Prognosis and Management of Invasive Well-differentiated Thyroid Cancer

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Gross involvement of the trachea or esophagus is almost a certain sign against curability, and yet one may be tempted into an extensive and dangerous operation to remove the diseased tissue…. 

\textit{D Balfour, Medical Record, 1918}\textsuperscript{1}

The rapid increase in well-differentiated thyroid cancer, in particular papillary thyroid cancer, has led to a proportionate increase in the volume of thyroid surgery performed in the United States and abroad.\textsuperscript{2,3} The 3 primary disciplines involved in treating thyroid cancer are surgery, endocrinology, and nuclear medicine.

Surgery remains the initial form of treatment of virtually all patients who have well-differentiated thyroid malignancies. The surgeon performing that surgery is charged with the responsibility of removing all evidence of disease located in the central compartment of the neck, including the mediastinum, as well as nodal disease that is often present in the lateral compartments of the neck. That surgery is currently being performed by surgeons with a range of training experience in performing routine thyroidectomy, paratracheal node dissection, lateral compartment nodal dissection, and mediastinal dissection. Although most cases of well-differentiated thyroid cancer do not require the skill sets to manage aerodigestive tract involvement or nerve

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involvement, when the disease requires that such intervention is essential for a complete resection, it is incumbent on the surgeon to be able to manage such cases of advanced disease in the primary setting. Closing the wound after performing a more limited resection and referring the patient to a surgeon who performs that type of surgery after the patient develops a recurrence has been shown to lead to a less favorable outcome.4

Specialties that are involved in the surgical management of thyroid cancer include otolaryngologists, endocrine surgeons, general surgeons, and surgeons with fellowship training in surgical oncology. Although statistics show that most of the incremental new cases of thyroid cancer that are treated each year are for early stage disease, there remains an ever-present danger that a patient presenting with thyroid cancer may have invasive disease that will complicate the surgical procedure and challenge the surgeon to perform a complete resection and render the patient functionally intact. It is imperative that all specialties performing thyroid cancer surgery are trained in all aspects of upper aerodigestive tract resection and reconstruction so that they are prepared to meet the demands that disease in these patients can present.

IDENTIFYING THE PATIENT WITH INVASIVE THYROID CANCER

One of the major challenges in treating patients with invasive thyroid cancer is that most patients with this form of the disease are asymptomatic and the disease takes the patient and the surgeon unawares. Four types of patients can be identified before surgery as having an increased likelihood of invasive disease:

1. Asymptomatic patients who present with an abnormal examination related to either vocal cord dysfunction or evidence of a subglottic or tracheal mass. The identification of vocal cord paralysis is 1 of the first clues that the surgeon is dealing with invasive disease that has extended outside the normal bounds of the thyroid gland to involve the recurrent laryngeal nerve (RLN).
2. Patients with recurrent thyroid cancer in the central compartment.
3. Symptomatic patients with biopsy-proven thyroid cancer who present with a change in voice, dyspnea, hemoptysis, or dysphagia.
4. Patients with documented invasive disease based on preoperative cross-sectional imaging of the central compartment showing invasion of the central viscera, or lateral compartment nodal metastases showing extracapsular extension.

All patients in the first 3 groups should undergo cross-sectional imaging before surgery to better anticipate the extent of the surgery that is required to achieve a complete resection. One additional category of patient is the one who presents with pulmonary or other systemic metastases that are found to be of thyroid origin. Such patients should undergo cross-sectional imaging of the neck and the mediastinum.

Despite the ominous appearance of an intraluminal tracheal mass in a patient with biopsy-proven thyroid cancer, the surgeon should be aware that all that is present in the trachea is not always invasive thyroid cancer. In 1 of my own memorable cases of thyroid cancer arising in an opera singer, preoperative imaging showed the presence of what was believed to be intraluminal extension of her disease, only to find out on the final pathologic review that the tracheal component was actually a benign thyroid rest that was not identified as benign disease until after the tracheal resection had been performed.5 In another symptomatic patient with a biopsy suspicious for thyroid cancer, preoperative imaging identified an intraluminal mass that proved to be
a chondrosarcoma arising from a tracheal ring. The fine-needle aspiration had traversed the thyroid and led to a false-positive cytologic report (Fig. 1). A patient with a large thyroid mass and a suspicious cytology was found to have intraluminal narrowing on preoperative imaging performed because of her symptomatic respiratory difficulty. The thyroidectomy proved to be benign, and the tracheal narrowing was caused by a benign tracheal stenosis of unknown cause (Fig. 2). Yet another patient developed severe airway compromise as a result of intraluminal extension of a paratracheal mass, which proved to be a schwannoma of the RLN (Fig. 3). Although most patients with an intraluminal mass and biopsy-proven thyroid cancer do indeed have invasive thyroid disease, it is not always the case.

There is a well-documented entity known as a collision tumor of the upper aerodigestive tract that results from 2 separate neoplastic processes arising in a contiguous manner to involve either the thyroid gland alone with 2 separate histologic subtypes, or the thyroid gland and the aerodigestive tract. The author recently reported such a case in which a papillary thyroid cancer was diagnosed preoperatively and a coexistent vocal cord paralysis led to cross-sectional imaging. The computed tomography (CT) scan showed findings that were interpreted as invasive thyroid cancer. Fiberoptic examination did not show any signs of a mucosal-based neoplastic process; however, because of destruction of the cricoid in this older male patient, the decision was made to proceed with a total thyroidectomy and a total laryngectomy. Final pathologic review identified a subglottic squamous cell cancer that had caused the cartilage destruction, and abutted against the intraglandular papillary thyroid cancer.6

**INCIDENCE OF INVASIVE WELL-DIFFERENTIATED THYROID CANCER**

It is difficult to know the true incidence of invasive thyroid cancer because it seems to be a moving target. With the increased incidence of small thyroid cancers detected as a result of more widespread use of ultrasonography, the percentage of cases of invasive disease has decreased accordingly.2 However, there are several institutional case series that give a glimpse of the reported incidence of aerodigestive tract invasion in tertiary referral centers. The range of invasive well-differentiated thyroid cancer is 1% to 23%.7 In the Mayo Clinic series reported by Djallil and colleagues8 18 patients had thyroid cancer extending into the lumen of the larynx or trachea out of a total of 2000 patients treated for thyroid cancer at that institution from 1913 to 1973. The risk of upper aerodigestive tract involvement, nerve involvement, and muscle involvement is directly related to the presence of extrathyroidal extension (ETE) of the primary

![Fig. 1. Chondrosarcoma of the thyroid ala misdiagnosed as an invasive thyroid cancer.](image-url)
tumor and extracapsular invasion in a metastatic lymph node. Numerous prognostic factors have been evaluated and adopted by the various staging systems for well-differentiated thyroid cancer; among them:

1. Size of the tumor
2. Age of the patient
3. Presence of ETE.

The incidence of extrathyroidal disease increases with increasing size of the primary malignancy; however, even micropapillary cancers can extend outside the thyroid gland to place the RLN, the tracheal cartilage, the larynx, and esophagus at risk. The risk of ETE is related to the biology of the tumor as well as its geographic location within the thyroid lobe, whether it is in the middle or on the periphery of the gland. The incidence of ETE in micropapillary carcinomas has been reported to be as high as 31.9%. The presence of ETE is associated with an increased incidence of recurrent disease and death caused by disease. Breaux and Guillamondegui reviewed the institutional experience with invasive thyroid cancer at MD Anderson Cancer Center and found that primary tumor size greater than 4 cm was associated with an increased incidence of mortality from disease. Involvement of more than 4 structures by the invasive disease was reported to be uniformly fatal. Similarly, primary tumor size greater

Fig. 2. (A) Thyroid nodule with calcifications (yellow arrow). (B) Benign tracheal stenosis (blue arrow).

Fig. 3. Benign schwannoma of the RLN.
than 4 cm was identified as a significant adverse prognostic factor by Andersen and colleagues\textsuperscript{13} in patients older than 45 years with invasive thyroid cancer.

The presence of disease extension outside the capsule of lymph nodes has been identified as a significant negative prognostic factor in patients with metastatic squamous cell cancer. Few studies have reported the incidence and prognostic significance of extracapsular extension in nodal metastases from papillary thyroid cancer. Yamashita and colleagues\textsuperscript{14} reported the results of a multivariate analysis in 1997 in which they concluded that disease extension outside the capsule of a lymph node harboring metastatic papillary thyroid cancer had a significant effect on the risk of distant disease as well as the risk of dying from disease. In addition, these investigators identified the risk of extranodal extension as being higher in larger lymph nodes than smaller nodes, and also found that large nodal deposits and extrathyroidal invasion correlated with the development of distant disease and death. In the Yamashita study, 50\% of the patients who died of disease succumbed within the first 10 years following treatment. Akslen and colleagues\textsuperscript{15} reported that extracapsular extension of well-differentiated thyroid cancer was associated with a short recurrence-free survival interval, but not with increased 10-year mortality. It is unclear whether the lack of longer-term follow-up led to this discrepancy between these 2 studies.

\textbf{STRUCTURES INVOLVED BY INVASIVE THYROID CANCER}

A variety of different structures can be involved in invasive thyroid cancer. Central compartment disease can invade the viscera and nerves of the central compartment as well as to extend laterally or extend caudally to involve mediastinal structures. Those structures can be divided in several different ways: they might be classified based on visceral structures, muscles, nerves, and vessels; alternatively, dividing the structures at risk based geographically on central compartment and lateral compartment is the more common way to approach this topic.

The central compartment viscera include the larynx, trachea, and esophagus. In addition, the strap muscles are the structures most commonly involved by invasive thyroid cancer. The RLN is the nerve most commonly affected by invasive disease in the central compartment. The superior laryngeal nerve is rarely reported separately in large series of invasive thyroid disease. The caudal portion of the central compartment extends to the mediastinum, where the innominate artery and vein are at risk.

In the lateral compartment, the major vascular structures are the internal jugular vein and the common carotid artery. The neurologic structures include the vagus nerve, cervical sympathetic chain, phrenic nerve, and the spinal accessory nerve. Although theoretically possible, it is rare that the hypoglossal nerve is invaded by nodal disease in the upper jugular region. The sternocleidomastoid (SCM) muscle can also be invaded by extracapsular extension of metastatic nodes.

Some series have identified the incidence of involvement of various cervical structures by invasive thyroid cancer. In the series reported by Breaux and Guillamondegui,\textsuperscript{9} 47 patients with invasive disease were analyzed. The RLN was involved in 22 (47\%), the trachea was involved in 28 (60\%), the larynx in 16 (34\%), the esophagus in 8 (17\%), and the strap muscles or platysma in 20 (43\%) patients. In addition, the vagus nerve was involved in 2 (4\%) patients, the jugular vein in 6 (13\%), the carotid artery in 3 (6\%), and the skin in 2 (4\%) patients. In Nakao’s series of 31 patients requiring tracheal resection, the following structures also required resection: RLN (61\%), phrenic nerve (10\%), vagus (13\%), and spinal accessory nerve (6\%), strap muscles or SCM (78\%), jugular vein (45\%), and esophageal muscle in 29\%. Transmural extension to involve the esophageal mucosa was reported in only 6\% of patients.\textsuperscript{16} Nishida and
colleagues\textsuperscript{17} reported the following structures involved by invasive thyroid cancer in 117 patients: trachea (59%), esophagus (31%), internal jugular vein (38%), carotid artery (7%), strap muscles and SCM (77%), vagus nerve (8%), and RLN (61%). Kowalski and Filho\textsuperscript{17} reported the following structures involved in 46 patients with invasive thyroid cancer: trachea (46%), muscle (41%), RLN (33%), larynx (24%), major vessel (13%), and esophagus (9%). From a review of these 4 series alone it is apparent that there is significant variability in the incidence of the various structures involved. The incidence of esophageal involvement ranges from 9% to 31%, the involvement of the RLN ranges from 33% to 61%, tracheal involvement ranges from 46% to 100%, and carotid artery involvement from 0% to 7%.

In the Mayo Clinic series reported by McCaffrey and colleagues, the invasion of different structures was found to have a different effect on survival. In that series, the involvement of muscle was found in 53%, the trachea in 37%, the RLN in 47%, esophagus in 21%, larynx in 12%, and a variety of other sites in 30%. Analysis of the different subsites identified the trachea and esophagus as having a statistically significant independent effect on survival, whereas completeness of resection approached statistical significance. Alternatively, invasion of muscle, the RLN, and larynx did not have a significant independent effect on survival.\textsuperscript{18} It is unclear why involvement of different structures should lead to a different effect on survival. The biology of ETE and extracapsular invasion from a lymph node is seemingly the same and is a reflection of the aggressiveness of the tumor, although the actual structures involved are in part a product of the geographic location as well as the size of the tumor within the thyroid gland or the location of the lymph node within the central or lateral compartments of the neck or mediastinum.

DECISION MAKING IN MANAGEMENT OF INVASIVE THYROID CANCER

The central premise of managing patients with invasive thyroid cancer is to clear the central compartment of the neck to protect the patient’s vital functions of being able to breathe comfortably, speak, and maintain nutrition through oral alimentation. Although a tracheostomy and a feeding gastrostomy tube can be placed, the unchecked growth of disease in the central neck challenges the patency of even a surgically created airway. The histology of the tumor, the degree of differentiation and the age of the patient are critical parameters in determining the opportunity and the likelihood of success of treating invasive thyroid cancer with adjuvant therapy once a resection has been performed. The likelihood of disease response to radioiodine (\textsuperscript{131}I) therapy has significant importance for the surgeon in terms of how complete a resection must be accomplished and what the implications are of leaving macro- or microscopic disease.

Recurrent thyroid cancer most often presents as nodal recurrence and often has a documented biology that is resistant to \textsuperscript{131}I therapy. The decision to perform extensive central compartment resections in patients with metastatic disease involves a complex decision-making process. It raises the issue as to how extensive the work-up should be before performing surgery. The most commonly reported sites for metastatic thyroid cancer are the lung and bone. The liver and brain are less frequently involved.\textsuperscript{19} In contemporary thyroid cancer management, the performance of a positron emission tomography CT scan can provide valuable information regarding the extent of disease as well as the likelihood of \textsuperscript{131}I uptake. However, the luxury of obtaining that information is lost when the invasive nature of a thyroid cancer is unsuspected before the initiation of the surgery.
SITE-SPECIFIC MANAGEMENT OF INVASIVE THYROID CANCER

Strap Muscle and SCM Muscle Invasion

Involvement of the strap, platysma, and the SCM muscles rarely causes any specific symptoms (Fig. 4). The initial approach during thyroid surgery involves elevation of the sternothyroid muscle off the surface of the thyroid gland. Adherence of the strap muscles to the surface of the gland can be seen with thyroiditis but it is often the first indication for the surgeon of the biologic aggressiveness of the thyroid cancer. Resection of the strap muscles and the SCM muscles causes little functional effect on most patients, except for professional voice users, who may be negatively affected by loss of the accessory muscles of voice production. Resection of the SCM muscle has little functional effect but does lead to loss of volume in the lateral neck, producing a contour deformity. In most instances, a cuff of muscle should be resected to obtain clearance around a biologically aggressive thyroid cancer (Fig. 5).

Laryngotracheal Complex

Because most patients who die of thyroid cancer die of airway obstruction due to invasion of the structures in the midline visceral compartment with encroachment on the airway, surgeons probably should expend as much effort on the problem of what to do at the primary operation when there is invasion of the visceral compartment, superficial or otherwise, as they do on the problem of cervical lymph node metastasis.

Djallilian M, 1974

Involvement of the larynx and trachea led to preoperative symptoms in 28% and 18% of patients, respectively with documented invasive thyroid cancer in Kowalski’s series (Fig. 6). In the series by McCarty and colleagues, 40 patients with frank airway invasion were analyzed and 11% reported hemoptysis, dyspnea was reported in 5%, and only 22% were found to have hoarseness. The poor correlation between voice changes and the presence of vocal cord paralysis is discussed in the section on nerve involvement. However, the development of dyspnea is seen only when the cross-sectional airway of the trachea has been narrowed by at least 50%, either by intrinsic disease or extrinsic compression. The rate of narrowing of the airway also

Fig. 4. Muscle invasion.
affects the patient’s awareness of dyspnea. When the process occurs slowly, patients often report that they accommodate in remarkable ways and often are incorrectly diagnosed with reactive airway disease or sleep apnea before the correct diagnosis is established.

Virtually all patients who are advised to undergo thyroid surgery have had an ultrasound examination as part of their preoperative evaluation. The performance of cross-sectional imaging is less common unless symptoms, the presence of recurrent disease, or physical findings warrant that intervention. Shimamoto and colleagues reported the sensitivity for ultrasound detection of tracheal invasion was 42.9% and for esophageal invasion it was 28.6%. Yamamura and colleagues reported a higher level of sensitivity, with 9 of 10 patients with intercartilaginous involvement predicted by ultrasound along with 9 of 10 patients with mucosal involvement. The experience of thyroid ultrasonographers varies greatly. In addition, the number of cases of invasive thyroid cancer that are seen regularly by most endocrinologists who are performing thyroid ultrasound and ultrasound-guided biopsies makes it unlikely that most patients with invasive disease are accurately diagnosed before surgery.

The mechanism for invasion of the upper aerodigestive tract by an invasive thyroid cancer has been delineated by McCaffrey and colleagues. Disease may gain access to the airway by way of the primary tumor in the thyroid or via a paratracheal node involved by metastatic disease. Fig. 7A illustrates the routes of invasion around the posterior thyroid ala to gain access to the paraglottic space. In Fig. 7B the entry is from a paratracheal node, which can directly invade the tracheal cartilage or gain entry to the membranous wall of the trachea at the level of the tracheoesophageal groove.
Direct invasion of the thyroid cartilage may occur through larger primary thyroid malignancies (see Fig. 7C). Anterior airway invasion may occur through primary tumors involving the isthmus or from delphian or pretracheal lymph nodes involved by metastatic disease manifesting extracapular extension (see Fig. 7D). A delphian lymph node involved by metastatic papillary thyroid cancer is shown in Fig. 8.

Shin and colleagues\textsuperscript{25} characterized 4 stages of airway invasion (Fig. 9):

- In stage 1 tracheal invasion, the tumor shows ETE and abuts the perichondrium, but does not invade through it.
- In stage 2 invasion, there is evidence of cartilage erosion but no evidence of transmural extension.
- In stage 3, the tumor extends through the cartilage along natural pathways that include vessels traversing the tracheal wall (Fig. 10). The disease is present within the trachea but not through the mucosa.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig7.png}
\caption{Mechanisms of tracheal and laryngeal invasion of thyroid cancer. (A) Direct invasion around the posterior border of the thyroid ala to involve the paraglottic space. (B) Invasion of the trachea by a metastatic lymph node. (C) Direct invasion of the thyroid ala from a primary tumor in the superior pole of the gland. (D) Direct invasion of the anterior trachea from a primary tumor in the thyroid lobe or isthmus. (Adapted from McCaffrey T, Bergstralh E, Hay I. Locally invasive papillary thyroid carcinoma: 1940–1990. Head Neck 1994;16:168; with permission.)}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig8.png}
\caption{Total thyroidectomy showing multifocal disease and a metastatic papillary thyroid cancer involving the paratracheal, pretracheal, and delphian lymph nodes (yellow arrow).}
\end{figure}
Stage 4 disease extends through the mucosa and is present within the lumen of the trachea.

From a prognostic perspective, Shin and colleagues reported that none of the patients with stage 1, 2, or 3 disease died within the first 5 years following initial therapy, but 1 patient did succumb to disease after 5 years. In the cohort of 11 patients with stage 4 disease, 5 of the patients succumbed within the first 5 years and 1 died of disease after that period.

In addition to these findings it is evident that preoperative tracheobronchoscopy in patients with stages 1, 2, and 3 disease would not show any abnormal tissue for biopsy unless a transmucosal biopsy is performed in stage 3 disease. Randolph and Kamar reported a series of 21 patients with invasive thyroid cancer and found that tracheobronchoscopy was abnormal in 6 of the 7 patients in whom the procedure was performed. The exact abnormal findings were not described; however, these investigators reported that the prediction of tracheal invasion by preoperative imaging was achieved in only 3 of 15 patients in whom that disease was identified at the time of surgery. Although ETE is deemed to be important in virtually all staging systems, the depth of airway invasion is not accounted for in any of the current staging systems.

Nakao and colleagues reported the depth of invasion of tumor involving the tracheal wall and found adventitial involvement in 6%, intercartilaginous extension
of disease in 10%, submucosal involvement in 48%, and mucosal involvement in 35%. They did not report the effect of the depth of invasion on prognosis.

Dralle and colleagues\textsuperscript{27} classified 6 types of laryngotracheal resections that are required based on the extent and location of the visceral invasion (\textbf{Fig. 11}):

- Type 1 was described as a limited area of invasion at the laryngotracheal junction, less than 2 cm in the longitudinal direction and less than or equal to one-third of the circumference. In type 1, the RLN is often invaded.
- Type 2 has a similar dimension but is located lower in the trachea away from the larynx.
- Type 3 tumor invasion is similar in location to type 1, at the laryngotracheal junction, but differs because of the larger dimension, greater than 2 cm longitudinally or more than one-third of the circumference.
- Type 4 invasion involves the trachea with dimensions that are greater than 2 cm longitudinally or more than one-third of the circumference.
- Type 5 invasion involves so much of the larynx that the only option for a complete resection is to perform a total laryngectomy. The minimum critical portion of the larynx that must be retained to reconstruct and restore function has been characterized in the extensive literature on laryngeal cancer surgery.\textsuperscript{28} The critical structure needed to restore function is an intact cricoarytenoid joint with a functioning RLN. Sophisticated reconstructive techniques have been described to import lining and structure to restore an adequate caliber to the laryngotracheal lumen and a sphincter to allow protection of the airway during deglutition.\textsuperscript{29}
- Type 6 resections involve the entire laryngopharynx and possibly the cervical esophagus requiring a total laryngopharyngectomy with or without a cervical esophagotomy. There are numerous options for reconstruction of this type of defect,
which include a tubed cutaneous free flap or a free visceral flap such as jejunum or a gastro-omental flap.\textsuperscript{30}

One of the important points for a surgeon is to estimate the amount of the laryngotracheal complex that must be resected to achieve clear margins around the tumor. One of the important challenges is encountered by the surgeon who is unaware of the invasive nature of a thyroid cancer that is found serendipitously to be extending outside the thyroid gland and involving the tracheal, cricoid, or thyroid cartilages. It is evident from the work of Shin and colleagues\textsuperscript{25} that looking from the outside, the surgeon risks underestimating the full extent of the disease extent on the luminal aspect of the airway. Without imaging it is difficult to know whether the disease has reached the extent of stage 1 or stage 4. Ozaki and colleagues\textsuperscript{31} evaluated the difference in the external extent of the disease and compared it with the internal extent of the disease (Fig. 12). The results of that pathologic assessment showed that the

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\textbf{Fig. 11.} Different types of laryngotracheal involvement with the appropriate design of resection and repair. (Adapted from Dralle H, Brauckhoff, M, Machens A, Gimm O. Surgical management of advanced thyroid cancer invading the aerodigestive tract. In: Clark OH, Duh QY, editors. Textbook of endocrine surgery. Philadelphia: WB Saunders; 2005. p. 325; with permission.)
extirpative surgeon runs the risk of underestimating the circumferential extent of the luminal portion of the tumor more than the longitudinal extent of the disease. As a result the surgeon can fairly accurately gage the longitudinal resection parameters based on the longitudinal extent of the external involvement of the tumor but may have to take a greater circumference than indicated based on what is seen on the external surface.

One of the significant challenges in performing surgery on the aerodigestive tract for patients with well-differentiated thyroid cancer is to decide how much of the structure of the airway to resect, with the goal of achieving clear margins. Complete surgical resection has been identified as a significant prognostic factor in well-differentiated thyroid cancer.\(^3\)\(^2\) In high-risk patients with invasive disease, in particular, the surgeon should do everything possible to achieve a complete resection. Kowalski and Filho\(^1\)\(^8\) identified incomplete resection, along with age greater than 45 years, and preoperative diagnosis of ETE as significant predictors of worse prognosis in patients with invasive thyroid cancer. The value of intraoperative frozen sections to achieve that goal has been questioned. Nakao and colleagues\(^1\)\(^6\) reported 2 patients with negative margins on frozen section, but who were found to have positive margins in the adventitial layer on permanent histologic review of the tracheal resection. These 2 patients developed recurrence at the anastomotic site; however, 6 patients with similar false-negative frozen sections did not develop anastomotic recurrence.

Patients with invasive thyroid cancer are more often older and more often have less differentiated forms of the disease, which are less likely to be treated successfully with radioactive iodine therapy. As a result, the ability to effectively treat residual disease with adjuvant modalities is usually not known at the time of surgery, but should not be assumed by the surgeon. Rather than making the intraoperative decision that “I can leave some disease because I can always give radioactive iodine,” complete extirpation of the disease should be sought in all cases.

A variety of surgical procedures are currently in use to manage invasive thyroid cancer that involves the larynx and trachea:

Shave resections are defined as the removal of macroscopic disease from the surface of the trachea without a full thickness resection of the airway. Window resections are defined as full thickness resection of a portion of the airway and closure of that window using a variety of techniques (Dralle types 1 and 2, see \textbf{Fig. 11}). It is usually considered that a maximum of one-third of the

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**Fig. 12.** Extent of invasion of the trachea, showing the greater risk of underestimating the circumferential extent rather than the longitudinal extent based on visible extent of tumor from the outside of the trachea.
circumference of the trachea can be resected without compromising the structure of the airway.

Sleeve resections of the trachea are defined as circumferential resections that require repair using end-to-end anastomoses, with or without laryngeal release procedures (Dralle types 3 and 4, see Fig. 11).

Shave excisions of the laryngotracheal complex do not require reconstruction because the structural integrity and the lining of the airway are not disrupted. In window resections, 3 common techniques can be used to reconstruct the airway defect:

1. The first is a sliding tracheoplasty or the excision of added portions of the airway to allow primary repair to be performed free of tension (Fig. 13).
2. The second is to patch the defect with either an inferiorly based or a superiorly based SCM flap to seal the defect. This technique results in remucosalization of the exposed muscle in the lumen of the airway.33

![Fig. 13](image)

Fig. 13. (A) Invasion of the anterior trachea and lower portion of the cricoid (yellow arrow) from a papillary thyroid carcinoma arising in the isthmus. (B) Disease on the surface of the first tracheal ring is readily apparent. (C) Following a window resection, the opening in the trachea is extended bilaterally (white lines) to facilitate primary repair. (D) The resulting defect can be closed primarily with direct suturing. (E, F) Sutures are placed and then secured, completing the repair.
3. The final technique is a staged repair of the airway with the initial creation of a formalized tracheal trough by suturing the skin to the mucosa. Following a 2-week period of healing, the second stage is performed by placement of a titanium mesh deep to the skin adjacent to the trough. In the final stage the composite flap composed of skin and mesh is turned inward to reline the airway with skin and provide structural integrity with the alloplast, which at that point has become incorporated through ingrowth of native tissue between and around the mesh (Fig. 14). Although this technique works well and allows for greater than one-third of the circumference to be resected, it does require a staged repair and is not favorable when the cervical skin is hair bearing, as is often the case in men. Planned postoperative external beam radiotherapy eliminates the problem of growth of hair on skin transposed into the airway.

Sleeve resection and end-to-end repair is a useful and reliable technique to achieve wide margins around the disease and primary reconstitution of the airway. The key to success in this technique is to achieve a tension-free repair to avoid the short-term risk of an anastomotic breakdown with the risk of fistula formation resulting in cervical or mediastinal infection, or the complete disruption of the airway repair with catastrophic

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**Fig. 14.** Staged repair of a window resection by creation of a tracheal trough, followed by placement of titanium mesh in the subcutaneous tissue in stage 2. The final stage involves the transposition of the fabricated composite flap with placement of the skin into the lumen and then coverage of the neck with regional skin.
consequences. The surgeon must remember that the blood supply to the trachea enters laterally (see Fig. 10) and must be preserved to avoid ischemia of the mobilized tracheal segment. Therefore mobilization of the cervical and mediastinal portions of the trachea is best accomplished with blunt dissection along the anterior wall with minimal lateral dissection. When a tension-free repair cannot be achieved with blunt dissection and flexion of the neck, then a suprahyoid or infrahyoid release of the larynx should be performed to allow several additional centimeters of mobilization of the larynx to be achieved (Fig. 15). Monofilament sutures are placed in the airway with the knots placed outside the lumen to create as little intraluminal reaction as possible and the attendant risk of forming a tracheal stenosis (Fig. 16).

A growing body of literature is centered around the controversy regarding how radical the resection of the laryngotracheal complex needs to be to achieve long-term control. This literature is flawed for several reasons because of the lack of a prospective randomized trial that appropriately stratifies patients according to the extent of the local disease based on the depth of invasion across the wall of the trachea, distinguishing between primary and recurrent disease, limiting the series to well-differentiated cancers, reporting the iodine-trapping ability of the tumor, the use of adjuvant external beam radiotherapy, the presence of distant metastases, the presence of regional adenopathy, and the adequacy of the margins around the resection. In addition, the appropriate length of follow-up is critical to determine the efficacy of the type of resection in controlling local disease. Control of local disease is a critical parameter in the successful management of thyroid cancer, because viable central compartment disease has been reported in half of the patients who die of thyroid cancer. A review of this literature shows proponents of the more limited shave resection, as well as others who believe that all patients should have a sleeve resection to ensure clearance of transmural disease. A prospective, randomized, and appropriately stratified study of that nature cannot be performed at any single institution.

When the surgeon elects to perform a shave excision of a thyroid carcinoma that is adherent to the trachea it is difficult, if not impossible, to obtain an accurate assessment of the margins of resection. A shave excision is performed by sharply separating

![Fig. 15. Release of the larynx through either a supra- or an infrahyoid approach can facilitate the tension-free repair of the trachea.](image-url)
the thyroid gland from the wall of the trachea and is usually coupled with removal of an additional layer of cartilage. Using this technique, it is impossible to comprehensively address disease extension through the incartilaginous spaces where lymphatic and vascular channels penetrate to the luminal aspect of the trachea and provide access for unrecognized disease extension (see Figs. 9 and 17). McCarty and colleagues reported that residual microscopic disease was left on the wall of the trachea in all 35 patients in whom they performed a shave excision; however, only 17% of these patients developed local recurrence at a mean follow-up of 82 months. Alternatively, Park and colleagues reported that 10 of 16 patients who underwent a shave procedure developed central compartment recurrence and 7 died of disease. The obvious advantage of performing a sleeve resection of the airway is that it provides an opportunity to assess the depth of invasion while also providing the most complete resection of the circumferential extent of the disease. This technique may be performed in the primary setting or, less optimally, in patients who are referred to a tertiary center after identifying invasive disease inadvertently. However, this technique should be part of the armamentarium of head and neck surgeons entrusted with providing surgical care of patients with thyroid cancer. Sleeve resections and primary end-to-end anastomoses can be performed successfully with acceptable risk and a low rate of operative mortality. There is a risk of tracheal stenosis as well as permanent tracheostomy, depending on the function of the RLNs.

Although uncommon, a total laryngectomy may be required in patients with extensive laryngeal involvement in whom a functional cricoarytenoid joint cannot be preserved safely without compromising the oncologic soundness of the procedure. Although sophisticated reconstructive techniques can be used to restore a patent laryngeal airway and a functional laryngeal sphincter, such extensive surgery may be warranted in younger patients with well-differentiated thyroid cancer, whereas it is not appropriate in older patients.
Because of its malleable nature, the esophagus is rarely involved transmurally. None of the patients with esophageal invasion in Kowalski’s series had symptoms before surgery (Fig. 18). More often than not, the extent of involvement is limited to the muscular layer, and with the help of a bougie placed into the lumen, the muscle layer can be removed without creating a mucosal defect in the esophagus (Fig. 19). In the absence of mucosal involvement, the muscular layer can be safely removed with seemingly little effect on the swallowing mechanism. However, as with many such statements, no true objective studies have evaluated the effect of removing varying degrees of the esophageal musculature so we do not know the exact effect on the swallowing mechanism. It is rare that the necessity to remove the esophageal musculature is performed in isolation, without removal of the RLN or other associated central
compartment structures. As a result, the functional effect on the patient is often multifactorial.

If there is transmural invasion by biologically aggressive thyroid cancer, then the extent of the circumference involved determines whether primary repair can be accomplished or alternatively whether there is a need to import epithelial tissue to reconstitute the normal caliber of the esophagus. Skin represents the most readily available replacement tissue for esophageal mucosa and can be transferred to the neck as a regional flap or as a free flap. For long segments of circumferential involvement, options for management include the transfer of skin that is sutured to form a tube that provides an epithelial lined conduit. Alternatively, there is considerable experience with the transfer of segments of jejunum that can be used to replace segmental esophageal defects. The greater curvature of the stomach can also serve as a source of vascularized mucosa that can be transferred with the greater omentum to create a mucosal conduit. The added benefit of this donor site is that the greater omentum provides a unique flap of well-vascularized tissue that is extremely useful for severely compromised wounds with anticipated impaired wound healing, most commonly following external beam radiation therapy. When the disease extends to the thoracic esophagus then the time-honored approach to reconstruction is to perform a gastric pull-up procedure that allows the pharyngogastric anastomosis to be placed in the neck and to avoid placement of the anastomosis in the mediastinum, where a leak can have serious, life-threatening consequences.
The techniques described earlier can also be readily used in patients who require resection of the larynx and esophagus with the creation of a permanent tracheostome. In rare situations in which extensive disease requires resection of the laryngopharynx and portions of the thoracic trachea, a tracheal lengthening procedure can be performed with the use of a funnel-shaped tubed radial forearm flap.\textsuperscript{30}

**VASCULAR INVASION**

It is rare that the major vessels in the neck and mediastinum are involved by disease that is deemed to be resectable (Fig. 20). In the 6 patients with major vessel involvement in Kowalski’s series, only 1 had symptoms before surgery.\textsuperscript{18} The exception to vascular invasion is the internal jugular vein, which can readily be removed without any morbidity to the patient. The clinical scenario that most often presents with jugular vein involvement is a metastatic node with extracapsular extension. Alternatively, venous involvement by disease extending along intraluminal pathways from the draining veins of the thyroid has been described (Fig. 21).\textsuperscript{36–38} Resection of the internal jugular vein can be performed with little effect on the patient provided that the disease does not involve both internal jugular veins. In the event of bilateral involvement, a staged resection of the jugular veins should be performed, with a minimum of 2 weeks’ delay to allow collateral venous circulation to develop.

The necessity for carotid artery resection is uncommon in invasive thyroid cancer. In most instances a carotid peel procedure can be performed, provided that there is a plane of resection that does not compromise the integrity of the wall of the carotid artery. In instances in which the artery is circumferentially involved or in which no surgical plane can be established, then a segmental resection of the artery can be considered. The usual guideline for such an undertaking in other malignancies arising in the head and neck is predicated on identifying that the disease that is adherent to the carotid artery is the only portion of the disease that stands in the way of achieving a complete resection. The inherent morbidity of interrupting the flow of the carotid

![Fig. 20. Carotid artery and jugular vein at risk of invasion by advanced thyroid cancer.](image-url)
artery involves the risk of neurologic sequelae. In theory, carotid involvement by primary thyroid cancer represents a safer area to perform a carotid resection and replacement than what is usually encountered in squamous cell carcinoma involvement of the carotid artery. In the latter situation, the carotid bulb is most commonly involved, necessitating resection of the common carotid and a portion of the internal carotid arteries. Successful bypass requires temporary cross-clamping and interruption of flow to the brain. In thyroid cancer that involves direct extension from the gland to the lower portion of the common carotid artery, there is usually an opportunity to preserve the circulation through the region of the carotid bifurcation that permits cerebral protection through reverse flow from the external carotid artery (Fig. 22). It is therefore less likely that such a surgical undertaking of replacing the common carotid artery for an invasive thyroid cancer will result in as high a risk of neurologic sequelae.
as has come to be associated with resection of the carotid artery for squamous cell cancer, in particular when the carotid bifurcation is involved. One final note of caution is related to the increased surgical risk of replacing the carotid artery in patients following entry into the upper aerodigestive tract, where the potential for postoperative fistulae can lead to catastrophic vascular complications.39

There are no data to provide information regarding the oncologic value of extending the resection to include the internal jugular vein or the carotid artery. The age of the patient, the degree of differentiation of the tumor, the presence of metastatic disease, the extent of prior therapy and the opportunity to treat with radioactive iodine are all important parameters that affect that decision. As noted earlier, the decision to replace the carotid artery should be made only after the surgeon is convinced that the disease adherent to the carotid artery is the only remaining gross disease that stands in the way of a complete resection of the tumor.

NERVE INVOLVEMENT

The range of nerves involved by invasive thyroid cancer includes virtually the entire spectrum of central and lateral compartment nerves (Fig. 23). The RLN is undoubtedly the most common nerve to be reported as being affected by invasive disease. In Nakao's series on invasive cancer,16 the RLN was affected in 61%, whereas the vagus was involved in 13%, the phrenic nerve in 10%, and the spinal accessory nerve in 6% of 31 patients. As noted earlier, it is rare that the superior laryngeal nerve is reported as a separate nerve in the large series on invasive thyroid cancer.

Randolph and Kamani26 reported a series of 21 patients with invasive thyroid cancer and compared the preoperative laryngeal examination with a group of 344 patients with either noninvasive thyroid cancer or benign thyroid disease who required surgery. RLN paralysis was identified in 70% of patients with invasive disease compared with only 0.3% of patients with benign or noninvasive disease. Voice change was identified in only 40% of patients with documented vocal cord paralysis.

The appropriate management of the RLN that is involved by a thyroid cancer within the gland or metastatic to a paratracheal node depends on several factors: the presence or absence of preoperative vocal cord paralysis, the involvement of the opposite RLN, and the histology of the tumor. If the vocal cord is functional, then the decision to sacrifice the nerve is more difficult. In these cases the nerve should be preserved as long as all gross disease can be removed. In the case of tumor involving the only functioning RLN, then that nerve should rarely be sacrificed in light of the need to perform a tracheostomy and subsequent lateralization procedures. Disease left in proximity to

Fig. 23. Nerve invasion by thyroid cancer in the central or lateral compartments.
a functioning RLN leads to the necessity to treat postoperatively with radioactive iodine and possibly external beam radiotherapy. The decision to leave microscopic disease attached to the RLN does not seem to affect the survival or the risk of recurrence compared with the decision to perform a resection of the nerve.40

If an RLN has to be sacrificed there are 3 options for management of the resulting deficit:

1. The first is to perform a medialization procedure postoperatively.
2. The second is to perform an immediate nerve graft to bridge the gap between the 2 ends of the nerve.
3. A third alternative approach is to perform an anastomosis between the distal RLN and a motor branch of the ansa cervicalis (Figs. 24 and 25).

In either of the last 2 procedures, the patient may benefit from a temporary medialization procedure to achieve a functional improvement while the nerve is regenerating.

Involvement of other lateral compartment nerves is most often secondary to metastatic disease to cervical nodes. The vagus nerve is most often at risk and the surgeon should be aware of the lymphatic pathways that exit the central compartment of the neck along the inferior thyroid artery that courses deep to the carotid artery (Fig. 26). Lymph node involvement deep to the carotid artery is a common scenario and the surgeon should have a high index of suspicion to search for nodes along that lymphatic pathway in the primary and recurrent setting. In such situations, the structures within the carotid sheath are placed at risk from disease extending outside the capsule of the node (Fig. 27).

**PROGNOSIS OF PATIENTS WITH INVASIVE THYROID CANCER**

Although radioactive iodine is routinely administered to patients with advanced thyroid cancer, invasive thyroid cancers in patients with locally invasive disease, especially
Fig. 25. (A) RLN encased by an invasive papillary thyroid cancer (white arrows). (B) Histologic section shows nerve invasion. (C) The distal branches of the ansa cervicalis are exposed. (D) The anastomosis of the distal ansa cervicalis to the distal RLN is shown (yellow arrow).

Fig. 26. Various nodal groups associated with the thyroid gland and the pathway for lymphatic spread outside the central compartment. The route along the inferior thyroid artery deep to the common carotid artery is shown.
those in an older age group, have often lost the ability to trap iodine and therefore the ability to be effectively treated with this adjuvant modality. There is an increasing use of external beam radiotherapy in patients with this clinical profile; however, it has not been evaluated in a prospective fashion. In the contemporary series published by Chow and colleagues, external beam radiotherapy was found to reduce the risk of locoregional failure in the particular subgroup of patients with gross residual disease following surgery. In that series of 842 patients with papillary thyroid cancer treated between 1960 and 1997, the 4 factors that were identified on multivariate analysis as leading to a poor prognosis were distant metastases at presentation, age greater than 45 years, gross residual locoregional disease following surgery, and lack of radioactive iodine treatment. The investigators used the following parameters to recommend external beam radiation: presence of gross locoregional disease, extensive ETE, and extensive lymph node metastases. Chow and colleagues reported that the presence of postoperative residual disease was more important than other prognostic factors such as ETE, tumor size, lymph node involvement, and type of surgery.

Numerous survival statistics and local control rates have been reported for patients with invasive thyroid cancer. However, the heterogeneous nature of the patients in these series makes it difficult to draw meaningful conclusions. After complete resection of thyroid cancer invading the trachea, the 3-, 5-, and 10-year survival rates have been reported to be 87%, 78%, and 78%. In the Mayo Clinic series reported by McCaffrey and colleagues, the overall survival at 5 years was 79%, 63% at 10 years, and 54% at 15 years.

One of the more challenging clinical scenarios occurs in the patients who present with advanced local disease in conjunction with metastatic disease. The surgeon must decide how aggressive the treatment of the primary tumor should be in light of the adverse prognostic finding. Sugitani and colleagues reported 86 patients with distant metastases, of which 42 were discovered at the time of presentation and 44

Fig. 27. (A) Recurrent thyroid cancer presenting with a lymph node (green arrow) deep to the common carotid artery. (B) At the time of the resection the vagus nerve (yellow arrow) was adherent to the capsule of the lymph node (blue arrow).
were identified from 1 to 25 years following initial thyroidectomy. Disease-specific survival in the group of 86 patients was 65% at 5 years and 45% at 10 years. The factors that appeared to be associated with a worse prognosis were metastatic disease to sites other than the lung, distant metastases greater than 2 cm, cervical nodal metastases greater than 3 cm, and less well-differentiated histologic features. All but 1 patient in that series underwent curative resection of the primary tumor and only 5 patients were identified as dying as a result of local disease progression or recurrence. The development of recurrent local disease was a poor prognostic feature: 60% of the patients who developed recurrent local disease in the face of distant metastases succumbed to thyroid cancer. The investigators concluded that the presence of distant metastases at the time of diagnosis of invasive local disease, whether primary or recurrent, should not preclude an aggressive approach to the resection of that local disease. They cautioned that a specific subset of patients with distant metastases at nonpulmonary sites and poorly differentiated papillary thyroid cancer were at highest risk of early demise as a result of distant disease and should not be treated with aggressive surgery.

SUMMARY

The successful management of well-differentiated thyroid cancer requires a preparedness on the part of the surgeon for whatever circumstance the disease may present. Identification of the patient at risk and performing appropriate imaging studies to determine the full extent of the disease are critical to educating the patient and preparing for what is necessary for complete resection of the disease. Prevention of disease progression and disease recurrence in the central compartment is vital to the overall strategy for successful oncologic management. Various structures are at risk from invasive thyroid cancer or disease extending beyond the capsule of a metastatic lymph node. Effective management of those structures is critical to achieving a complete resection of the disease and a restoration or preservation of an optimal level of function for the patient.

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