OXFORD

European Society of Endocrine Surgeons (ESES) consensus statement on advanced thyroid cancer: definitions and management

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Introduction

Thyroid cancer is the most common endocrine malignancy and consists of a diverse group of histological entities[1]. Although ranging from indolent and well differentiated to aggressive and rapidly developing carcinomas, advanced disease may present in each histological subtype. Even though the characteristics of advanced thyroid cancer are recognized intuitively by experienced surgeons in the field, a common definition among scientific societies is yet to be reached[2]. General definitions of advanced disease are included in the broader management guidelines for each cancer subtype, such as the American Thyroid Association (ATA) guidelines for differentiated thyroid cancer (DTC)[3], medullary thyroid cancer (MTC)[4], and anaplastic thyroid cancer (ATC)[5]. In the European setting, the 2019 European Society of Medical Oncology (ESMO) guideline[6] on thyroid cancer includes a subsection on the management of advanced disease for each thyroid cancer type. Given the recent progress and new developments in targeted therapy, depending on the genetic alterations of the tumour, new interest has emerged in better defining advanced thyroid disease and selecting candidates for tailored therapy, either in an adjuvant systemic or neoadjuvant setting. This is reflected in the most recent published position statement by the American Head and Neck Society (AHNS) and International Thyroid Oncology Group[7], as well as the clinical practice guidelines update by ESMO for the use of systemic therapy in advanced thyroid cancer[8]. Nevertheless, existing efforts to define advanced thyroid cancer and to produce management guidelines have been burdened by a common denominator, the lack of high-quality evidence, especially regarding definitions and surgical management.

In May 2023, the European Society of Endocrine Surgeons (ESES) organized the 10th biennial conference with the topic 'Consensus meeting on advanced endocrine malignancies', in Mainz (Germany). One working group was tasked to evaluate the current evidence on advanced thyroid carcinoma, and to produce a position statement to be discussed and voted for by the ESES assembly at the Mainz conference. The members of this working group are the authors of the present manuscript.

Methods
Working group composition, original draft, and statements production

The working group consisted of 14 surgeons with expertise in the management of thyroid malignancies and an endocrinologist (C.D.) with extensive involvement in similar projects[6,8]. The working group was tasked with carrying out an extensive up-to-date literature review, constructing the initial draft, and

proposing subsequent relevant statements. This process was undertaken via web-based meetings and supplemented with additional regular electronic communications. Performing a systematic review of the literature with the aims set for this position statement was deemed non-feasible and counterintuitive for several reasons. First, the term 'advanced thyroid cancer' is not clearly defined, which would result in the omission of a multitude of publications, whereas, in contrast, a significant number of publications include this term without referring to the specific criteria used. Hence, the literature search was performed extensively by subgroups of three or four working group members for each section, whereas the remaining working group members were invited to review the data and supplement the results with relevant, high-quality references. In addition, several statements were the products of expert opinion because no relevant supporting data had been published at the time. The initial draft and relevant statements were then circulated among the working group members for revisions before commencing the modified Delphi process.

Panel composition and modified Delphi process

The modified Delphi method is a well established process used to achieve consensus systematically, and has been recently applied in several publications on thyroid cancer[7,9,10]. To reflect the diversity of clinical practice in Europe, while maintaining high expertise among contributing voters, the working group invited members of the Executive Council of ESES, the examiners of the Division of Endocrine Surgery, and the national delegates from each country represented in the ESES, to participate in a two-round modified Delphi process. The latter, along with the working group members, formed a panel of 41 participants (full list in Acknowledgements) who voted on a dedicated invite-only electronic interface, powered by Qualtrics© (Qualtrics, Provo, UT, USA) thus providing coded data for analysis. Panellists voted on their level of agreement according to a Likert scale ranging from 1 (strongly disagree) to 9 (strongly agree). The survey also allowed panellists to provide feedback and free-text comments on the statements during the first phase. Panellists with missing answers or with difficulties interpreting the statements were contacted individually through subsequent mailings to provide definite answers. Appropriate revisions of the initial statements were made by the methodology leadership (M.R., N.V.) according to the first survey feedback.

The statements were considered to meet consensus if there was a mean score of at least 7.0 (agree), and either four or fewer outlier responses, or six or fewer outlier responses with fewer than three responses below 5 (disagreement). Near-consensus was assigned to statements with a mean of 6.50 or greater and, in addition, eight or fewer negative outliers. Non-consensus was the default if the above conditions were not met. Outliers were defined by any value at least 2 Likert points away from the mean. Negative outliers refer to outliers where the response was that of disagreement (below 5). The quality of evidence for each statement was stratified as high, moderate, low, or expert opinion, depending on the type of publication that data were extracted from. Data stemming from RCTs were considered to represent high-quality evidence, whereas those from non-randomized prospective trials were of moderate quality, and data from retrospective analyses or case series were deemed to be of low quality. Where no supportive data were available, the term expert opinion was used.

Finalization of position statement and organizational approval

During the 10th ESES biennial conference in Mainz, Germany, the results of the survey were discussed in a dedicated General Assembly (GA) meeting. For statements that reached near-consensus, a GA vote was undertaken, both to classify the statements as accepted or not, and to honour the ESES tradition of active participation of all members in position statement production[11,12]. Voting options were limited to agree—neutral—disagree. An agreement level of equal to or more than 80% of total voters with less than 10% negative votes was set as a threshold for reaching consensus. The entirety of the consensus statement was finally approved by the GA, and thereby has full organizational support as an ESES statement. A summary of the statements is presented in *Tables S1–S6*.

Results
Definitions and incidence

Concerning extent, invasiveness, and distant spread, advanced thyroid cancer has been associated with the presence of one, or a combination, of three main features: local, regional, and distant advanced disease. Evaluating all 25 262 thyroid cancer cases registered between 1 January 2015 and 31 December 2021 in the Eurocrine® registry, 3917 were considered to be characterized as advanced disease. Distant metastases were present in 525 patients (2.1%), extended regional (nodal) disease in 3008 (11.9%), and locally advanced disease in 1147 (4.5%) (unpublished data - M.R., N.V., T.M.).

Most of these features are well defined in existing classification systems, such as the eighth edition of the AJCC Staging Manual[13]. The focus, however, of such classifications is oncological parameters, such as mortality, and they were not created to portray with accuracy a complex issue such as advanced thyroid disease. To better capture this concept, disease-specific morbidity, as well as the surgical and non-surgical challenges of managing these patients, should also be considered. That said, the TNM classification is globally the most widely recognized and used system and, in that sense, any major deviations from its application when defining advanced disease might render any new definition impractical for everyday clinical and research use.

Locally advanced disease

Locally advanced disease in thyroid cancer has been associated repeatedly with worse prognosis and increased mortality both for DTC[14–17] and MTC[18–22]. Morbid sequelae of local invasion, such as airway obstruction and haemorrhage, are commonly involved in disease-specific causes of death from DTC[15,16]. This is also depicted in the eighth edition of the AJCC classification, in which the presence of T4 tumours upstages patients from II to III (for age 55 years and over) in DTC, from III to IVa for MTC, and from IVa to IVb in anaplastic cancer[13]. Concerning the point of infiltration among T4 tumours, the most frequent site reported is the recurrent laryngeal nerve (RLN) in up to 69% of patients, followed by the trachea/larynx in up to 42%, and the oesophagus/pharynx in 21%[23–27]. Fortunately, intraluminal tracheal and oesophageal infiltration, which carry a worse prognosis, are less common[25,26]. T3b tumours, although infiltrative, mainly concern the strap muscles. *En bloc* removal of the strap muscles can be performed quite easily in most centres, without the need for reconstruction or accompanied by

increased complication rates for the patient[9]. In addition, gross extrathyroidal extension (ETE) involving only the strap muscles does not affect disease-specific survival according to recent publications[14,28,29]. As such, T3b tumours could be omitted from the definition of locally advanced cancer. Another controversial point in defining locally advanced tumours is infiltration of the RLN alone, regarding which there are discrepancies in the literature. In the landmark study by McCaffrey *et al.*[23], which analysed 262 patients with invasive papillary cancer, no significant independent impact on survival was shown with muscle, laryngeal, and RLN invasion. When only the RLN was involved, favourable outcomes were also reported by Ito *et al.*[30] concerning relapse-free survival, whereas other research groups reported no difference in disease-specific survival[14]. Regardless of oncological outcomes, management of RLN infiltration demands a high level of surgical expertise in balancing preoperative and intraoperative options with local disease control and patient expectations, because voice complications and impaired swallowing function can be permanent and debilitating[31–33].

Statement 1: All thyroid primary malignancies classified as pT4 according to the AJCC 8th edition have to be considered locally advanced tumours.
    Consensus: Yes (8.05)
Outliers: 2
Evidence level: Low
Except for invasion of subcutaneous soft tissue
Consensus: No (4.72)
Outliers: 32
Evidence level: Low
Except for RLN invasion.
Consensus: No (3.92)
Outliers: 33
Evidence level: Low

Regional advanced disease

Regional lymph node metastases are commonly observed both in patients with DTC and those with MTC. Metastases to the regional lymph nodes occur in approximately 30–80% of patients with papillary thyroid carcinoma (PTC)[34,35] and 34–81% of those with MTC[36–40]. The impact of nodal involvement in DTC has been verified in large studies of the Surveillance, Epidemiology, and End Results database. Podnos *et al.*[41] reported that the overall survival rate at 14 years was 82% for patients with node-negative and 79% for those with node-positive disease ($P < 0.050$), whereas others[42] observed that cervical lymph node metastases conferred an independent risk of death in all patients with follicular carcinoma, and in patients with PTC aged at least 45 years, but did not affect survival in patients with PTC younger than 45 years. Although not portrayed in the AJCC eighth edition stratification, individual publications have consistently reported a worse prognosis in terms of disease-specific survival and recurrence in patients with N1b compared with N1a disease, especially in older age groups[43–47]. For patients with MTC, the HR for disease-specific survival in patients with regional lymphadenopathy was 9.44 (1.62 to 56 - CI 95%)[48]. Neck dissections have been described as one of the most complicated operations of the human body, requiring expert knowledge of regional anatomy and expertise[49]. Surgical excision of bulky or extensive central and lateral neck disease has been associated with an increased risk of complications,

including RLN injury, hypoparathyroidism, and, especially for the lateral neck, injury to various critical neurovascular structures and lymphatic leak[50–53]. Concerning mediastinal nodes in PTC, in an insightful publication by Moritani[54], patients requiring sternotomy for nodal disease excision had significantly worse disease-free survival than those who underwent cervicotomy alone. In patients with MTC mediastinal nodal disease at presentation, Machens *et al.*[55] showed this to have prognostic significance equivalent to the presence of distant metastatic disease. Two more features can be associated with advanced cancer: bulky nodal disease and extranodal extension (ENE). According to the 2015 ATA guidelines[3], patients with PTC are classified into high-risk groups for recurrence if any metastatic lymph node is 3 cm or larger. Lymph node metastasis size is, however, not included in the AJCC staging system[13], despite several publications supporting the notion that larger lymph node metastases are associated with worse prognosis[46,56–58]. Concerning ENE, although definitions and populations vary between studies, there is an overwhelming number of publications supporting its detrimental impact on disease-free and disease-specific survival, and it has been incorporated as a significant risk factor for recurrence in the ATA 2015 guidelines[3,58–60].

Statement 2: Thyroid malignancies have to be considered regionally advanced when one or more of the following features are present:
    Bulky (at least 3 cm) metastatic nodes or ENE, independently of neck compartment involved (central and/or lateral).
    Consensus: Yes (7.49)
Outliers: 4
Evidence level: Low
ENE, independently of neck compartment involved (central and/or lateral).
Consensus: Yes (7.43)
Outliers: 5
Evidence level: Low
Lateral neck nodal disease.
Consensus: No (6.17)
Outliers: 20
Evidence level: Low
Mediastinal nodal disease (below innominate artery level).
Consensus: Yes (7.68)
Outliers: 6
Evidence level: Low

Metastatic disease

Metastatic disease is one of the main characteristics of advanced thyroid cancer, and its presence significantly alters patient management[3–6,8]. In DTC, although patients may achieve favourable long-term outcomes[61], metastatic disease significantly influences disease-specific and overall survival[13,47]. Especially for patients with MTC, the presence of distant metastasis detrimentally lowers 10-year survival rates to 40%, compared with rates in patients with regional (75%) or local (96%) disease only[21,22,62]. Surgical resection of locoregional disease in metastatic thyroid cancer is generally recommended in DTC, when appropriate and feasible, to both prevent complications of local progression and facilitate adjuvant treatment with radioactive iodine (RAI)[3]. In MTC, more conservative surgical options have been suggested, balancing surgical morbidity in terms of speech, swallowing, and parathyroid function with the potential oncological benefits of locoregional control[4].

Statement 3: In the presence of distant metastasis, thyroid tumours are considered advanced, independently of local and regional status.
Consensus: Yes (8.49)
Outliers: 1
Evidence level: Low

Special considerations- Anaplastic thyroid cancer

ATC is one of the most aggressive and lethal malignancies in humans. Although accounting for only 1–2% of all thyroid cancers[63,64], it is responsible for up to 50% of thyroid cancer deaths[63]. The median life expectancy of patients with ATC is 4–5 months, 1-year survival rates are lower than 20%, and its disease-specific mortality rate reaches 100%[65,66]. In addition, the majority of patients present with distant metastases and locoregional extension, requiring a tailored multidisciplinary approach[5,67].

Statement 4: All anaplastic thyroid carcinomas should be considered as advanced thyroid cancer.
Consensus: Yes (8.31)
Outliers: 4
Evidence level: High
Exceptions to this might apply for small (less than 2 cm) intrathyroidal tumours without distant metastasis.
Consensus: No (5.73)
Outliers: 26
Evidence level: Low

Special considerations - Poorly differentiated thyroid cancer and aggressive histological variants of papillary thyroid carcinoma

Poorly differentiated thyroid carcinoma (PDTC) has been reported as the main cause of death from non-anaplastic follicular cell-derived thyroid cancer[68,69]. Because of its distinct morphological and behavioural characteristics, it holds an intermediate position between differentiated and fully dedifferentiated ATCs[70]. Clinical studies of PDTC are limited because of the relative rarity of the disease, but the aggressive nature and poor prognosis of this entity have been demonstrated repeatedly[71–73], and current staging might underestimate its potential detrimental prognosis especially for stage I and II disease[69]. Aggressive histological tumour variants, that is columnar cell variant, hobnail variant, tall cell variant of PTC, and features such as tumour necrosis, and high mitotic activity and Ki-67 labelling index, have been related to increased risk of recurrence and/or worsening of disease-free survival and, as such, could potentially be considered as advanced disease[74–77].

Statement 5: PDTCs should be considered as advanced thyroid cancer.
Near-consensus: (6.98) Rejected
Outliers: 19
Evidence level: Low
GA voting: Agree 65.8%, Disagree 23.00%, Neutral 11.2%
Aggressive histological variants of PTC and tumours with aggressive histological components should be considered as advanced thyroid cancer.
Consensus: No (5.3)
Outliers: 23
Evidence level: Low

Special considerations - Indications for resection of inoperable tumours

Inoperability and resectability of thyroid tumours are subjective issues. Only experienced, appropriately trained and high-volume endocrine surgeons should judge a thyroid tumour as inoperable. Where locoregional disease control requires extensive interventions such as tracheal resection, laryngectomy or oesophagectomy, the oncological benefits of such an intervention and patient preferences and wishes should be weighed against surgical morbidity[2,9]. Finally, a multidisciplinary team (MDT) should manage patients in all phases of care, including neoadjuvant treatment if appropriate[8,78].

Statement 6: Indications for resection in locoregionally advanced thyroid carcinomas have to be evaluated in a multidisciplinary setting, balancing oncological benefits, potential surgical morbidity, patient life expectations, quality of life after resections, and patient willingness for treatment.
Consensus: Yes (8.71)
Outliers: 0
Evidence level: Expert opinion
Considering recent advancements in neoadjuvant and new targeted systemic therapies, resectability status is a dynamic process, which must be re-evaluated based on systemic treatment response.
Consensus: Yes (8.41)
Outliers: 0
Evidence level: Low

Special considerations - Recurrence

Management of recurrent or persistent disease can be challenging and such patients should be treated in high-volume referral centres. The decision to reoperate should be made by a MDT, as patients with regional disease are at high risk of disease persistence and new recurrence[79]. The presence of scar tissue and alterations in the thyroid bed anatomy pose an additional risk of complications such as RLN injury and hypoparathyroidism[80,81], although in experienced centres reoperations seem to be safe and feasible[82,83].

Statement 7: Recurrent thyroid disease is not a sufficient condition by itself to characterize a thyroid carcinoma as advanced.
Consensus: Yes (7.44)
Outliers: 4
Evidence level: Low
Persistent thyroid disease is not a sufficient condition by itself to characterize a thyroid carcinoma as advanced
Consensus: Yes (7.49)
Outliers: 4
Evidence level: Low

Preoperative management and work-up
Imaging

In patients with advanced thyroid cancer, in addition to the ultrasound imaging, neck axial CT or neck MRI is recommended[84]. Neck CT and/or MRI is used to evaluate the invasion of surrounding structures, including large vessels, and in deciding whether to perform a tracheobronchoscopy to assess the extent of invasion of the airway lumen. CT is considered superior to ultrasonography and more reproducible for precise

three-dimensional assessment of airway invasion[9], with a mean sensitivity, specificity, and accuracy in detecting tracheal invasion of around 60, 90, and 83% respectively[85].

Superficial infiltration of the pharyngolaryngotracheal system is particularly difficult to determine. The extent of tracheal infiltration has long been stratified by Shin *et al.*, as well as other teams[86–89]. In stage I, infiltration includes perichondral invasion with adherence to the trachea, but no airway resection is required; in stage II, the cartilage is invaded, but not the mucosa; and in stage III or IV, the mucosa is invaded or the spread extends into the lumen respectively. CT should be performed with contrast, to give the most precise information and to distinguish superficial (Shin I–II) *versus* deeper (Shin III–IV) infiltration with a diagnostic accuracy potentially reaching more than 90%. MRI seems to have lower diagnostic accuracy than ultrasound imaging and CT, with a tendency to overestimate the actual depth of airway invasion[90]. In summary, cross-sectional neck CT with contrast is recommended in patients with thyroid carcinomas with evident or high clinical suspicion of locoregional advanced disease, as described previously, as well as large primary tumours (4 cm or larger), and in MTC where there is extensive neck disease, evidence of distant metastases or a calcitonin level above 500 pg/ml. It is also imperative in ATC to obtain adequate pretreatment local staging[2].

MRI may be useful if there is suspicion of oesophageal invasion. MRI has a sensitivity of 80% and specificity of 94% for detecting oesophageal invasion, although the effectiveness of MRI in deep layers is slightly reduced[91].

The role of metabolic imaging with PET using [^{18}F] fluorodeoxyglucose (FDG) seems to be a valuable diagnostic tool in patients with non-iodine-avid thyroid tumours, particularly where there are gradual increases in serum thyroglobulin levels or high suspicion based on other imaging tests. FDG PET has also been very useful in patients with PDTC or ATC, which are known to have increased glucose metabolism and limited or no radioiodine uptake. FDG PET can provide prognostic information and therefore may be useful in identifying patients at higher risk of recurrent and metastatic disease[92].

Endoscopic evaluation

Laryngoscopy is mandatory before any thyroid procedure. This is particularly true in the presence of suspected or proven advanced thyroid carcinoma[9,93]. Indeed, up to 30% of cases of laryngeal nerve invasion are asymptomatic[94]. In fact, finding a unilateral RLN palsy should prompt the request for more targeted investigations as mentioned above (cross-sectional imaging studies) to determine and precisely evaluate potential airway involvement, both quantifying its radial (depth) and axial extent. Laryngotracheoscopy allows appreciation of airway invasion when the airway submucosa is reached (Shin III–IV) but misses Shin I–II tracheal invasion in up to 10% of the series of patients evaluated with endoscopy and imaging[95]. Endobronchial ultrasonography (EBUS) is the last imaging technique used for assessment of the presence and degree of airway invasion by thyroid cancer, with a sensitivity and specificity of 92 and 83% respectively[96]. EBUS is still, however, used relatively infrequently owing to its high cost and limited utility in evaluating tumours infiltrating at the level of the upper thyroid poles[85]. Oesophagoscopy should be performed selectively when endoluminal penetration of a tumour is

suspected, based on cross-sectional imaging or, rarely, based on symptoms[97].

Statement 8: Assessment of the aerodigestive tract by means of sectional imaging, laryngoscopy, and digestive endoscopy is mandatory in all patients with advanced thyroid cancer and suspected aerodigestive tract involvement.
Consensus: Yes (7.85)
Outliers: 2
Evidence level: Low

Fine-needle aspiration and core biopsy

Fine-needle aspiration (FNA) is generally the first type of biopsy undertaken, but the cytological diagnosis of aggressive types of thyroid cancer may not be easy for the pathologist, and is often associated with interobserver variability. When the cellular yield is insufficient, core biopsy may be diagnostic and often permits a broader range of molecular testing[98]. If the FNA results are limited or non-diagnostic, core biopsy should be performed to confirm the diagnosis[99]. Some cases of advanced thyroid cancer/ ATC are, however, diagnosed only after surgical/open biopsy despite the patients undergoing FNA and/or core biopsy.

Molecular testing

Advances in understanding of the molecular biology of thyroid tumours have led to the development and approval of several targeted therapies for patients with advanced thyroid cancer. This allows the delivery of a coordinated, evidenced-based, and individualized treatment plan to the patient, and there may be benefit from referral to a tertiary-care setting where additional resources are available.

BRAF V600E mutational status should be evaluated in patients with advanced DTC/PDTC to search for additional therapeutic options, and especially in patients with ATC, as this information can be used for targeted BRAF inhibition[5]. Somatic mutational testing for *RET*, *NTRK1*, *NTRK3*, and *ALK* gene fusions should be undertaken for patients with advanced DTC testing negative for *BRAF* V600E. This can be achieved optimally using next-generation sequencing of tumour RNA or DNA where available, or other validated approaches including fluorescence hybridization[7].

Patients with locally advanced MTC may be offered somatic *RET* mutational testing if the patient is to be considered for neoadjuvant systemic therapy or as part of a clinical trial[5].

In recent years, the tumour mutational burden has emerged as a promising response factor to immunotherapy. It should be analysed before initiation of immunotherapy as it may inform on response to antiprogrammed cell death 1 therapy. Although it is true that experience in advanced thyroid carcinoma is limited, studies of solid tumours, including thyroid cancers, have demonstrated that high tumour mutational burden is associated with response to pembrolizumab[100].

Statement 9: Depending on local availability, somatic mutational testing should be offered to patients with advanced thyroid disease.
Consensus: Yes (8)
Outliers: 2
Evidence level: Low
Optimally, a multiplexed next-generation sequencing panel should be used.
Consensus: Yes (7.67)

Outliers: 5
Evidence level: High
Alternatively, a step-up approach could be followed, based on individual patient and tumour characteristics.
Near-consensus: (7.28) Approved
Outliers: 7
Evidence level: Low
GA voting: Agree: 83.06%, Disagree: 7.65%, Neutral: 9.29%
In regions where availability is limited, surgery should not be postponed.
Near-consensus: (7.29) Approved
Outliers: 7
Evidence level: Expert opinion
GA voting: Agree: 83.06%, Disagree: 7.65%, Neutral: 9.29%

Patient information, consent, and preferences

Advanced thyroid cancer is a foreboding disease, characterized by locoregional infiltration of vital structures of the aerodigestive tract and/or distant metastases, and thus accompanied with high rates of morbidity, worsening of quality of life, and high risk of recurrence and death[2].

After completing the preoperative evaluation, diagnostic procedures and MDT assessment, patients should be fully informed about expectations regarding possible complications, postoperative outcomes, and chances of disease-free survival and death. In general, patient information should include type and extent of operation, use of neuromonitoring and autofluorescence, duration of hospital stay, rate of complications, and risk of recurrence or reoperation[101,102].

As advanced thyroid cancer may affect voice, breathing, and swallowing functions, the complications should be presented in detail, and the morbidity depending on operation extent should be clarified thoroughly[9]. It is also of paramount importance to present the patient with the imminent risks of selecting a more conservative or neoadjuvant treatment, delaying surgery, or opting for no intervention at all[103,104].

The feasibility of achieving complete locoregional clearance of disease, and how it will be proven after operation, should also be included during the patient consent process. Treatment of advanced thyroid cancer may involve a long-term intertwined multidisciplinary process, and thus the potential postoperative types of treatment, depending on thyroid cancer histology, and their possible complications, should also be mentioned. Explaining the total rates of survival, quality of life after operation, and the need for adherence to follow-up is also essential. It is important to have direct and detailed conversations with patients before operation to enable them to understand their options and the potential sequelae of treatment. Some patients may prefer less aggressive surgical resection in favour of preserving voice and/or swallowing functions, whereas others may opt for a more aggressive surgical approach to maximize the chances of disease control or avoid the future need for active surveillance.

During preoperative communication with patients, intraoperative decision-making should be discussed, especially as it relates to management of the RLN and airway. It is imperative to review the impact of various surgical decisions on both functional and oncological outcomes so that patient choice is appropriately and adequately informed.

Statement 10: Informed consent should be obtained after carefully elucidating to the patient the benefits and possible morbidity deriving from each treatment choice, as well as highlighting the oncological sequelae in case of patient denial or delay to intervention. Surgical extent and intraoperative concerns that might arise should also be discussed beforehand and patient preferences respected.
Consensus: Yes (8.76)
Outliers: 0
Evidence level: Expert opinion

Patient health status

Patient health status should be taken into consideration, and all co-morbidities must be accounted for and addressed if possible[3,105]. Cardiovascular and respiratory disorders should be under control and anticoagulants replaced with low molecular weight heparin.

Patients with advanced thyroid cancer, especially when the aerodigestive tract is involved, present with increased morbidity and may have anorexia, cachexia, and malnutrition, which deteriorate after operation, leading to compromised nutritional status[106]. Patient nutritional status should be assessed before surgery and during follow-up. This is becoming more critical as multikinase inhibitors (MKIs) are gaining ground[8] in the treatment of select patients with advanced thyroid cancer. MKIs may have reduced toxicity compared with conventional chemotherapy, but present different challenges in patient management[106]. As MKIs may cause weight loss, nausea, anorexia, stomatitis, and diarrhoea, leading to further deterioration in health, ensuring and maintaining adequate nutrition during preoperative and postoperative care is critical.

Head and neck malignancies can be associated with malnutrition owing to cancer-specific symptoms, such as dysphagia, anorexia, and malabsorption. In locally advanced thyroid cancer and anaplastic cancer, for which the use of MKI systemic therapy might be proposed as adjuvant, as well as neoadjuvant, treatment, maintaining good nutrition status is critical[7,8].

Especially in patients with suspicion of oesophageal involvement or distant metastasis, and/or candidates for MKI treatment, nutritional screening should be carried out before surgical treatment and initiation of MKI treatment by evaluation of BMI, weight loss, food intake, and measurement of caloric intake by several validated tools approved by the European Society for Clinical Nutrition and Metabolism[106]. Nutritional therapy should start even in patients who are not yet malnourished, with oral intake first; enteral and parenteral fluids should be considered in the event of more severe malnutrition.

Statement 11: The health and nutritional status of selected patients with advanced thyroid cancer should be evaluated and ideally optimized before operations for advanced thyroid cancer, also taking into account the potential urgency of the operation.
Consensus: Yes (7.46)
Outliers: 5
Evidence level: Low

Multidisciplinary team

Optimal advanced thyroid cancer treatment goes way beyond the selection of an optimal surgical operation, leading to a disease-free neck, but also encompasses adjuvant therapy

options after operation, and neoadjuvant treatment in some patients[2,6,8]. As new therapeutic modalities for advanced thyroid cancer are constantly emerging, the need for evidence-based and competence-based decisions requires the assembly of a MDT to offer an individualized approach for each patient[7].

A MDT should consist of endocrinologists, endocrine/head and neck surgeons, nuclear medicine physicians, oncologists, radiotherapists, pathologists, and radiologists. For selected patients, thoracic, vascular, and/or other specialists should be invited to participate in the discussion. The MDT should be approved by the hospital and local authorities, and convene on a regular basis[107,108].

Tumour board representatives should follow the patient in the preoperative setting, evaluating all the diagnostic and molecular tests, make proposals on optimal treatment strategies, and plan follow-up and adjuvant therapy based on surgical findings, histology results, and patient preferences.

It is proposed that patients with advanced thyroid cancer are referred to tertiary institutions, holding multidisciplinary tumour boards, to be evaluated before any intervention is scheduled.

Statement 12: Patients with advanced thyroid cancer must be evaluated before and after surgery by a MDT, optimally consisting of an endocrinologist, endocrine/head and neck surgeon, nuclear medicine physician, oncologist, radiotherapist, pathologist, and radiologist.
  Consensus: Yes (8.12)
  Outliers: 3
  Evidence level: Low
  Oncologists should participate only in selected cases.
  Consensus: No (5.36)
  Outliers: 24
  Evidence level: Low

General treatment principles

As mentioned above, advanced thyroid cancer is optimally managed in a high-volume tertiary referral centre led by a MDT. Half of the disease-specific mortality from DTC is due to progressive invasion of the aerodigestive tract[109], with incomplete resection increasing the risk of local recurrence. In advanced cancer owing to an anaplastic tumour, neoadjuvant treatment strategies should form part of the initial management. A favourable therapeutic response may make the patient a candidate for later surgery and thus provide a new baseline for surgical decision-making.

Complete tumour clearance as part of the primary index procedure or in treatment of local recurrence is paramount, and improves the prognosis even in the presence of distant metastases. Five-year survival rates of up to of 90% have been described after full-wall tracheal resection. The management of tumours with infiltration of the trachea and/or oesophagus places the highest demands on the expertise of a MDT to develop and successfully implement a personalized therapeutic strategy. Preoperative assessment is vital to allow the execution of successful surgery. In resectable disease, the therapeutic aim is curative or achieving locoregional control as a minimum[110].

Several factors need to be considered before making a decision regarding a surgical approach: existing co-morbidities, the extent and depth of the infiltration of muscles, trachea and/or oesophagus, existing lymph node metastasis, and reconstruction options.

Statement 13: Surgery for advanced thyroid cancer should be performed only by high-volume surgeons, optimally in tertiary referral centres.
  Consensus: Yes (8.51)
  Outliers: 1
  Evidence level: Low
  Surgery for advanced thyroid cancer should be performed only by high-volume surgeons in tertiary referral centres when multiple surgical specialties are required.
  Consensus: No (7.1)
  Outliers: 9
  Evidence level: Low

Invasion of aerodigestive tract

Apart from the Shin classification[89] mentioned previously, the stages of laryngotracheal invasion have been further described by Dralle *et al.*[87] and Brauckhoff[88]. Several European centres prefer the latter classification[88], and so it will be described here in short. A distinction is made between four stages of infiltration depth. In stage I, the tumour adheres only to the perichondrium of the trachea or larynx. In stage II, there is superficial but no transmural infiltration. In contrast, in stage III, the tumour reaches the lamina propria of the tracheal mucosa but does not penetrate the epithelium. Finally, the stage 4 tumour presents with endoluminal infiltration of the tracheal mucosa. Depending on the site and depth of invasion, preservation of the recurrent nerve may be impossible; however, resection of both nerves will significantly add to morbidity, and adjunctive procedures will be required at a later stage to facilitate decannulation of the patient. Masuoka and Miyauchi[33] described strategies to be employed in recurrent nerve involvement. Voice and swallowing symptoms at presentation are common in advanced thyroid cancer involving infiltration of the trachea, oesophagus, and RLN. Oesophageal muscle is commonly infiltrated, but intraluminal invasion through the mucosa is exceedingly rare. Oesophageal muscle can be resected easily down to the mucosa, requiring no further repair.

In the setting of a pre-existing recurrent nerve palsy or in the presence of gross infiltration, resection of the nerve can be followed by non-selective reinnervation using a branch of ansa cervicalis. This is quite easy to do, requiring no more than two 8/0 Prolene® (Ethicon, Edinburgh, UK) sutures placed through the epineurium. This should be performed at the end of the procedure and after haemostasis before wound closure, and can be carried out with × 2.5–3.5 loupes or even the naked eye. Selective reinnervation using a branch of the phrenic nerve is for a specialist laryngologist. Optimal functionality does not occur, but reinnervation helps reduce intrinsic laryngeal muscle atrophy. Additional postoperative procedures, such as vocal cord augmentation, for example by injection of materials or implants in the paraglottic space, may improve voice outcomes.

Dralle *et al.*[87] and later Brauckhoff[88] described different scenarios for full-wall resections of the trachea. They distinguished resection involving disease at the laryngotracheal junction, in which preservation of the recurrent nerve on the infiltrated side is usually not possible or it is paralyzed at presentation, from more distal tracheal resection. Cervical and intrathoracic resections need to be distinguished, although many of these patients require a manubrial split as advanced

disease is usually seen in the elderly with a short spondylitic neck. Furthermore, access to the distal trachea is important to facilitate mobilization of the tracheal ends to achieve a tension-free anastomosis. It is important to avoid excessive mobilization as the blood supply to the trachea is poor and arises predominantly from horizontal paraoesophageal blood vessels. Up to 50% of the trachea can be resected with an end-to-end anastomosis in the young, but much less of the calcified and relatively inelastic elderly trachea. Pericardial release through a right thoracotomy can provide an extra 1–2 cm of mobilization. In anastomotic tension, laryngeal release by suprahyoid or infrahyoid techniques can be used, although swallowing rehabilitation and aspiration in these patients is invariably a postoperative challenge. Previous radiotherapy to the trachea has such a high complication rate for tracheal resection that it should be considered as a contraindication to surgery. The anastomosis invariably breaks down and salvage laryngectomy is the most likely result.

In disease involving the cricoid and larynx, the cricothyroid and constrictor muscles can be resected down to the hypopharyngeal mucosa with minimal morbidity. A cricoid shave can be performed but full cricoid cartilage should not be resected as this will destabilize the larynx. The lamina of the thyroid cartilage can be resected down to the perichondrium, but the anterior commissure should be preserved as this will affect the vocal cords at Broyles' ligament.

It is important to preserve, where possible, the internal branch of the superior laryngeal nerve as this will influence swallowing by affecting the afferent part of pharyngo-oesophageal phase swallowing.

Measures to reconstruct and secure an anastomosis have been described in detail by Musholt[111]. A significant risk comes from dehiscence of the tracheal anastomosis. As a result of radical tumour resection, the common carotid artery and the brachiocephalic trunk are in close proximity to the anastomosis. Air leaks with the spread of infection into the surgical area can subsequently lead to erosion of the vessel wall and fatal bleeding. To avoid this often lethal complication, it is recommended to reinforce the anastomotic site with remaining strap muscles, which at the same time can also strengthen the anastomosis.

Statement 14: In patients with invasion of the aerodigestive tract, where local disease control requires full-thickness excision, the decision on resection and eventual reconstruction must be tailored to patient and tumour characteristics in high-volume referral centres based on MDT discussion and willingness for treatment.
  Consensus: Yes (8.51)
  Outliers: 0
  Evidence level: Low

Statement 15: In patients with oesophageal involvement that does not extend into the lumen, only the involved musculature should be resected.
  Consensus: Yes (8.00)
  Outliers: 3
  Evidence level: Low

Resection in major vessel involvement

Where invasion of major vascular structures is suspected, preoperative planning must be thorough. Appropriate imaging must be performed, securing the patency of the Willis' circle when major arteries are involved[9,112]. Consultation and participation of vascular surgeons must be considered according to surgeon expertise and local protocols. The internal jugular vein (IJV) is the most commonly affected structure, mostly from bulky nodal disease[112]. For major vein involvement, if one IJV is affected, it can be excised without anticipating serious complications[9]. In patients with bilateral IJV involvement, reconstruction of one side with an autologous graft can be considered to avoid serious venous congestion of the head and neck[112,113]. Arterial (common carotid artery) involvement is less frequent and usually it is possible to preserve arterial integrity. If there is overt invasion, requiring arterial resection for complete tumour removal, management should be individualized and possibly planned at the MDT level before operation.

Statement 16: In unilateral IJV involvement, the vein may be excised without reconstruction if contralateral venous patency is adequate.
  Consensus: Yes (8.49)
  Outliers: 0
  Evidence level: Low

Statement 17: At least unilateral reconstruction of the IJV should be performed in bilateral involvement, after vascular surgeon consultation and/or participation.
  Near-consensus: (7.41) Rejected
  Outliers: 8
  Evidence level: Low
  GA voting: Agree: 74.30%, Disagree: 12.85%, Neutral: 12.85%

Lymph node involvement with extent of IIa–Vb and/or VI–VII compartments

In the presence of lateral compartment nodal disease, levels IIa, III, IV, and Vb are dissected routinely. Preservation of the spinal accessory nerve, with rare exceptions, should occur as shoulder morbidity can have a significant and negative impact on quality of life. In addition, attention to preserving the cervical plexus nerves is important, when feasible, to reduce neuropathic pain. In level IV, particular attention should be made to dissecting involved nodes from Chassaignac's triangle, a common site of nodal involvement. Meticulous caution is very important to avoid injury to the lymphatic duct, phrenic nerve, and sympathetic trunk during dissection. Lateral compartment dissection is invariably accompanied by dissection of level VI and occasionally VII central neck compartments. Prophylactic lateral and central neck surgery is not recommended in general, as this has not been shown to either improve survival or decrease locoregional recurrence. These strategies are discussed further in dedicated sections below.

Metastatic disease and systemic therapy

Patients with thyroid cancer who have locally advanced disease and/or distant metastases, and are not amenable to surgery, minimally invasive locoregional treatments or RAI, may warrant systemic therapy. The choice of whether and when to treat should be individual to each patient, and informed by a range of factors, including patient performance status, clinical manifestations of disease (because side-effects of medicinal therapy may significantly affect daily activities in an otherwise asymptomatic patient), tumour burden and site (with lesions likely to cause signs and symptoms of disease being referred for

treatment), documented and significant structural disease progression[114] (as a significant proportion of patients may have spontaneous and prolonged stability of disease[115]), and risk of disease progression based on tumour aggressiveness (poorly differentiated or undifferentiated malignancies).

Thus, the risks and benefits of systemic therapy should be weighed carefully after MDT assessment. The treatment landscape for advanced thyroid cancer has changed significantly in the past decade[8]. A number of MKIs have entered clinical practice for the treatment of DTC (lenvatinib and sorafenib as first-line therapies; cabozantinib as second-line therapy) and MTC (cabozantinib and vandetanib). More recently, the therapeutic options for DTC, PDTC, ATC, and MTC have been further enriched with new drugs, including selective targeted therapies for tumours harbouring driver, actionable mutations (for example mutations in *BRAF*, *NTRK*, and *RET*) and immunotherapy. Currently, the optimal treatment sequence and decision-making algorithm is based on regulatory constraints, expected treatment response, and drug safety profile[8]. It is worth noting that the potential of novel therapies to reduce tumour volume is also paving the way for the use of these drugs in a neoadjuvant setting. Evidence for specific subtypes is discussed in the following sections.

Facilitating adjuvant treatment

The use of external beam radiation therapy (EBRT) after surgery for ATC is usually recommended[5]. Concerning DTC, although most studies of the role of EBRT are retrospective, with heterogeneity in terms of patient selection, tumour features, and methodology, it is a viable option for locoregional disease control in patients with R1 or R2 resection[116,117]. Indeed, the AHNS[118] has published a relevant statement on indications for EBRT that includes patients with gross residual or unresectable locoregional disease after complete resection (except for those aged less than 45 years with limited gross disease that is RAI-avid), and in selected patients aged over 45 years with a high likelihood of microscopic residual disease and low likelihood of responding to RAI.

> **Statement 18:** In cases of anticipated R1 or R2 resection, liberal use of titanium clips to delineate the dissection bed, to facilitate the targeting of potential EBRT, has to be considered.
> **Near-consensus:** (7.22) Approved
> **Outliers:** 8
> **Evidence level:** Low
> **GA voting:** Agree 83.33%, Disagree 8.62%, Neutral 8.05%

Follicular cell-derived non-anaplastic thyroid cancer

Surgery remains the cornerstone for achieving control of locoregional advanced disease in non-anaplastic follicular cell-derived thyroid cancer, while facilitating management and treatment of distant metastasis[3]. Among 23 703 DTCs (93.8% of all thyroid carcinomas registered in the surgical Eurocrine® database), 3261 (13.7%) were advanced thyroid cancers. In 893 patients (27.4%), DTCs were locally advanced (T3b/T4), 2542 (77.9%) presented with regional disease (pN1b), and (10.8%) with distant metastases (M1) (unpublished data - M.R., N.V., T.M.). With new developments in systemic and adjuvant treatments, more conservative options are available that may reduce surgical morbidity and improve patient quality of life[6,8,119–122]. In primary

DTC, incomplete surgical excision has been associated with higher mortality rates[27,123]. The aim of this section is to discuss and make suggestions depending on the point of disease invasion.

Management of local disease

If total thyroidectomy, when feasible, is the mainstay treatment option for locally advanced non-anaplastic follicular cell-derived thyroid cancer, *en bloc* resection of invaded adjacent structures should be balanced against the operative risk of morbidity and oncological expectations. Invasion of local structures most frequently involves the strap muscles, RLN, and trachea, whereas spread to the larynx, oesophagus, and major vessels is rarer[9]. In the Eurocrine® database, between 2015 and 2021, among 161 patients with T4 DTC or poorly DTC in whom the site of infiltration was clearly reported, it involved the RLN in 65.59%, the trachea in 13.04%, the oesophagus and major vessels in 8.69%, and the larynx in 3.1% (unpublished data - M.R., N.V., T.M.).

Infiltrated laryngeal nerves

RLN invasion is the most common infiltration site among T4 tumours. The invasion may be directly from the tumour or from paratracheal metastatic lymph nodes, and the degree may vary from simple adherence to complete encasement, and from superficial epineural to deep endoneural invasion[9,124]. The management of patients with an involved RLN requires a high degree of expertise, and implementation of preoperative and intraoperative protocols for optimal tailored results. Preoperative[3,125,126] and postoperative[110,127] laryngeal examination is recommended in all patients with locally advanced thyroid cancer and preoperative glottic function should be assessed. Intraoperative neuromonitoring is an indispensable tool for making the optimal decisions on nerve management, especially in the event of infiltration[93,128]. If the intraoperative findings suggest RLN infiltration, this should be confirmed optimally with a frozen-section examination[9]. Before deciding on the management approach, the surgical team should always consider the following: disease characteristics, metastatic status, patient age and occupation, patient preference and wishes, adjuvant therapy options in the event of microscopic/macroscopic remnant disease, possible disease progression if the nerve remains unresected, preoperative vocal fold function, preoperative and intraoperative status of the contralateral RLN, and electromyographic (EMG) signals from the affected nerve (normal along the whole course of the nerve or normal only distal to the infiltrated site)[2,124]. If preoperative laryngeal function is normal, and EMG nerve signals and signals proximal to the infiltration site are normal, every effort should be made to retain the structural integrity of the RLN[93,94,129]. In the above scenarios, and especially in superficial invasion, shave or partial nerve sheath excision may achieve macroscopic disease clearance and retain RLN functionality, without a negative impact on survival[24,130–132]. More conservative approaches that preserve structural nerve integrity are considered an acceptable choice in DTC, even when a small disease remnant might remain, as there are no adequate data to support the survival benefits of complete resection over shave resection and adjuvant therapy[9,133]. It has, however, been reported that, in certain debulking scenarios, patients required extensive further resection, including laryngectomy and sternotomy, signifying that the location of nerve infiltration (for example close proximity to laryngeal entrance) should be taken into account[133]. On the other hand, in patients with non-functioning nerves, with evidence from preoperative laryngoscopy, and verified during surgery by the

absence of an EMG signal along the whole course of the RLN, especially when RLN infiltration is extensive, the RLN should be excised[9]. Complete resection can also be considered in special circumstances, such as aggressive subtypes, recurrence, and previous EBRT, where adjuvant treatment has or is expected to fail, when justified by projected survival or disease-free benefits[31]. To reduce the risk of bilateral vocal fold paralysis, the International Neural Monitoring Study Group (INMSG)[93] has proposed detailed algorithms to facilitate surgeon decision-making. Among other recommendations, the INMSG proposes to start, or switch, the dissection on the contralateral side of the non-functioning invaded nerve[93]. Similar decisions should be individualized based on patient and tumour characteristics. Indeed, if there is preoperative lack of function on the affected side, primary tumours should be removed as comprehensively as possible, and dissection on the contralateral side should be weighed against the extent of the disease and the expected oncological benefits. Finally, recent data suggest that, in certain patients with ATC and advanced PTC, the function of invaded nerves may recover before surgery during neoadjuvant therapy[134]. Although these data stem from a limited case series, it is a promising concept for future management of patients with nerve invasion.

> **Statement 19:** For invaded RLNs with normal preoperative laryngoscopy:
> When it is possible surgically to achieve macroscopic disease clearance, they should be managed conservatively to maintain structural and, ideally, functional nerve integrity.
> **Consensus:** Yes (7.98)
> **Outliers:** 3
> **Evidence level:** Low
> When conservative management cannot achieve macroscopic disease clearance, the decision regarding resection should be individualized based on patient and tumour characteristics.
> **Consensus:** Yes (8.20)
> **Outliers:** 2
> **Evidence level:** Low
> The above scenarios should be discussed beforehand, and patient preferences considered.
> **Consensus:** Yes (8.10)
> **Outliers:** 2
> **Evidence level:** Expert opinion

> **Statement 20:** In unilateral vocal fold paralysis, with complete lack of EMG signal along the course of the RLN, and inability to maintain structural nerve integrity with conservative techniques, while achieving local disease control:
> Nerve resection should be applied, to obtain adequate oncological clearance on the affected side. Contralateral dissection should be weighed against extension of the disease and the expected oncological benefits.
> **Consensus:** Yes (8.27)
> **Outliers:** 1
> **Evidence level:** Expert opinion
> Dissection should start on the non-affected side, and decisions about proceeding with, and management of, the affected side should be individualized based on patient preferences and tumour characteristics.
> **Consensus:** No (3.70)
> **Outliers:** 21
> **Evidence level:** Expert opinion
> The above scenarios should be discussed beforehand, and patient preferences considered.
> Consensus: Yes (7.80)
> **Outliers:** 4
> **Evidence level:** Expert opinion

> **Statement 21:** In the event of ipsilateral vocal fold paralysis, but positive EMG signals proximal to the infiltration site of the RLN:
> When it is possible surgically to achieve macroscopic disease clearance, such patients should be managed conservatively to maintain structural nerve integrity.
> **Consensus:** Yes (7.49)
> **Outliers:** 4
> **Evidence level:** Low
> When conservative management cannot achieve macroscopic disease clearance, the decision regarding resection should be individualized based on patient and tumour characteristics.
> **Consensus:** Yes (7.60)
> **Outliers:** 5
> **Evidence level:** Low
> The above scenarios should be discussed beforehand, and patient preferences considered.
> **Consensus:** Yes (7.93)
> **Outliers:** 3
> **Evidence level:** Expert opinion

Infiltrated viscera and/or major vessels

Management of these patients should always be aligned with therapeutic goals, and surgery-related morbidities should be weighed against the sequelae of non-treatment/conservative surgery for the patient. As already discussed, preoperative evaluation and involvement of a MDT is essential. The surgeon should keep in mind that, especially in DTC, adjuvant therapy including RAI or EBRT is usually indispensable to completely control the disease locoregionally[2,9]. In addition, recent developments in systemic therapy, depending on genetic alterations in non-anaplastic follicular cell-derived thyroid cancer, may afford less extensive and morbidity-burdened operations in favour of systemic and even neoadjuvant treatment options[6–8].

Tracheal invasion

The three main techniques for disease control have traditionally been shave or window resection, and sleeve resection with end-to-end anastomosis[9,120]. For stages I and limited stage II involvement, according to the Shin classification[89], shave resection is considered appropriate and adequate. For more extensive infiltration, including the mucosa and lumen, sleeve resection must be considered, but detrimental complications might occur[2,9,120]. Formal segmental tracheal resection of the involved rings may offer, if feasible, the best results in terms of long-term oncological outcome[9]. As such, considering the risk of complication, the decision should be carefully weighed against patient and disease characteristics as well as patient wishes. In any event, management must be undertaken by a team with advanced skills and complemented by other surgical specialties according to endocrine surgeon expertise, and local protocols and legislature.

> **Statement 22:** In patients with limited (stage I or limited stage II according to the Shin classification) tracheal involvement, tracheal shaving should be performed.
> **Consensus:** Yes (7.95)
> **Outliers:** 3
> **Evidence level:** Low

Statement 23: In patients with extensive (stage III or IV) tracheal involvement, tracheal resection should be considered according to MDT goals of care and patient preferences.
Consensus: Yes (7.76)
Outliers: 2
Evidence level: Low

Laryngeal invasion

Extended invasion of the larynx reaching intraluminally is quite rare in DTC, but results in significant morbidity and sometimes death[135]. In the most common cases of extraluminal infiltration, a partial-thickness or shave excision, usually of the cricoid or thyroid cartilage, is preferable for local disease control[9,136]. Current data are conflicting and not clearly in favour of composite resection and reconstructions over conservative treatment and adjuvant therapy in terms of oncological results. Therefore, even in more extended invasion, local control should be achieved with surgical options carrying lowest morbidity[9,121,136]. If a more aggressive resection is required, it can be decided in a MDT setting, also considering patient preferences and expectations.

Statement 24: In patients with DTC and laryngeal involvement, local disease control should be achieved with shave or partial-thickness excision when feasible.
Consensus: Yes (7.73)
Outliers: 3
Evidence level: Low

Statement 25: In patients with extensive (stage III or IV) laryngeal involvement, resection should be considered according to MDT goals of care and patient preferences.
Consensus: Yes (7.95)
Outliers: 2
Evidence level: Low

Statement 26: Aggressive laryngeal resections should not be performed as index primary operations, but only in the event of failure of disease control after more conservative surgical treatment and adjuvant therapy, except where the tumour presents an overarching burden at presentation.
Near-consensus: (7.07) Approved
Outliers: 9 (3 negative)
Evidence level: Low
GA voting: Agree: 82.56%, Disagree: 5.81%, Neutral: 11.63%

Oesophageal invasion

Oesophageal invasion is predominantly limited to the muscularis in invasive DTC[23], and usually derives from the primary tumour[137]. Extension into the lumen is rare, but requires composite reconstruction when the defect following full-thickness resection is large and primary tension-free closure cannot be achieved safely[9]. As such, resection of the infiltrated layers is usually sufficient to achieve local control. Full-thickness resection and reconstruction should be performed only when there is definitive mucosal involvement, after discussion in a MDT setting[9]. The statements listed in the general treatment section above also apply to DTC.

Management of regional nodal disease

The adequacy of lymph node clearance in thyroid cancer, and especially in advanced disease, is critical to avoid recurrent and/ or persistent disease[138,139]. It has been documented that

approximately 60–75% of all neck recurrences occur in cervical lymph nodes[3,140]. In neck dissections, two principles should guide surgical extent. The first is the comprehension that cervical lymph nodes are without exception contained in the spaces defined by the muscular fascias and vascular aponeuroses. Consequently, in the absence of direct invasion, muscular, vascular, and neural vital structures should be preserved, whereas the fascia covering the fibrofatty tissue and nodes should be removed *en bloc*[139]. Second, it is important to understand the pattern of dissemination of lymphatic disease, and to balance disease-free and disease-specific survival depending on the compartments dissected[139]. To this end, the Surgical Affairs Committee Statement of the ATA[141] recommends that lateral neck dissection for macroscopic DTC metastases should comprise selective neck dissection of levels IIa, III, IV, and Vb. This was further reconfirmed in the American Association of Endocrine Surgeons (AAES) guidelines[142] in 2020. More extended dissection, including levels IIb, Va, and, exceptionally, I, should be undertaken only if there is evident involvement. For central neck dissection (CND), the levels involved are VI and VII. CND is indicated for all patients with clinically involved nodes, either determined before or during surgery, and is encouraged in patients with larger and locally more advanced tumours (T3 and T4)[3,110,142,143]. As an alternative to prophylactic bilateral CND, an ipsilateral approach with frozen-section examination of the ipsilateral central neck compartment could guide the extent of neck dissection and reduce patient morbidity while avoiding reoperations[53,144]. Concerning patients with DTC, lateral neck dissection should be performed only with therapeutic intent for known disease and not for prophylactic purposes and accompanied by bilateral CND[3,140–142,145].

Statement 27: When neck dissection for disease clearance has been decided:
Lateral neck dissection of levels IIa, III, IV, and Vb should be performed only with therapeutic intent for evident lateral neck spread. Levels I, IIb, and Va should be dissected only in the event of clinical involvement.
Consensus: Yes (8.15)
Outliers: 2
Evidence level: Low
Levels IIb and Va must be included.
Consensus: No (4.39)
Outliers: 18
Evidence level: Low

Statement 28: When lateral neck dissection for disease clearance has been decided, it should always be accompanied by CND, even in the absence of overt central neck involvement.
Near-consensus: (7.15) Rejected
Outliers: 7
Evidence level: Low
GA voting: Agree: 73.33%, Disagree: 19.44%, Neutral: 7.22%
In the absence of central neck involvement, and depending on tumour characteristics, unilateral CND could be performed, extended to the contralateral side if frozen-section examination is positive.
Consensus: No (6.33)
Outliers: 18
Evidence level: Low

Neoadjuvant and new systemic therapy options

Evidence for the value of neoadjuvant therapy in patients with DTC and PDTC can be found in a few case reports describing treatment with the MKIs lenvatinib and sorafenib[146]. These

reports include patients with a wide age range (20–81 years), receiving MKI compounds for preoperative treatment of advanced primary tumours or recurrent locally invasive cancers, with or without concomitant EBRT. None of the patients had gross ETE staged as T4b according to the TNM/AJCC eighth edition. All patients experienced significant tumour shrinkage, regardless of whether they had received EBRT, allowing limited surgical approaches in a subset of individuals, without extensive resections such as laryngectomy, oesophagectomy or resection of the great vessels. Notably, all patients undergoing MKI neoadjuvant therapy should be informed of, and assessed for, risk of fistula before initiation of treatment. Fistula has been reported in patients undergoing antiangiogenic MKI treatment and harbouring locally advanced thyroid cancers encasing the trachea, carotid artery, and/or mediastinal vessels[147]. Such an extent of disease is far from rare in patients in whom neoadjuvant therapy is considered. The use of selective targeted therapies, without significant antiangiogenic activity, is expected to reduce this risk. Larger studies that can explore the long-term benefit and risk of neoadjuvant therapy at a population level are warranted. These studies should also address specific questions, such as the therapeutic schedule (dosing and duration) and the profile of patients expected to benefit from such treatments.

There is no evidence for the use of MKIs or selective targeted therapies alone in patients with advanced thyroid cancer in an adjuvant setting. Selumetinib, a selective mitogen-activated protein kinase kinase 1 and 2 (MEK 1/2) inhibitor, has been investigated in combination with adjuvant RAI to evaluate its benefit in improving complete remission rates in patients with DTC at high risk of primary treatment failure. Eligible patients had a large primary tumour (over 4 cm), gross ETE, and significant neck lymph node involvement (at least 1 metastatic lymph node(s) of 1 cm or larger, or at least 5 lymph nodes of any size). The combination therapy was compared with RAI alone in a placebo-controlled, double-blind RCT[148]. The addition of selumetinib to RAI failed to improve the primary outcome of complete response rate, while exposing patients to a higher rate of treatment-related adverse events of at least grade 3.

> **Statement 29:** Neoadjuvant MKI therapy may be an option in properly selected patients with DTC to reduce primary tumour burden and facilitate subsequent surgical resection for local disease control.
> **Consensus:** Yes (7.37)
> **Outliers:** 4
> **Evidence level:** Low

Medullary thyroid cancer

Advanced MTC comprises four clinical scenarios: local, regional, systemic, and combined locoregional and systemic advanced MTC. In advanced MTC, clinical outcomes do not differ between sporadic and hereditary disease, and so they will be addressed as one. A markedly raised calcitonin and/or carcinoembryonic antigen (CEA) level without evidence of structural disease is not considered advanced MTC. Lymph node involvement of the central and/or lateral compartment without infiltration of neighbouring structures owing to ENE does not represent advanced MTC, based on oncological outcomes. As mentioned above, N1b might, however, represent advanced disease as it is associated with a higher morbidity rate, requiring treatment in high-volume

referral centres, as well as being linked to worse prognosis in individual studies[149]. In the Eurocrine® database, between 2015 and 2021, among 1242 MTCs (4.9% of all registered thyroid carcinomas), 363 (29.2%) were advanced MTCs, sporadic in 89% of the patients. Sixty-three (17.35%) were locally advanced (T3b/T4), 340 (95.8%) presented with regional disease (pN1b), and 64 (17.6%) with distant metastases (M1) (unpublished data - M.R., N.V., T.M.).

Locally advanced medullary thyroid cancer

ETE in MTC is associated with systemic disease and poorer prognosis, and therefore is considered advanced MTC[18,149–151]. ETE starts with breach of the thyroid capsule and advances to various degrees of direct infiltration into neighbouring structures, namely the RLN, strap muscles, soft tissue, trachea, oesophagus, larynx, jugular vein, and common carotid artery. It should be noted that, in MTC, there is not enough evidence in the literature on the impact of the specific point of ETE (such as strap muscles only or RLN) on oncological outcomes.

Regionally advanced medullary thyroid cancer

Cervical lymph node metastases with ENE are considered regional advanced MTC independently of extension of the primary tumour[152]. Often ENE in lymph node metastases is present synchronously with locally advanced MTC.

Systemic medullary thyroid cancer

Evidence of distant metastases in one or more regions, such as mediastinal lymph node, pulmonary, liver, bone, brain, or skin metastases, indicates systemic advanced MTC. Combined local, regional, and/or systemic advanced MTC is represented by any combination of the above.

Specific considerations in pretreatment medullary thyroid cancer diagnostics

Measurement of basal calcitonin and CEA levels must be done before treatment as a baseline evaluation and to direct the diagnostic algorithm. Moreover, calcitonin and, less so, CEA levels are important factors used to assess disease burden and response to neoadjuvant or definitive treatment during follow-up. Cervical ultrasound imaging, clinical evaluation, and symptoms may provide early evidence of advanced MTC, whereas whole-body 18F-6-fluoro-L-dihydroxyphenylalanine (F-DOPA) PET–CT is the most sensitive investigation for assessing disease burden and prioritizing adequate treatment. Complementary cross-sectional imaging (contrast-media CT, MRI), and endoscopy of the trachea, bronchi, and/or oesophagus, should be performed accordingly whenever resection of locoregional advanced MTC is planned to direct the surgical strategy[153]. In MTC, FNA or core-needle biopsy does not serve to confirm the diagnosis, but may be used for molecular pathology investigation with the aim of evaluating neoadjuvant or palliative treatment modalities.

> **Statement 30:** In advanced MTC, the following must be determined before treatment:
> Both basal calcitonin and CEA levels.
> **Consensus:** Yes (8.07)
> **Outliers:** 6
> **Evidence level:** Low
> Only basal calcitonin levels.
> **Consensus:** No (7.60)
> **Outliers:** 19
> **Evidence level:** Low

Statement 31: Before surgery for advanced MTC, whole-body
F-DOPA or ^{68}Ga-labelled DOTATATE PET–CT should be
preferred, when available, to assess the tumour burden and
align surgical measures.
  Near-consensus: (6.83) Rejected
  Outliers: 14
  Evidence level: Low
  GA voting: Agree: 74.71%, Disagree: 10.34%, Neutral: 14.94%

Treatment

Locally advanced disease

Locally advanced MTC without evidence of distant disease in
primary surgery aims at margin-free oncological resection,
ideally followed by biochemical cure. The extent of resection
must be adapted to patient general health performance status
(Eastern Cooperative Oncology Group and ASA), co-morbidities,
and specific risk factors (for example pre-existing neural
dysfunction, such as laryngeal nerve palsy), age, and patient
preferences. Following MDT recommendation with the
anticipated risk–benefit evaluation, patient counselling is
mandatory before surgical intervention. In primary surgery and
where free resection margins are expected with optional
biochemical cure, total thyroidectomy with bilateral
compartment-oriented CND is necessary in most patients. In the
rare exception of a small primary tumour with distant
metastases (for example pulmonary) and without evidence of
lymph node metastasis, lobectomy with or without ipsilateral
central node dissection can be considered[154,155]. Surgical
resection of ETE in advanced MTC, without transluminal
resection of the trachea and/or oesophagus, is carried out
according to the structures involved. The infiltrated strap
muscles and central neck compartment are resected *en bloc* with
the thyroid and primary tumour. Where the strap muscles are
uninvolved or only partially involved, full- or outer-layer
preservation enables their use for fortification or closure of
tracheal and/or oesophageal transluminal resections. In
superficial tracheal invasion (Shin I–II), shaving is performed[89].
In extramucosal oesophageal infiltration, wall resection with
preservation of mucosal integrity is undertaken. In both
procedures, intraoperative frozen-section confirmation of
tumour-free margins will direct the resection strategy.
Intraoperative evidence of unilateral RLN infiltration with
bilateral intact preoperative vocal cord function requires
functional preservation of the contralateral RLN to be confirmed
before oncological RLN resection. In the event of unilateral RLN
infiltration with preoperative vocal cord palsy and oncological
RLN resection, the indication for surgery on the contralateral
side must be evaluated carefully. Intraoperative evidence of
bilateral RLN infiltration with intact vocal cord function requires
tailored decision-making regarding which resection procedure is
most likely to preserve quality of life and have prognostic
benefit. Options are unilateral oncological RLN resection with
contralateral RLN preservation, bilateral RLN resection and
tracheostomy, or intended palliative resection with preservation
of the infiltrated RLN. A specifically demanding area of RLN
infiltration is the laryngeal–tracheal groove, where tumour
infiltration is rarely restricted to the RLN but involves the
trachea, larynx, and oesophagus simultaneously. Whenever
possible, margin-free tumour resection of the infiltrated RLN
entering the larynx, encompassing necessary tracheal shaving,

extramucosal oesophagus, and partial resection of infiltrated
areas of the larynx, should be performed. Fortification or plastic
reconstruction is not required unless relevant vascular
compromise with secondary necrosis is anticipated, and the
tracheal or oesophageal lumen are opened. Transluminal types
of tracheal resection (window, sleeve or segmental) are
performed according to the longitudinal and circumferential
extension of tumour invasion, as are transmural resections of
the oesophagus that are restricted in extent owing to limited
options for vascular preservation. Multidirectional tumour
infiltration involving the RLN, larynx, trachea, and oesophagus
may require multivisceral resection with laryngectomy, tracheal
and oesophageal resection, a free jejunal transplant
reconstruction of the digestive tract, and terminal tracheostomy
for airway management. These complex procedures are
associated with considerable complication rates; however,
selected patients benefit from these salvage manoeuvres. For
such multivisceral infiltrative scenarios, neoadjuvant treatment
is introduced, and is discussed below. Data on the outcome and
prognosis of extended resections involving the trachea, larynx,
and oesophagus in MTC are scarce, and show dismal results
compared with those for patients with DTC. Therefore, the
indication for extended and multivisceral procedures in MTC
must be weighed carefully[156,157].

Statement 32: The main goal of surgery in advanced MTC is
local control and optimization of adjunctive treatment
modalities. Therefore, resection of the RLN, trachea,
oesophagus, larynx, and lymph node dissection are
recommended when local control can be achieved. The
diagnosis of advanced MTC should not preclude surgical
evaluation of resectability.
  Consensus: Yes (7.39)
  Outliers: 3
  Evidence level: Low

Regionally advanced and metastatic disease

In MTC, lymph node metastases are strongly associated with
desmoplasia and breach of the thyroid capsule. Both features
are expected in advanced MTC, and can be assessed by
frozen-section analysis. This allows alignment with preoperative
and intraoperative evidence of lymph node metastases, and
direction of the extent of lymph node dissection at the time of
primary tumour resection[158]. To achieve cancer-free resection
margins and local control, bilateral central compartment lymph
node dissection is generally necessary. In the event of unilateral
RLN dysfunction or oncological RLN resection, the indication for
contralateral central compartment lymph node dissection needs
to be carefully weighed and should be performed only with
therapeutic intent. Any type of prophylactic lymph node
dissection to the central, and even more so, the lateral
compartments is discouraged. In the rare scenario of a locally
advanced MTC for which radical (R0) resection and biochemical
cure can be expected with therapeutic lymph node dissection,
the central and lateral compartments can be dissected accordingly.

Mediastinal tumour manifestation for direct tumor diffusion or
lymph node metastasis should be resected whenever technically
possible as secondary complications frequently occur[159].
Tracheal, bronchial, and oesophageal resections in the
mediastinum are prone to complication and associated with
very poor outcomes. These should, therefore, be discouraged in

favour of neoadjuvant treatment or palliative measures involving stenting and multimodal treatment modalities[4,156].

In the event of persistent and recurrent advanced MTC, full measured tumour staging must precede evaluation of surgical options, and the surgical principles outlined above for primary surgery apply to resection of persistent and recurrent disease.

In MTC, distant metastases infrequently represent systemic disease. Resection of the primary tumour can be undertaken in such patients without extended neck resection and thus benefit local disease control in the neck[160]. The role of surgery in systemic advanced MTC, as well as in combined local, regional, and systemic disease, is directed at local tumour control, to alleviate symptoms or prevent complications.

Recently, neoadjuvant treatment for MTC has been introduced, and may also reshape the role of surgery in systemic MTC, as surgery can be extended according to treatment response[161,162]. Palliative surgery is indicated whenever structural tumour growth presents with symptoms that can be alleviated and/or to prevent expected complications when progressive local infiltration cannot be stalled in a timely manner by other means. Surgery in these scenarios is directed at the local or regional problem at hand.

MTC in general is a rare entity, and advanced MTC even more so. The diagnosis of advanced MTC should not preclude evaluation by an experienced specialized surgeon. Patients with advanced MTC are at increased risk of surgical morbidity, and surgery should therefore be carried out by high-volume surgeons in centres with extensive experience. The oncological results of thyroid cancer surgery are significantly better when performed by high-volume surgeons[163]. A recent study[164] showed that surgeon volume was a significant factor for disease recurrence (HR 2.28; $P = 0.004$).

Statement 33: In advanced MTC, compartment-oriented lymph node dissection:
Should be carried out to the extent that is required therapeutically. Any type of prophylactic lymph node dissection should not be performed.
Consensus: No (5.85)
Outliers: 29
Evidence level: Low
Prophylactic CND should be performed routinely.
Near-consensus: (6.71) Rejected
Outliers: 18 (7 negative)
Evidence level: Low
GA voting: Agree: 78.97%, Disagree: 16.41%, Neutral: 4.62%

Statement 34: Surgery for advanced MTC should be performed only by high-volume surgeons in high-volume centres.
Consensus: Yes (8.49)
Outliers: 0
Evidence level: Low

Neoadjuvant and new systemic treatment options

Little evidence is available on the role of systemic therapy in the preoperative management of locally advanced MTC. Reports in the literature do not go beyond clinical cases and case series. No evidence at all is available on the adjuvant use of pharmacological therapy.

The approval of selective RET kinase inhibitors (pralsetinib and selpercatinib) by international medicine regulatory authorities, their increasing use in clinical practice, the growing body of

evidence on their safety and efficacy profile, and the significant proportion of patients carrying *RET* mutations have all favoured therapeutic attempts in the neoadjuvant setting. In a recent retrospective single-centre case series[165], four patients were treated with neoadjuvant selpercatinib followed by surgery. Patients underwent 4–6 months of neoadjuvant therapy, with drug withdrawal 3 days before surgery. All experienced tumour shrinkage, with three of four patients achieving a partial response according to Response Evaluation Criteria In Solid Tumours 1.1. None of them had structural evidence of disease after surgery (median follow-up 2 (range 0.7–3.6) years) and one patient experienced an RLN injury. Although this approach holds promise, larger studies are warranted. A clinical trial exploring the value of neoadjuvant selpercatinib treatment in patients with MTC harbouring somatic or germline *RET* mutations is currently under way (NCT04759911).

Owing to the scarcity of data and experience with neodjuvant treatment in advanced MTC, important practical aspects, such timing of surgery, discontinuation of drugs before and after operation, as well as treatment-free intervals are mainly based on experience with the available substances in adjuvant and palliative settings in MTC, and may need to be adjusted with increasing experience. The time point of surgery in neoadjuvant treatment planning may be chosen when the structural response according to imaging indicates expected safe and radical tumour resection. Systemic treatment with any type of kinase inhibitor and/or immune checkpoint inhibitors should be discontinued at least 5–7 days before surgery, and likewise after surgery until successful wound healing has resumed owing to infrequent compromise in wound healing and the risk of fistula formation. Most of the data referring to experience with complications in this regard are, however, not based on advanced MTC.

Statement 35: Neoadjuvant *RET*-targeted therapy may be an option in selected patients with MTC to reduce the primary tumour burden and facilitate subsequent surgical resection for local disease control.
Consensus: Yes (7.41)
Outliers: 4
Evidence level: Low

Anaplastic thyroid cancer

Owing to its fatal prognosis, ATC is always classified as stage IV by the AJCC TNM system[13]. ATC is labelled as stage IVa in the event of a tumour confined to the thyroid gland, stage IVb if there is tumour extension outside the thyroid but confined to the neck, and stage IVc in the case of distant metastasis. ATC requires an immediate multidisciplinary assessment to ensure the best multimodal treatment. A thorough, expeditious, and complete preoperative work-up is imperative, as discussed previously, with emphasis on the need for efficiency and haste. Once the status of the disease has been determined, goals of care should be set by the MDT, in accordance with patient preferences, following a candid, comprehensive, and meticulous discussion. Individualized treatment options should be offered to patients, and they should be informed about possible complications after radical surgery, or denial of therapy. Additionally, patients should be informed about the possibility of permanent tracheostomy, feeding tube placement, and delay in starting medical treatment after major surgery.

> **Statement 36:** In ATC, multidisciplinary evaluation should be undertaken with the outmost haste and efficiency, and possible morbidities of aggressive surgery, and the potential benefits this surgery may provide to the patient, should be well evaluated and balanced.
> **Consensus:** Yes (8.46)
> **Outliers:** 0
> **Evidence level:** Low

Resectability

Surgery plays a critical role in the management of ATC, with the aim of achieving potentially curative (R0) or complete macroscopic (R1) resection of the tumour. Several studies[166–170] have documented a survival benefit in patients with ATC when complete resection (R0/R1) is achieved. Although diagnosed rarely, patients with stage IVa disease are candidates for total *en bloc* resection[5,171]. On the other hand, the resectability of stage IVb tumours should be assessed carefully based on the structures involved. The potential benefit of mutilative surgery is questionable considering the poor prognosis of the tumour, and the morbidity related to extensive resections needs to be evaluated carefully. Tumour invasion of the prevertebral fascia, and invasion or encasement of the carotid artery and/or mediastinal vessels, are considered features indicative of unresectability. Moreover, aggressive resections, such as laryngectomy or pharyngo-oesophagectomy, often appear inappropriate because of the associated morbidity[172]. Nonetheless, patients with previously unresectable stage IVb ATC may benefit from recently developed neoadjuvant treatment modalities, which may render some cancers resectable[5,7,8,78,173–175].

The role of surgical treatment in stage IVc ATC is controversial. Optimal management must be discussed within a MDT. Individual studies[170,176] have reported that surgery of the primary tumour in combination with multimodal therapy is associated with improved overall survival. Moreover, surgery may play a role in terms of preventing potentially fatal complications caused by local tumour growth, such as airway obstruction, haemorrhage, and vena cava superior syndrome. Besides, immunotherapeutic and targeted therapies have been introduced for the treatment of advanced and metastatic ATC, yielding promising results and rendering resectability a dynamic process[170,174].

> **Statement 37:** Involvement of the aerodigestive tract and/or major vascular structures of the neck and mediastinum, requiring extensive resections, are factors indicating unresectability, and surgery is generally not recommended.
> **Consensus:** Yes (7.88)
> **Outliers:** 2
> **Evidence level:** Low

Palliative care versus aggressive, non-curative surgery

Palliative surgery may be undertaken to reduce airway or oesophageal obstruction, or to reduce pain associated with bulky tumours. Local treatments undertaken by means of interventional bronchoscopy, in particular endotracheal stent placement and endotracheal laser treatment, can be performed to decrease airway obstruction or intratracheal invasion and improve respiratory symptoms[177]. Nonetheless, such endoscopic treatments do not influence the prognosis of the tumour.

Tracheostomy may be performed if there is dyspnoea or stridor. It may also be carried out preventively in selected patients to ensure respiratory airway patency in the event of impending airway compromise. The decision to perform tracheostomy always requires endoscopic tracheal examination and imaging studies to assess the tracheal profile and displacement.

Tracheostomies in these patients may be technically challenging because of the presence of the thyroid mass, and may require isthmusectomy or thyroid debulking[178]. The decision to perform tracheostomy must, however, be individualized, evaluated accurately by a MDT, and discussed with the patient and their relatives. Tracheostomy is often associated with increased secretions, and may lead to considerable worsening of quality of life, increased wound complications, potential tumour extension from the stoma, and bleeding. Moreover, the tracheostomy may be displaced owing to tumour growth and may delay appropriate therapy[178]. For all these reasons, it is generally recommended to postpone tracheostomy for as long as possible.

In patients with compromised oral feeding due to oesophageal obstruction, enteral feeding must be ensured. Enteral feeding may be achieved by means of a nasogastric tube, oesophageal stent or gastrostomy. Notwithstanding, tumour invasion may lead to oesophageal stenosis that could hinder or preclude endoscopic gastrostomy. In such instances, surgical intervention may be required. Gastrostomy ensures enteral feeding even when there are side-effects from radiotherapy and allows patients to undertake chemotherapy.

Definitive indications and definitions regarding debulking surgery are still lacking. Overall, it is generally not recommended because debulking may delay palliative care options and does not prolong survival[170]. Debulking may be undertaken when tumour resection is required to expose the tracheal surface to perform tracheostomy[178]. Moreover, selected patients may be candidates for debulking surgery when huge tumour reduction can be achieved (at least 90%). Indeed, some reports[179] have documented longer survival after palliative debulking procedures combined with radiotherapy and/or chemotherapy compared with best supportive care.

> **Statement 38:** Non-curative, debulking operations are generally not recommended, although can be considered in combination with adjuvant/systemic therapy in selected patients in whom:
> Remnant disease is anticipated to be of very low volume.
> **Consensus:** Yes (7.12)
> **Outliers:** 4
> **Evidence level:** Low
> It facilitates palliative treatment.
> **Near-consensus:** (6.90) Rejected
> **Outliers:** 14
> **Evidence level:** Low
> **GA voting:** Agree: 71.91%, Disagree: 11.24%, Neutral: 16.85%

> **Statement 39:** A tracheostomy should not be placed pre-emptively, but only when absolutely necessary for airway management.
> **Consensus:** Yes (8.12)
> **Outliers:** 1
> **Evidence level:** Low

Surgical extent and significance of R status

In recent years, it has been observed that the average survival of patients with ATC has increased. The contribution of recent advancements in molecular targeted therapies and radiotherapy in this development should not be overlooked. Although adjuvant and systemic treatment options will evolve, surgery

remains the cornerstone of complete disease control. With that consideration, it might be appropriate to push the limits in selected patients.

Looking at the historical development and importance of surgical resection, in a study by Tan *et al.*[180], patients treated between 1968 and 1992 had a mean overall survival of 4.5 months, whereas mean survival was 131 months among patients in whom complete surgical resection was achieved. In another study[181], of 28 patients in total, palliative surgery was performed in 6, and curative surgery was attempted in 12. The results showed that surgical resection, absence of distant metastasis, and tumour size below 6 cm indicated a survival benefit in selected patients. In a large series[182], including 121 patients from 1950 up to 1987, average survival was 7.2 months, and the study demonstrated that young age and absence of metastasis had a survival benefit. Patients also survived longer if they underwent total or subtotal thyroidectomy, and if they received radiotherapy, chemotherapy, or both. There was, however, no statistically significant difference between treatment types. In all three studies, patients receiving adjuvant radiotherapy after surgery had a favourable outcome, or a significant increase in overall survival. Tennvall *et al.*[183] conducted a prospective study of 55 patients between 1984 and 1999, with the patients divided into three groups. Different doses of hyperfractionated radiotherapy were given to each group. Local recurrence was not observed in any patient in the group in which the entire dose of radiotherapy was administered before surgery.

Local control in the treatment of ATC may increase patient quality of life and provide control of the causes of death owing to tumour invasion of the surrounding tissues, such as asphyxia and bleeding. In a multicentre study[184] from Korea, 329 patients from 19 different centres were assessed. Curative resection and adjuvant radiotherapy, or chemoradiotherapy, provided survival advantages in stage IVa and IVb, but not in stage IVc disease. Patients who actively underwent total thyroidectomy and therapeutic neck dissection had better survival rates than those who had no therapeutic management. A favourable trend towards improved survival was also observed for R0 over R1 resection. Regarding surgical management of patients with stage IVb disease, the majority of pertinent publications favoured resection when R0/R1 was feasible. Ito *et al.*[185] reported no significant difference in survival between patients with stage IVa and IVb disease when curative surgery was undertaken. In addition, no significant difference was found between patients with stage IVb and IVc disease in whom curative surgery could not be performed. In line with these results, surgical intervention was recommended by the 2021 ATA guidelines[5] for patients with resectable stage IVb disease. Prophylactic central or lateral neck dissection was not recommended, but every attempt to remove clinically apparent disease was, however, encouraged.

In a retrospective cohort study[170] published in 2022, surgical resection (R0/R1) of the tumour increased the average survival in patients with stage IVc ATC. Debulking (R2) surgery did not show any survival advantage. In addition to surgery, radiotherapy, chemotherapy, multimodal therapy, and being aged under 65 years were also shown to increase average survival[170]. In another report by Yamazaki *et al.*[176], surgical resection was performed in 36 of 54 patients with metastatic disease. A survival advantage was shown in the resection group. When R0/R1 was compared with R2 resection, average survival was significantly longer for the R0/R1 group (13 *versus* 1.7 months). Thus, R2 resection was not recommended by the authors, and might even have proven harmful, highlighting the

need for careful selection of candidates for surgery[176]. Goffredo *et al.*[172] reported that absence of surgery was associated with compromised survival for patients with stage IVa (HR 2.58; $P < 0.001$) and stage IVc (HR 1.35; $P = 0.033$) disease, whereas a negative trend was observed for stage IVb disease (HR 1.33; $P = 0.063$). No differences in survival were observed for patients with disease staged IVb and IVc based on resection margin status. A recent systematic review[186] of 40 publications revealed that approaches to unresectability and interpretations of resection vary widely. Patients with stage IVb disease undergoing surgery had significantly longer survival than those managed non-surgically (6.6 *versus* 2.1 months).

In a Japanese study[187] of the extent of resection, patients were divided into four groups: super-radical surgery, radical surgery, palliative surgery, and non-surgical treatment. Super-radical surgery was defined as segmental or total laryngectomy, tracheal resection, oesophageal resection, mediastinal surgery with an ostomy, and major cervical artery resection. The prognostic index (PI) was used in selecting patients with stage IVb ATC for super-radical surgery. PI criteria included acute symptoms, leucocytosis, tumour size greater than 5 cm, and distant metastasis. Each criterion scored 1 point. Patients with a PI value of 1 or less who underwent super-radical surgery had a 50% survival rate at 1 year. In the 10 patients with a PI value of 2 or higher, the 1-year survival rate was 11%. The authors concluded that super-radical surgery may provide a survival advantage in selected patients[187]. Similarly, in a study by Brown *et al.*[188], aggressive complete surgery, including laryngectomy and oesophagectomy, followed by radiotherapy, showed a survival advantage in selected patients with stage IVb disease (without distant metastasis or invasion into the lateral aspect of the carotid artery). In this series, 14 of 16 operated patients did not develop local recurrence.

According to a preliminary analysis of the Eurocrine® database, outcomes of 253 patients who had surgery between 2015 and 2021 revealed that achieving an R0 resection seemed to increase life expectancy. Meanwhile, only 20% of operated patients received R0 and 44% R1 resection. Mean tumour size was 52.5 mm. Postoperative vocal cord paralysis rates were 45, 41, and 35% for R0, R1, and R2 resections respectively. According to the Clavien–Dindo classification, morbidity was significantly higher after R2 procedures. Metastasis rates were 33% in R0, 42% in R1, and 72% in R2 resections. The median survival rate was 100 days. Life expectancy was highest after R0 procedures (260 days for R0, 159 days for R1, and 78 days for R2). Regarding neoadjuvant therapy, no significant difference was found between groups ($P = 0.56$). The use of neoadjuvant therapy had no impact on postoperative vocal cord palsy rates and morbidity ($P = 0.11$). Neoadjuvant treatment tended to have a favourable effect on survival time, but the numbers of patients were not adequate to yield a significant result (unpublished data - M.R., N.V., T.M.).

Evaluating the past 30 years of ATC treatment has revealed an improvement in survival in the past 10 years. Surgical treatment still seems to be the only definitive cure option. There is consensus in stage IVa disease, and surgical treatment of resectable disease is recommended[5,184,185]. In stage IVb disease, surgical treatment is more controversial and should be tailored. The most common causes of death are related to local invasion, such as respiratory failure, bleeding, malnutrition, and vena cava syndrome. When stage IVb disease is deemed resectable, aggressive R0/R1 resection is considered advantageous with individualized, multidisciplinary evaluation and treatment[5,170,176,187,188]. There is almost complete consensus among publications that R2

resection does not provide an advantage, and that it increases patient morbidity and 30-day mortality[170,172,176]. There is a lack of objective and evidence-based criteria for deciding which patients with stage IVb disease should undergo surgical treatment. In stage IVc and unresectable stage IVb disease, neoadjuvant targeted therapies that have emerged in recent years offer some hope. Neoadjuvant treatments may render tumours resectable, and surgical treatment can subsequently be attempted. More studies are needed to strengthen and validate these results. Palliative surgery of the primary tumour is only recommended for patients to avoid lethal complications. There are, however, studies[170,176] showing that local control of the disease can reduce mortality caused by the invasion of vital structures by the tumour.

Statement 40: For stage IVa/IVb ATC, where R0 and R1 resection is anticipated, surgical intervention is recommended, after thorough patient counselling and MDT discussion.
Consensus: Yes (7.88)
Outliers: 2
Evidence level: Low

Statement 41: Patients with distant metastasis (stage IVc) may be considered for surgical treatment for:
Palliative reasons or to prevent imminent complications of local involvement.
Near-consensus: (6.85) Rejected
Outliers: 19 (7 negative)
Evidence level: Low
GA voting: Agree: 60.33%, Disagree: 31.52%, Neutral: 8.15%
Palliative reasons only.
Consensus: No (4.58)
Outliers: 15
Evidence level: Low
Preventing imminent complications of local involvement only.
Consensus: No (5.28)
Outliers: 20
Evidence level: Low

Statement 42: In selected patients with distant metastasis (stage IVc), if locoregional R0/R1 resection is anticipated, decisions on possible surgical intervention should be tailored, after thorough patient counselling and MDT discussion.
Consensus: Yes (7.56)
Outliers: 3
Evidence level: Low

Statement 43: Local control in the treatment of ATC may improve patient quality of life, and provides control of the causes of death owing to local invasion.
Consensus: Yes (7.61)
Outliers: 2
Evidence level: Low

Statement 44: Total thyroidectomy, with appropriate therapeutic dissection of the central and lateral neck lymph node compartments, is the optimal surgical treatment in patients with resectable disease involving both lobes.
Consensus: Yes (7.66)
Outliers: 3
Evidence level: Low

Statement 45: For unilateral intrathyroidal tumours, when R0 resection can be achieved with hemithyroidectomy:
It should be preferred over total thyroidectomy.
Consensus: No (6.00)
Outliers: 21
Evidence level: Low
It should be preferred only in patients with unilateral RLN invasion to avoid potential bilateral vocal cord paralysis.
Consensus: No (5.18)
Outliers: 22
Evidence level: Low

Neoadjuvant and new systemic therapy options

The shift from traditional chemotherapy to targeted therapy inhibiting specific driver mutations (selective kinase inhibitors) or immunotherapy has changed the ATC treatment pathway. The increased efficacy of new drugs in reducing tumour burden has paved the way for attempts at neoadjuvant therapy to facilitate subsequent surgical resection.

In one study[78], six patients with *BRAF* V600E-mutated ATC underwent neoadjuvant dabrafenib and trametinib therapy followed by surgery and adjuvant chemoradiation. Four patients had stage IVb and two had stage IVc diseae. R0 resection was achieved in four patients and R1 resection in two. Two of six patients died during follow-up from disease progression at distant sites. The remaining patients had no evidence of structural disease at the time of last follow-up (median follow-up from start of neoadjuvant therapy 15 months (range: 6.4–25.2). Similar results were reported in a case series[175] that including one patient presenting with a *BRAF*-mutated ATC who received neoadjuvant dabrafenib and trametinib therapy, and two patients with wild-type *BRAF* who had immunotherapy (pembrolizumab in combination with lenvatinib). Postoperative histology revealed two R0 and one R1 resections. These experiences demonstrated the feasibility of this approach, it being associated with complete resections and durable locoregional control. Evidence for the value of using neoadjuvant, targeted therapies has also emerged from a study[66] that comparing historical cohorts and treatment strategies. Patients were divided into three groups based on the time of diagnosis and treatment, 2000–2013, 2014–2016, and 2017–2019. The average survival time was 0.67, 0.88, and 1.31 years respectively. Multifactorial analysis showed that the 2017–2019 group was significantly associated with better survival. Notably, targeted therapies were only administered to patients in the 2017–2019 group, and 20 patients (8 of whom had stage IVc disease) underwent surgery after neoadjuvant BRAF inhibitor therapy, with an average 1-year survival rate of 94%.

Neck radiotherapy, systemic therapy, or the combination of both after complete or near-complete resection (R0 or R1) should be considered after surgery, as they have been associated with a lower rate of locoregional recurrence or progression, and more favourable long-term survival[5,6]. No evidence is available yet on the value of targeted therapy or immunotherapy in an adjuvant setting.

Final approval in the dedicated general assembly meeting

After a thorough discussion of the results, a separate vote was held to approve the above position statement in its entirety. Of the 184 participants, 173 (93.51%) voted in favour, 8 (4.32%) remained neutral, and 4 (2.16%) voted against the statement.

The present position statement was thus approved by the ESES members and could represent a guide for uniform definition, management, and treatment of patients with advanced thyroid carcinomas.

Author contributions

Marco Raffaelli (Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing—original draft, Writing—review & editing), Nikolaos Voloudakis (Conceptualization, Data curation, Formal analysis, Methodology, Writing—original draft, Writing—review & editing), Marcin Barczyński (Supervision, Writing—review & editing), Katrin Brauckhoff (Writing—original draft, Writing—review & editing), Cosimo Durante (Conceptualization, Methodology, Writing—original draft, Writing—review & editing), Joaquin Gomez-Ramirez (Conceptualization, Methodology, Writing—original draft, Writing—review & editing), Ioannis Koutelidakis (Conceptualization, Methodology, Writing—original draft, Writing—review & editing), Kerstin Lorenz (Conceptualization, Methodology, Writing—original draft, Writing—review & editing), Ozer Makay (Conceptualization, Methodology, Writing—original draft, Writing—review & editing), Gabriele Materazzi (Methodology, Writing—original draft, Writing—review & editing), Rumen Pandev (Methodology, Writing—original draft, Writing—review & editing), Gregory Randolph (Supervision, Writing—review & editing), Neil Tolley (Methodology, Writing—original draft, Writing—review & editing), Menno Vriens (Methodology, Writing—original draft, Writing—review & editing), and Thomas Musholt (Conceptualization, Methodology, Supervision, Writing—original draft, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The data that support the findings of this study are openly available in Figshare at http://doi.org/10.6084/m9.figshare.25060868[189]. Further data can be made available upon reasonable request to the corresponding author.

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