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REVIEW ARTICLE

Classification of aerodigestive tract invasion from thyroid cancer

Michael Brauckhoff

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Abstract
Background Widely invasive extrathyroidal thyroid cancer invading the aerodigestive tract (ADT) including larynx, trachea, hypopharynx, and/or esophagus occurs in 1–8 % of patients with thyroid cancer and is classified as T4a (current UICC/AJCC system). The T4a stage is associated with impaired tumor-free survival and increased disease-specific mortality. Concerning prognosis and outcome, further subdivisions of the T4a stage, however, have not been made so far.
Methods This study is based on a systematic review of the relevant literature in the PubMed database.
Results Retrospective studies suggest a better outcome in patients with invasion of the trachea or the esophagus when compared to laryngeal invasion. Regarding surgical strategies, ADT invasion can be classified based on a three-dimensional assessment determining surgical resection options. Regardless of the invaded structure, tumor infiltration of the ADT can be subdivided into superficial, deep extraluminal, and intraluminal invasion. In contrast to superficial ADT invasion, allowing tangential incomplete wall resection (shaving/extramucosal esophagus resection), deeper wall and intraluminal invasions require complete wall resection (either window or sleeve). Based on the Dralle classification (types 1–6), particularly airway invasion, can be further classified according to the vertical and horizontal extents of tumor invasion.
Conclusions The Dralle classification can be considered as a reliable subdivision system evaluated regarding surgical options as well as oncological outcome. However, further studies determining the prognostic impact of this technically oriented classification system are required.

Keywords Thyroid cancer · Airway invasion · Classification

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M. Brauckhoff (✉)
Department of Surgery, Haukeland University Hospital, Jonas Lies vei 65, 5021 Bergen, Norway
e-mail: michael.brauckhoff@k2.uib.no

M. Brauckhoff
Department of Clinical Sciences, University of Bergen, Bergen, Norway

Introduction

According to the current classification systems by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), the widely invasive extrathyroidal thyroid cancer (TC) is classified as potentially resectable (T4a, e.g., invasion of the airway, esophagus, or muscles) or usually not resectable (T4b, e.g., invasion of large arteries or the prevertebral fascia) [1–4].

Invasion of the aerodigestive tract (ADT) including larynx, trachea, hypopharynx, and/or esophagus can be found in 1–8 % of all patients with TC, more often (10–20 %) in local recurrent TC [5–7]. The majority of patients with ADT invasion (about 60–70 %) present with poorly differentiated TC (PDTC) or anaplastic thyroid cancer (ATC) [3, 5].

ADT invasion is associated with significant morbidity (e.g., dyspnea, dysphagia, and bleedings) and mortality. The impact of ADT invasion by TC is illustrated by the fact that about 50 % of fatal outcomes in TC are caused by local tumor complications [8].

Due to anatomical reasons, patients with widely invasive TC present mainly with airway invasion (50 %). Esophagus invasion can be found in 25 % of T4 patients. In the majority of the cases, invasion of the ADT originates from primary tumors or local recurrences, but in 10–20 %, lymph node metastases (LNM) or soft tissue infiltrates may invade the trachea or the esophagus [5].

Several treatment options (e.g., surgical resection, radioiodine treatment in differentiated TC (DTC), external radiation, intraluminal treatment options (e.g., laser, stent), chemotherapy, tracheostomy, or percutaneous endoscopic gastrostomy) are available. The only treatment that can offer curative intention, however, is surgical resection [5].

ADT invasion by TC occurs stepwise from the outer parts of these organs and differs biologically from primary tumors for that reason alone. In about 75 % of the patients, at the time of diagnosis, ADT invasion affects not the complete wall (non-transmural invasion), but in 25 %, transmural invasion with intraluminal tumor manifestation can be found [5, 9]. In many cases, though, the tumor can be removed by tangential incomplete wall resection and without opening the lumen of these organs. In more advanced cases, however, complete wall resection is required for complete tumor removing which on the other hand is not necessarily meaning circular (sleeve) resection. For noncircular wall resections (window), several types of wall reconstruction have been developed [10].

As indication to surgery, all these resection options have never been studied in controlled studies. It can be assumed, however, that complete tumor resection particularly in DTC, regardless of the type of resection, is of benefit in terms of local control and survival [9–11]. In other words, the least radical resection that is required for receiving resection-free margins seems to be adequate: there are no data showing that the extent or the type of resection matters if a R0 resection could be achieved.

The present paper classifies the ADT invasion from thyroid cancer based on surgical considerations.

Pathophysiology of aerodigestive tract invasion from thyroid cancer

Invasion of the ADT is, as mentioned, a stepwise process from the outer (superficial) into the deeper layers and last into the lumen (Table 1). This process differs somewhat between the anterolateral cartilaginous tracheal wall, the posterior part of the trachea, and the muscular wall of the esophagus. Remarkably, tumor invasion respects, however, over a relative long time period the inner layer, the mucosa. When the cartilage, the intercartilaginous, or the muscular layer are penetrated, the tumor very often grows firstly horizontally and vertically between the mucosa and the deeper layers before intraluminal manifestation occurs [12]. As a consequence, in intraluminal ADT invasion, the area of tumor invasion is very often much larger than expected from intraluminal assessment.

Regardless of the site of invasion, the invading process is probably triggered by the expression of matrix metalloproteinases (MMPs) and a reduced activity expression of E-cadherin [13, 14]. It could be shown that higher concentration of MMPs is associated with tissue degradation which is one precondition of tumor invasion [14]. The loss of E-cadherin leads to decreased intercellular adhesion which seems to be an important process in metastatic spread and invasion in TC [13, 15].

Table 1 Stages of laryngotracheal invasion in thyroid cancer (modified after Shin et al. [12])

Stage	Invasion	Definition
1	Adjacent	Perilaryngotracheal adhesion
2	Superficial	Invasion of the cartilage
3	Deep	Invasion of the intercartilaginous space and/or the mucosa without intraluminal manifestation
4	Intraluminal	Intraluminal tumor

Stage of disease assessment in aerodigestive tract invasion from thyroid cancer

With respect to (surgical) treatment strategies, ADT invasion from TC can be classified and assessed according to many parameters as there are the type of invaded structure (trachea, larynx, esophagus, or hypopharynx), treatment intentions (curative versus non-curative), surgical resectability (resectable versus non-resectable), the course of disease (slow versus rapid progression), tumor entity, tissue penetration (superficial versus deep versus intraluminal), or according to surgical considerations when planning complete well resections and the method of reconstruction (Table 2).

Concerning invasion of the trachea and the esophagus, there is no prognostic difference between both structures when all tumor tissue can be removed. Invasion of the larynx, however, reflects a more advanced stage of the disease [9] which should be considered in decision making regarding treatment options.

Tumor entity is a strong predictor of survival after surgery for ADT invasion. Whereas the 5-year survival rate in DTC is about 75 %, it declines to under 60 and 20 %, respectively, in patients with medullary thyroid cancer (MTC) and ATC [9].

Technically, resectability is given as long the prevertebral fascia (Fig. 1) and/or the large mediastinal arteries are not involved. Extensive invasion of the mediastinal trachea is limiting, too. Appropriate imaging excluding these conditions is required.

Another important aspect biasing surgical decision making is if surgery can be performed in curative intention (no distant metastases). As mentioned earlier, local control is of high impact in TC. Consequently, radical surgery may be indicated in patients with distant, but not or only slowly progressing metastases [5].

One of the main aspects requiring concern in the process of decision making is the status of the patient. It cannot be made

Table 2 Stage of disease assessment in aerodigestive tract invasion from thyroid cancer

Parameter	Definition	Comments
Invaded structure	Larynx/trachea/esophagus integrity of the recurrent laryngeal nerve	No prognostic difference between the trachea and esophagus; laryngeal invasion is associated with worse prognosis
Resectability	Maximum extent of invasion technically allowing complete removal of the tumor and respective reconstruction	Criteria for irresectabilty: invasion of the prevertebral fascia and/or the large (mediastinal) vessels (arteries)
Curability	Curative versus non-curative	Local control is of high impact in treatment of thyroid cancer but does not necessarily reflect curative treatment intention
Course of disease	Distant metastases	Progressive distant metastases usually excludes extensive surgery
Tumor type	Entity	Prognosis is determined by the tumor type (e.g., well-differentiated versus poorly differentiated thyroid cancer)
Patient	General health status	Higher age and reduced general health status usually exclude advanced resection
Depth of wall invasion	Extraluminal vs. intraluminal	Determines if complete or incomplete (tangential) wall resection would be reasonable; requires appropriate examination including CT/MRI/endoscopy/possible endoscopic ultrasound
Extent of invasion in horizontal and longitudinal dimentions in deeper wall invasion	See the Dralle classification [5]	Predicts type/extent of complete wall resection

abundantly clear enough that general health status (e.g., age, additional diseases, and compliance) and patients' attitude should be considered as much important as the local situation including previously performed surgery or radiation [5].

Technically, a three-dimensional assessment of the tumor (depth of invasion, horizontal and vertical extent) is mandatory. This determines mainly the type of surgery that will be required for complete tumor removal.

Fig. 1 Technically irresectable, poorly differentiated thyroid cancer on the right side with invasion of the larynx, esophagus, and prevertebral fascia in a 78-year-old man

Surgical strategies in aerodigestive tract invasion in thyroid cancer

From a technical point of view, when planning surgery in treatment of ADT invasion from TC, the strategy depends on (a) invasion site, (2) depth of invasion into the wall, and (3) horizontal and vertical extent.

Tangential, incomplete wall resections (without opening of the lumen) of the trachea (shaving) as well as of the esophagus (extramucosal resection of the muscle layer) offer excellent results in terms of tumor-free resection margins and outcome [9]. Deeper invasions, however, require complete wall resections. The challenge in all these situations without intraluminal manifestation is to determine the depth of invasion (Fig. 2).

CT, MRI, and endoscopic examination are always required in those situations. Transcutaneous or, particularly, endoscopic ultrasound can improve the accuracy regarding the question of which layer is affected or spared [16–19]. However, the depth on invasion usually is often somewhat overestimated by imaging procedures [6, 20] which should be taken into consideration.

The comparison of different surgical procedures is limited by several aspects (see below). All comparing studies available regarding incomplete (shaving) vs. complete resection on the trachea are retrospective. The patient cohorts usually are heterogeneous. Furthermore, a different extent of surgery reflects commonly different stages of invasion and disease [5, 6]. Whereas there is broad consensus that tumor debulking should not be performed routinely [9, 11], there is a

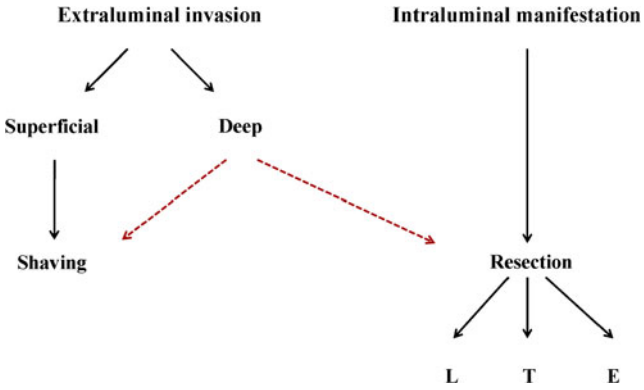

Fig. 2 Classification of aerodigestive tract invasion with respect to depth of wall invasion (superficial versus deep versus intraluminal) determining surgical resection strategy to achieve tumor-free resection margins. *L* larynx, *T* trachea, *E* esophagus

controversy how non-transmural invasion should be managed. In those situations, shaving gives good oncological results, in particular in DTC where adjuvant radioiodine treatment and/or external radiation improve local control even in microscopically incomplete resection [5, 6, 9].

Table 3 Surgical classification of complete airway wall resection (modified after Dralle et al. [5])

Resection type	Definition	Indication/technical remarks
1	Window resection within the laryngotracheal area	Unilateral tumor invasion in the laryngotracheal area; maximal extent 2 cm vertical and max. 1/4 horizontal of the circumference; RLN needs to be resected
2	Window resection of the tracheal wall	Unilateral tumor invasion of the (anterolateral) wall of the trachea; maximal extent 2 cm vertical and max. 1/4 horizontal of the circumference; RLN can be preserved in some cases
3	Circular wall resection within the laryngotracheal area	Unilateral tumor invasion >2 cm vertical and/or >1/4 horizontal of the circumference; RLN resection required; oblique resection required to preserve the contralateral RLN; temporary tracheostomy highly recommended
4	Circular wall resection of the trachea	Unilateral or bilateral wall invasion >2 cm vertically and/or >1/4 of the circumference; RLN can be preserved in some cases
5	Laryngectomy	Bilateral larynx invasion, invasion of the trachea >5–6 cm vertically
6	Cervical evisceration	Additional invasion of the esophagus over a longer distance

RLN recurrent laryngeal nerve

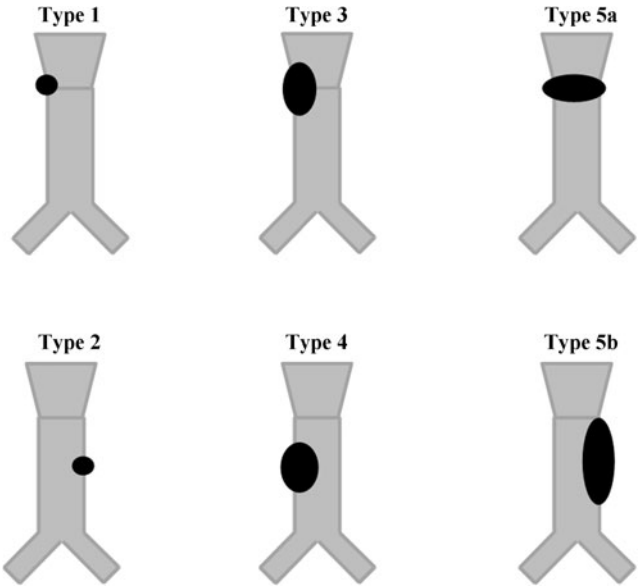

Fig. 3 Classification of deep or intraluminal airway invasion from thyroid cancer according to the Dralle classification of laryngotracheal resections [5]

Classification of deep airway invasion from thyroid cancer

According to the required surgery in deeper wall invasion, Dralle and coworkers [5] classified six types of complete wall resection on the larynx and trachea (Table 3, Fig. 3). Three main types of resection are distinguished: (1) non-circumferential wall resections (window resection), (2) circular wall resections (sleeve) with anastomosis, and (3) resection without

Fig. 4 Deep extraluminal type 2 invasion in a 72-year-old man with papillary thyroid cancer

reconstruction including laryngectomy and permanent tracheostomy. With respect to the localization of invasion (larynx versus trachea), the non-circumferential and the circular resection are subdivided since the surgical management, particularly regarding the recurrent laryngeal nerve (RLN), differs between these localizations. Window resections are classified in type 1 (larynx, laryngotracheal area) and type 2 (trachea only (Fig. 4)). Circular resection comprises type 3 (resection of the laryngotracheal region (Fig. 5)) and type 4 (trachea (Fig. 6)). In the case a laryngectomy is required, about 40–50 % of the patients present at the same time with advanced invasion of the esophagus, requiring complete evisceration [21]. The Dralle classification makes a distinction between laryngectomy only (type 5) and laryngectomy with extensive esophageal resection (cervical evisceration, type 6) [5, 7, 21].

The spectrum of surgical techniques regarding complete trachea wall resection is very heterogeneous. For sleeve resections, for example, different strategies with horizontal, oblique, or "step" resection has been developed [11, 15, 22–24] depending on the localization of the tumor or technical surgical considerations. The Dralle classification, however, simplifies all these different procedures with respect to the required reconstruction (defect covering with a flap versus primary tracheal anastomosis versus no airway reconstruction). More complex situations (e.g., invasion on two sites) can so readily be classified, too. Furthermore, the impact of

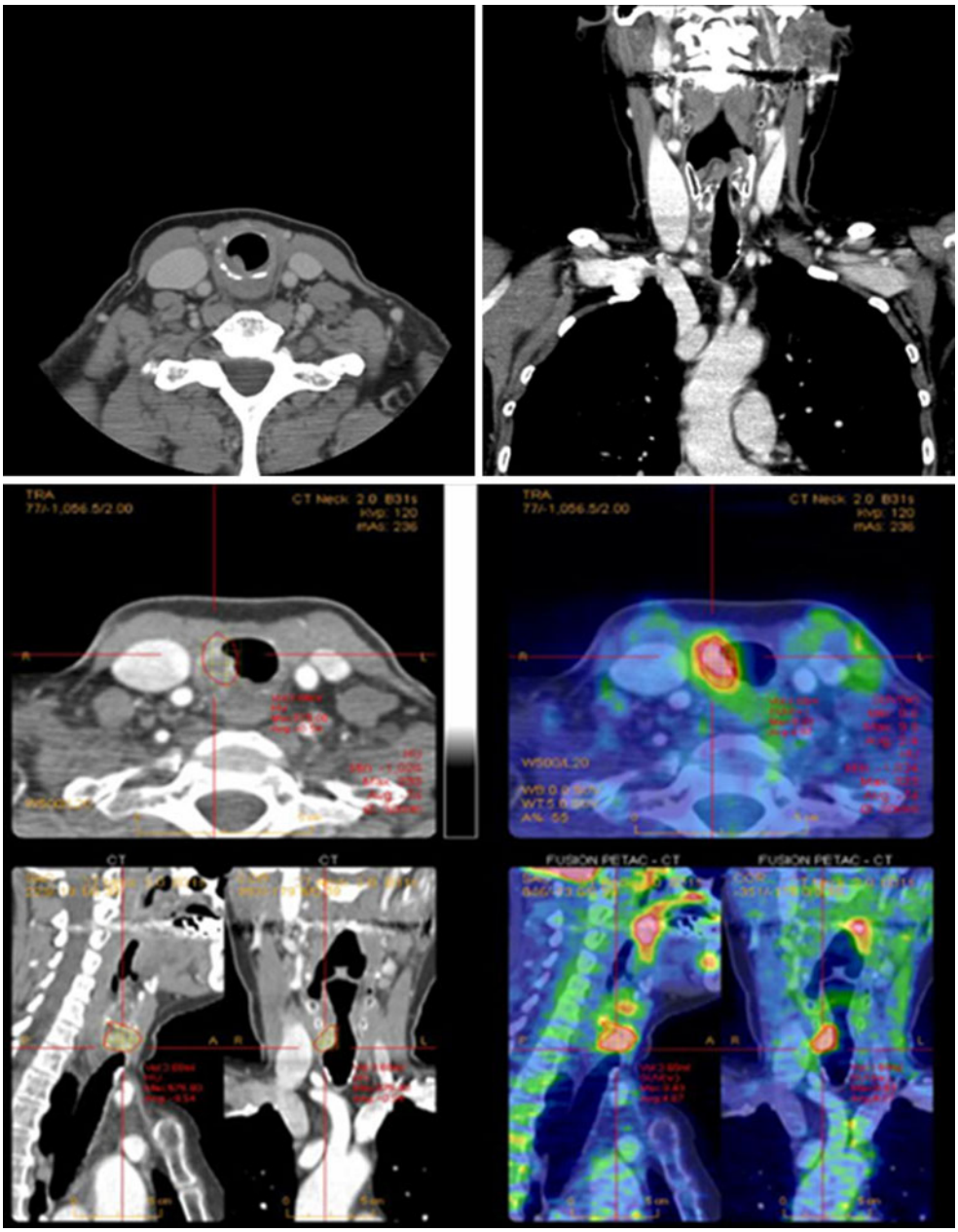

Fig. 5 Intraluminal type 3 laryngotracheal invasion on the right side in a 60-year-old female with recurrent papillary thyroid cancer

Fig. 6 Deep extraluminal type 4 tracheal invasion in a 66-year-old man with medullary thyroid cancer

this classification is evaluated in terms of associated morbidity as well as oncological results (rate of resection-free margins, recurrence-free survival, and disease-specific survival) [5, 9].

Based on this categorization of surgical procedures, deep laryngotracheal tumor invasion can be conclusively classified. However, there is an ongoing controversy regarding window versus sleeve resection [24]. Some surgeons argue in favor of sleeve resections, in principle, based on two main arguments. Firstly, window resection would be technically more difficult, in particular when the resected areas become larger and situated more laterally or even dorsally. Secondly, sleeve resection would offer better oncological results since the distance between the tumor and resection margins would be larger [10, 11, 24]. However, when compared to circular resection requiring bilateral dissection, window resection has the advantage that the contralateral RLN usually is not at risk during surgery. Moreover, in experienced hands and when considering the technical limitations (particularly regarding the maximum extent a window should not exceed, see above), a window resection is not more complicated than a sleeve resection and does not have a higher morbidity [9].

Regarding oncological outcome, a definitive conclusion cannot be made so far. Since window and sleeve resection reflect a different extent of the disease, it cannot be excluded that a sleeve resection in a situation when a window is technically possible would offer a better oncological outcome. However, there are no data showing that window resection is associated with worse oncological outcome when compared to sleeve resection [5, 6, 9].

The proposed Dralle classification has some limitations. Firstly, it defines more the surgical procedure than the type of invasion. Complex invasion (e.g., deep on one side, superficial on the other side) is disregarded. Secondly, it is focused on the trachea, and coincident invasion of the esophagus cannot be included. Thirdly, the classification is only reasonable for surgeons using window resections as alternative to sleeve resection in patients with limited extent of tracheal or laryngotracheal invasion.

Classification of esophageal invasion from thyroid cancer

Even a prognostic difference between localized and superficial and intraluminal extensive invasion of the esophagus can be assumed, no data endorsing this hypothesis or allowing any prognostic classification are available. As invasion of the airway, esophageal invasion, regardless of the extent, is classified as T4a according to the current UICC/AJCC system [1, 2].

Concerning the surgical strategies (e.g., incomplete versus complete wall resection), a comparable classification as for tracheal invasion has not yet been developed. The majority of patients presenting with invasion of the digestive system can be treated by resection of the muscle layer without opening the lumen. When primary suture of the muscle defect is not possible, muscle flaps can be used. In very rare situations, more radical resections are required. In those situations, however, local procedures (e.g., window or sleeve resection with muscle flap or primary anastomosis) are seldom as ever suitable. Usually, in those advanced situations, resection of the cervical esophagus requires complex reconstruction either by using a free jejunal flap or a gastric pull-up. Sleeve resection of the esophagus with complex reconstruction has been classified by Dralle as resection type 6 (cervical evisceration) [5, 6, 9, 21].

Nonetheless, since, clinically, the airway invasion usually dominates, esophagus invasion has so far not been classified using a separate system.

Results of surgery in aerodigestive tract invasion from thyroid cancer

As mentioned earlier, although ADT invasion from thyroid cancer is not a rare event and is associated with significant disease-related morbidity, no controlled studies have been performed so far. Besides many cohort studies, there are only a few retrospective studies available comparing different resection strategies. The majority of these studies include heterogeneous patient cohorts. A strong bias regarding the appraisal regarding the results of shaving versus complete wall resection is given by the fact that, in almost all cases, the decision making was based on invasion depth and disease-specific factors which means that for example shaving usually was performed in either superficial invasion or more aggressive tumors. It is, therefore, not clear if a complete wall resection in a superficial wall invasion would result in a better oncological outcome when compared to a tangential resection

only. Anyhow, shaving offers excellent long-term results with 5-year survival rates >90 % and low recurrent rates (<25 %). In 13 available comparative studies, significant differences between shaving and complete wall resection regarding tumor-free survival and/or disease-specific survival could be very seldom if ever determined. Depending on the follow-up, local recurrence rates after shaving and complete wall resection were found in 10–50 and 8–46 %, respectively. The 5-year survival rates varied between 64–98 and 62–100 %, respectively [9, 15, 24–34; review in 6].

Concerning the procedure-related morbidity, an increasing risk of complications has to be considered in more radical surgeries. Tangential resections are associated with low morbidity and mortality. In a large single-center study, morbidities of tracheal shaving and extramucosal esophagus resection were 22 and 18 %, respectively, without any mortality. After complete wall resection, however, the morbidity increased to 38 % [9]. In particular, cervical evisceration (Dralle classification types 5 and 6) was associated with relevant mortality [9, 21].

Conclusion

Clinical classification systems should simplify the description of clinically relevant, different disease stages or categorize treatment options. Regarding ADT invasion from thyroid cancer, no data suggesting a further subdivision of the UICC/AJCC T4a stage based on prognostic considerations are available. Concerning the surgical treatment options, however, a classification of the stepwise process of ADT invasion based on three-dimensional assessment is recommended. Whereas the depth of invasion determines if a tangential or a complete wall resection should be performed, the Dralle classification is categorizing the required extent of complete wall resection in horizontal and vertical dimensions of deep tracheal wall invasion.

Conflicts of interest None.

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