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Invasive thyroid cancer: management of the trachea and esophagus

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Most patients who present with thyroid carcinoma have well differentiated histology and intrathyroidal tumors that carry an excellent prognosis. Adverse prognostic factors have been well-established and include age, extrathyroidal extension, tumor histology, primary tumor size, and distant metastasis [1]. Extrathyroidal extension has the greatest negative impact on prognosis, with 10-year overall survival rates dropping to 45% in patients who have extrathyroidal extension compared with 91% for those who have encapsulated tumors [2]. The reported incidence of extrathyroidal extension in well-differentiated thyroid carcinoma varies but ranges from 6% to 13% [1–4]; therefore, extrathyroidal extension is a relatively frequent occurrence in a busy thyroid cancer practice. In a review of 262 patients with invasive thyroid cancer, the most commonly involved structures included the strap muscles (53%), recurrent laryngeal nerve (47%), trachea (37%), esophagus (21%), lateral neck structures including the great vessels and vagus nerve (30%), and larynx (12%) [5]. Invasion of extrathyroidal structures most frequently occurs by the primary tumor but may also occur from extranodal extension of metastatic disease [6].

Surgery remains the mainstay of therapy for locally advanced thyroid cancer, with complete resection with negative margins a fundamental goal. All agree that gross disease is best treated surgically; however, in the complex neck bases resection of critical structures such as the recurrent laryngeal nerve, trachea, and esophagus can be associated with significant morbidity. One must balance the need for gross disease resection with the morbidity of that resection. The morbidity of the extensive resection that may be necessary for locally invasive thyroid cancer has led some surgeons to attempt to conservatively approach these tumors using peeling or shaving techniques aimed at preserving function. Such conservative approaches rely on the administration of postoperative radioactive iodine (RAI) with or without external beam radiotherapy (EBRT) to manage microscopic disease. Many patients with locally advanced thyroid cancer tend to be older patients with more poorly differentiated histologic variants. Tumors in such patients can be non-RAI avid, and the response to RAI therapy can be disappointing. The degree of surgery for locally aggressive tumors has been the source of great controversy [2,7–9] fueled by the lack of prospective studies and based largely on small retrospective studies and personal opinion. This manuscript reviews the available literature regarding thyroid cancer invasion of central neck structures in these challenging clinical scenarios.

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Evaluation

Patients with invasion of the aerodigestive tract may present with clearcut symptoms that direct the examiner to the site of invasion, such as hoarseness, stridor, hemoptysis, and dysphagia [10]. Nevertheless, most patients presenting with a paralyzed vocal cord will present without acute voice changes due to gradual compensatory function by the contralateral vocal cord [4]. This presentation highlights the need for a thorough examination and routine fiberoptic or indirect office laryngoscopy on all patients presenting for thyroid surgery. The glottis needs to be examined before and after all thyroid surgery. Voice assessment alone is inadequate. The finding of preoperative vocal cord paralysis ipsilateral to a known thyroid cancer makes the diagnosis of invasive thyroid cancer and alerts the surgeon to the need for CT scanning to delineate the extent of invasion, specifically the need for airway surgery. In one study, the identification of vocal cord paralysis in a patient without previous neck or chest surgery was 70% sensitive and nearly 100% specific for invasive thyroid cancer [4]. In addition to CT scanning, patients with vocal cord paralysis warrant further airway evaluation, and using proper equipment and topical anesthesia, office or intraoperative tracheoscopy should be performed to assess for intraluminal extension of disease. Other findings suggestive of invasive disease include a fixed cervical mass, involvement of the skin, dysphagia/odynophagia, aspiration, hemoptysis, and dyspnea.

Patients with large tumors or signs or symptoms suggestive of invasive disease warrant further radiographic evaluation. The most common options for locoregional assessment include ultrasound, CT, and MRI. Ultrasound is standard at most institutions for the initial evaluation of thyroid disease and can be combined with fine-needle aspiration biopsy for diagnostic purposes. Although highly useful in the characterization of thyroid nodules, the sensitivity of ultrasonography for identifying tracheal invasion is variable, ranging from 42.9% to 91% [11–13]. When extrathyroidal extension of thyroid cancer is suspected based on the patient's history or physical examination, cross-sectional imaging with CT or MRI is essential.

CT, a modality especially useful because it is directly interpretable by the managing surgeon, allows for a direct visual assessment of the thyroid tumor with respect to adjacent neck structures and is optimal for the assessment of tracheal or cricoid cartilage involvement while also providing excellent resolution of cervical and paratracheal lymph nodes. Ishigaki and colleagues [14] have demonstrated that CT is more accurate at detecting extrathyroidal extension when compared with ultrasonography. Optimally, CT is used with iodinated intravenous contrast, which is associated with only a short delay in RAI therapy. Often, elderly patients have advanced tumors that are not RAI avid, and if any postoperative treatment is anticipated, it is EBRT. CT with contrast represents an ideal study for advanced surgical planning. MRI with gadolinium may be a good alternative that does not interfere with RAI therapy in selected cases. MRI has been shown to be useful in detecting recurrent laryngeal nerve, [15] esophageal [16], and tracheal invasion [17], and, like CT, has been shown to be superior to ultrasound in detecting local invasion [18]. Cross-sectional imaging with CT or MRI is also useful in examining the mediastinal structures not easily seen on ultrasound, particularly if lymph node metastases are suspected. Extrathyroidal extension is associated with a higher rate of distant metastases [19]; therefore, systemic imaging is appropriate before undertaking aggressive surgery. FDG-PET/CT scanning has been shown to be particularly useful for imaging more aggressive, poorly differentiated, and less RAI avid thyroid malignancies [20]. Although the presence of distant metastasis, such as pulmonary disease, would not in any way preclude the need for central neck surgical palliation, the preoperative surgical counseling is more informed if the disease is fully staged at the time of these discussions.

A preoperative barium esophagram can identify strictures or gross invasion, as well as the level and length of invasion. Patients with laryngeal involvement who may be candidates for partial laryngeal surgery should be considered for pulmonary function and swallowing evaluation to determine their ability to handle aspiration which can postoperatively flare and become significantly symptomatic, especially in the elderly with reduced pulmonary reserve. Additional investigations may be performed at the time of surgery, including bronchoscopy/tracheoscopy, and esophagoscopy. These procedures are tremendously helpful in surgical planning and blend with preoperative CT information by allowing sensitive assessment for submucosal masses or bulges, increased mucosal vascularity, or frank intraluminal invasion of the subglottis, trachea, and esophagus. Furthermore, endoscopic measurement of sites of intraluminal tracheal or esophageal invasion obtained on initial endoscopy may facilitate the localization of surgical entry into either structure at the time of open surgical resection.

Anesthesia Considerations

Patients with invasive thyroid cancer may have a distorted airway due to tumor compression, paralyzed vocal cords, or intraluminal tumor, with a potential for hemorrhage and airway distress. Close communication between the anesthesia and surgical team including a careful joint review of preoperative imaging studies is critical. Fiberoptic nasotracheal intubation using a pediatric flexible bronchoscope with topical anesthesia is appropriate in selected cases and is a superb option in patients who are judged to have a poor mask airway. The laryngeal airway can be jointly observed with the patient sitting up on the operating room table fully awake. The fiberoptic bronchoscope can be navigated around points of obstruction until the distal trachea is reached and the endotracheal tube advanced gently over the scope into the distal trachea. A small-diameter, lubricated endotracheal tube facilitates intubation past potential points of tracheal obstruction, compression, or narrowing. Often, after joint review of the imaging studies and larynx, a mask airway can be cautiously approached and, if reasonable, transoral intubation performed. Tracheostomy under local is generally a poor way of approaching diseased airways with control. Tracheostomy is avoided if at possible, because this leads to surgical bed contamination with tracheal secretions, complicates the surgical wound, and delays postoperative wound healing. In the unusual scenario in which tracheostomy is undertaken, the level of placement should be carefully planned based on endoscopy and cross-sectional imaging if airway resection and reconstruction are being planned.

Surgical Management of Locally Invasive Thyroid Cancer

Recurrent Laryngeal Nerve

The recurrent laryngeal nerve is one of the most commonly involved structures by locally invasive thyroid cancer [4–6,8,21–23]. Hoarseness occurs in approximately 23% to 33% of patients with invasion of this nerve [4,10]. Vocal cord paralysis is very specific for recurrent laryngeal nerve invasion, [4,24] although pressure on the nerve can also lead to vocal cord paralysis in the absence of invasion [24,25]. If a functioning recurrent laryngeal nerve is adherent to well-differentiated thyroid cancer but can be peeled cleanly off during surgery, the nerve may be structurally preserved without resection as long as no gross disease is left. A nerve that is preoperatively paralyzed and found to be invaded at the time of surgery is well treated by resection.

Studies from the Mayo Clinic and Japan of patients with preoperatively functioning nerves suggest that there are no differences in survival between patients in whom the nerve is resected when compared with patients in whom the nerves are preserved as long as patients receive postoperative RAI [22,25]. The RAI avidity of a thyroid cancer may not be known at the time of resection. Older patients with poorly RAI-avid thyroid cancers, aggressive histologic

variants (tall cell, Hurthle cell, insular), or poorly differentiated thyroid cancers with low RAI avidity should be considered candidates for more aggressive surgery.

If the vocal cord is nonfunctional and the nerve is suspected to be involved with tumor, it should be resected en block with the primary thyroid cancer resection. In the rare instance that the vocal cord is paralyzed secondary to pressure on the recurrent laryngeal nerve rather than invasion, the nerve may be dissected and preserved with some potential for recovery [24,25]. When the nerve is paralyzed and resected, one should give consideration to early medialization in the postoperative setting, particularly in elderly patients who are less likely to compensate for a paralyzed cord and may sustain greater morbidity including aspiration, poor voice, and ineffective cough. Other patients may be able to compensate over time with a wait-and-see approach. Yumoto and colleagues [26] studied greater auricular nerve reconstruction or primary anastomosis of resected recurrent laryngeal nerve and compared this approach with arytenoid adduction or no reconstruction. Similar stroboscopic and voice parameters were found in the two treatment groups, which were both superior to the untreated patients.

Bilateral vocal cord paralysis is a devastating complication that generally requires tracheostomy to maintain a patent airway. To avoid this situation, every attempt should be made to preserve at least one functioning recurrent laryngeal nerve; therefore, the thyroid cancer surgeon must be aware of the preoperative glottis examination. Studies have demonstrated the utility of intraoperative monitoring of the recurrent laryngeal nerve in the reoperative setting [27,28] and for thyroid cancers [28–30] to reduce the risk of inadvertent nerve injury. The authors have found great utility of the prognostic information gained from neural monitoring in such cases. Algorithms of prophylactic tracheotomy in cases in which the surgeon is unsure of the functional status of the recurrent laryngeal nerve at the completion of advanced thyroid cancer surgery can be abandoned with the current accurate assessment that neural monitoring affords. The basic tenet in management of the recurrent laryngeal nerve in invasive thyroid cancer is straightforward. With an understanding of the functional status of the recurrent laryngeal nerve at the beginning and end of surgery, all gross disease should be resected (Fig. 1A, B).

Laryngotracheal Invasion

Tracheal invasion occurs in one third of cases of locally invasive thyroid cancer and is the third most common site of local invasion following the strap muscles and the recurrent laryngeal nerve [5]. Laryngeal involvement is relatively rare, occurring in 12% of patients with locally invasive thyroid cancer [5]. Stridor is the presenting symptoms in approximately one third of patients with laryngotracheal invasion, with hemoptysis a less common presenting symptom [10].

Laryngeal involvement is sufficiently rare that specific recommendations must be tailored for each individual case. The surgical options are essentially peeling or shave procedures, partial laryngectomy, and total laryngectomy. Peeling or shave excision may be considered when there is no gross invasion of the perichondrium. Several retrospective studies including patients with laryngeal involvement have shown no difference in survival between radical resection and shave procedures when all gross disease is completely resected [5,10,31]. Friedman noted higher recurrence rates and worse survival in patients with incomplete resection when compared with those undergoing radical resection [32]. McCaffrey [10] noted that more extensive laryngeal invasion may be more amenable to vertical laryngectomy because of the lateral location of tumors. Others have noted success with partial laryngeal surgery for locally invasive thyroid cancer [33]. Friedman and colleagues [32] demonstrated that up to 50% of the external laryngeal framework could be removed with internal laryngeal preservation. The authors' experience is that 50% of the thyroid cartilage and approximately 30% of the cricoid may be resected without complex reconstruction or tracheotomy. Greater laryngeal resection

requires some form of vertical laryngectomy reconstructive effort. Indications for total laryngectomy include airway obstruction, luminal hemorrhage, intraluminal invasion, or lack of larynx function [34–37]. This approach has demonstrated good local control for extensive larynx invasion [38] and is less morbid than organ-preserving or palliative therapies [37].

Tracheal invasion has been more extensively studied and characterized due to its greater frequency relative to laryngeal involvement [10]. A widely cited staging system by Shin and colleagues [39] is based on the depth of tracheal invasion (Fig. 2). Stage I disease invades through the capsule of the thyroid gland and abuts but does not invade the external perichondrium of the trachea. Stage II disease invades into the cartilage or causes cartilage destruction. Stage III disease extends into the lamina propria of the tracheal mucosa with no elevation or penetration of the mucosa. Stage IV disease is full-thickness invasion with expansion of the tracheal mucosa that is visible bronchoscopically as a bulge or an ulcerated mass [39]. Nishida and colleagues [40] examined 54 patients with stage II or higher tracheal invasion who underwent airway resection (40 patients) or subtotal resection without airway resection and noted a much higher recurrence rate (79% versus 8%) and a shorter mean overall survival (1.5 years versus 8.7 years) in the subtotal resection group. When patients with stage I disease who underwent shave procedures were compared with patients with invasive well-differentiated thyroid cancer without airway involvement, there was no difference in local and regional recurrence, distant metastasis, or overall survival.

Several other investigators have noted similar survival [5,10,31,41] and local control rates [10] when comparing shave procedures with more radical resection for early stage lesions. Cody and Shah found no local recurrences in appropriately selected patients undergoing shave procedures [21]. Nevertheless, others have noted higher recurrence rates [32,42] and worse survival [8,32] in patients undergoing conservative resection of tracheal invasion. Patients who undergo shave procedures and develop tracheal recurrence have worse subsequent disease-free and overall survival when compared with patients undergoing tracheal resection at the initial presentation [7]. These findings support a more aggressive surgical approach to tracheal invasion, [7,32,36,43–46] although not without additional morbidity [45,46]. Leaving macroscopic disease leads to local recurrence and worse survival for these patients, and shave procedures should be reserved for carefully selected circumstances [5,10,21,31,32,40]. Conflicting results in the literature might be attributed to varying definitions of invasion, complete versus conservative resection, a wide range of histologies, and varying postoperative adjuvant therapy. In patients with superficial tumor adherence to the trachea, one should consider peeling or preservation procedures. RAI therapy should not be expected to compensate for inadequate surgical resection. In patients with more aggressive variants such as tall cell, insular, Hurthle cell, or poorly differentiated thyroid cancers, complete surgical resection is considered optimal therapy. Many factors need to be weighed in deciding who is best served with airway resection. For patients with a poor medical condition, other sites of extensive locoregional disease, or a high burden of distant metastases, conservative surgical peeling or shaving and avoidance of tracheal resection with plans for postoperative EBRT may be more appropriately considered.

When tumor has invaded into or destroyed tracheal cartilage, shave procedures are likely to leave behind macroscopic residual disease, and more aggressive therapy should be considered. Options include window resection or circumferential tracheal resection and reanastomosis. Window resection can be done for limited involvement of an anteriorly or laterally located tumor and can be closed primarily or with strap muscles and periosteum (Fig. 3) [31]. If more than one tracheal ring is to be excised, sleeve resection and reanastomosis is required. Tumors with intraluminal involvement and involvement of anterior and lateral tracheal wall are not amenable to window resection, and circumferential resection and primary anastomosis is required.

Critical considerations in tracheal resection include the tracheal blood supply, the length of the involved segment, and preservation of the recurrent laryngeal nerves. Tracheal blood supply enters laterally from the inferior thyroid artery to join two longitudinal vascular anastomoses. This lateral blood supply should be carefully preserved; therefore, one should avoid circumferential mobilization of the trachea [47,48]. A total of 5 to 6 cm of trachea can be resected and primarily reanastomosed without tracheal or laryngeal mobilization [31], but this varies from patient to patient and requires some degree of neck flexion. A supralaryngeal release involves division of the thyrohyoid musculature, yielding 0.5 cm of length, and division of the thyrohyoid membrane, producing an additional 2.0 cm [49]. Caution must be used with this maneuver to avoid creating a pharyngotomy. Additional length can be gained with division of the suprahyoid musculature [50]. Inferiorly, several centimeters can be gained by sternotomy and hilar mobilization, starting with the right hilus and inferior pulmonary ligament, dissection of the pulmonary artery and vein, and reimplantation of the left mainstem bronchus into the bronchus intermedius [51]. Fortunately, these procedures are rarely required.

When portions of the cricoid or larynx are involved in the resection, Grillo has described parallel bayonet or stair-stepped tracheal incisions to allow the inferior tracheal segment to fill in portions of the resected larynx [45]. Closure of the proximal and distal stumps should be undertaken with 3-0 to 4-0 simple interrupted Prolene sutures, with the knots tied outside the tracheal lumen. The closure starts in the midline of the membranous trachea and proceeds laterally. An air-tight closure should be confirmed by deflating the endotracheal tube, flooding the operative field with saline, and having the anesthesiologist perform a Valsalva maneuver. After the wound is closed, the submental skin should be sewn to the chest with a heavy stay suture to prevent inadvertent neck extension. This suture is left in place for 2 to 3 weeks. A low-pressure cuff endotracheal tube is left in place for at least 24 hours. A tracheostomy should be avoided because it can be a nidus for infection and granulation tissue formation. Complications include hypoparathyroidism, mediastinitis, anastomotic dehiscence, vocal cord paralysis, and death. Dehiscence occurs in approximately 4% of primary cases and 15% of reoperative cases [7].

A note of caution is warranted here for the head and neck surgeon. In patients requiring significant tracheal or cricoid resection and reconstruction, one must be acutely aware of glottic function at every stage of the procedure. If such patients have only one remaining recurrent laryngeal nerve preoperatively, which is common, the surgeon should exert extreme caution in its preservation during the ablative and reconstructive airway maneuvers of the procedure. Airway reconstruction will be of little benefit if the glottis is affected by bilateral vocal cord paralysis postoperatively.

Esophageal Invasion

Esophageal invasion most commonly occurs in association with tracheal invasion, [6,44] although it can also occur from extracapsular spread from paratracheal or paraesophageal lymph nodes. Esophageal invasion is found in approximately one fifth of patients with locally invasive thyroid cancer [5,6]. Esophageal invasion by thyroid cancer is a poor prognostic factor and is associated with a significant decrease in overall survival [5,40]. At the time of surgery, an esophageal bougie or feeding tube placement can be helpful in identification of the esophageal lumen. Most frequently, esophageal invasion involves only the muscularis layer and spares the mucosa and submucosa [5]. In such cases, a cuff of muscularis provides the margin around tumor and avoids frank esophageal entry. If a full-thickness defect is created in tumor exenteration, it can often be closed primarily if the closure is not under tension and if the tissue is healthy, non-irradiated tissue. One should achieve a water-tight multilayer closure. More extensive circumferential involvement may require segmental resection, which can be closed primarily or with a large variety of tissue transfer options. Larger defects may

require tissue transfer such as a myocutaneous pedicled flap, fascial or fasciocutaneous flap, or gastric, colonic, or jejunal tissue transfer. The choice of reconstruction technique is often related to the experience and preferences of the reconstructive team. In inoperable patients, esophageal stents can be used for palliation [52].

Adjuvant Therapy

Adjuvant therapy is a critical component of treatment for locally invasive thyroid cancer. This patient population is at increased risk for postoperative local recurrences, regional nodal recurrence, and distant metastasis. The mainstay of postoperative adjuvant therapy is RAI and thyroid-stimulating hormone (TSH) suppression. Cooper and colleagues [53] demonstrated an association between the degree of TSH suppression and disease progression in high-risk patients, but this association lost significance after inclusion of RAI in the analysis. A meta-analysis demonstrated a decrease in adverse clinical events associated with TSH suppression [54]. The current recommendation by the American Thyroid Association for high-risk patients is TSH suppression below 0.1 mU/L [55]. Mazzeferri has demonstrated improved locoregional control, decreased distant metastasis, and fewer cancer-related deaths in patients over 40 years old treated with postoperative iodine 131 remnant ablation [56]. Others have demonstrated improved local control but no survival advantage [57].

Patients with locally invasive thyroid cancer are more likely to have aggressive histologic variants that may not effectively concentrate RAI [8,9]. For patients with only anterior strap muscle invasion and complete tumor resection, no additional therapy may be required. For patients at risk for residual microscopic disease or with significant local invasion into the trachea, larynx, esophagus, or recurrent laryngeal nerve, one should consider EBRT. Several retrospective studies have demonstrated improved locoregional control with EBRT for differentiated thyroid cancer [57–61]. Tubiana and colleagues [61] demonstrated improved local control at 15 years in patients receiving EBRT over 50 Gy for locally invasive well-differentiated thyroid cancer when compared with a cohort of patients who did not receive radiation, despite the larger and more extensive tumors in the EBRT-treated patients. Similarly, Tsang and colleagues [57] found improved local control and cause-specific survival in patients with papillary thyroid carcinoma receiving EBRT for microscopic residuum when compared with patients who did not. Among patients with gross residual disease, over a third of patients will achieve complete regression, with a similar fraction experiencing no regression when receiving doses over 60 Gy [60]. Farahati and colleagues [58] investigated the role of postoperative radiotherapy in patients with extrathyroidal extension of papillary and follicular thyroid cancer and found improved local and regional control in patients older than 40 years and improved recurrence-free survival in patients older than 40 years with invasive papillary thyroid carcinoma and lymph node involvement. There appears to be a dose response, with greater local control achieved with doses over 50 Gy [59], but higher doses are also associated with greater late complications [61]. These effects may be improved with intensity modulated radiotherapy [62].

The order of treatment of EBRT versus RAI is best discussed jointly by the head and neck surgeon and endocrinologist. The authors favor EBRT first in cases where gross residual disease is present after surgery and in cases of high-grade histology.

Standard cytotoxic chemotherapies have shown little promise in treating advanced thyroid cancers. The most commonly used agent is doxorubicin, which has been used alone or in combination with other agents with 30% to 40% partial response rates but poor long-term results [63]. More recently, molecular targets have become areas of study in these patients. These targets include RET kinase inhibitors, B-RAF mutation targeting drugs, as well as agents

that restore RAI uptake, including retinoids and histone deacetylase [64]. These agents are in preclinical or early clinical evaluation at this time.

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Fig. 1.
Recurrent laryngeal nerve (RLN) management flow chart.

Fig. 2.
Staging system for tracheal invasion as devised by Shin and coworkers. (From Shin DH, Mark EJ, Suen HC, et al. Pathologic staging of papillary carcinoma of the thyroid with airway invasion based on the anatomic manner of extension to the trachea: a clinicopathologic study based on 22 patients who underwent thyroidectomy and airway resection. *Hum Pathol* 1993;24 (8):866–70; with permission.)

Fig. 3. Partial window-type tracheal resection for invasive thyroid cancer. Such a defect can be closed with a regional muscle flap without tracheotomy. Care must be taken to ensure that malignancy has not tracked circumferentially around the involved tracheal rings, which may require a sleeve resection rather than window resection.