Addis Ababa with. I am deeply grateful for her bounteousness and the numerous stimulating conversations we shared while enjoying good food. Her strength and determination as a single woman in Ethiopia was truly inspiring. The same applies to my Amharic teacher Zebib Sultan, who opened my eyes and ears to the beauty of this unique language and enabled me to converse.

Ultimately, I would like to thank my family for their enduring support, understanding and interest in my work. And I would also like to thank my close friends (and climbing partners) for offering welcome distraction, such as stunning hikes far from Addis' pall of smog.

I am grateful to all of the persons I mentioned above. Nonetheless, I would like to thank everyone else, who somehow was involved in the process of this work and whom I did not name above. I believe, that the present study is a result of the contribution of a large amount of people and I am grateful to be able to present the findings within the framework of this dissertation thesis. Above all, I am thankful to the fortunate opportunity to have been able to contribute time and money to this research. The process of working on this dissertation was enriching and enabled me to constantly learn and understand more.