Management of invasive well-differentiated thyroid cancer: An American Head and Neck Society Consensus Statement

AHNS Consensus Statement

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ABSTRACT: *Background.* Invasive differentiated thyroid cancer (DTC) is relatively frequent, yet there is a paucity of specific guidelines devoted to its management. The Endocrine Committee of the American Head and Neck Society (AHNS) convened a panel to provide clinical consensus statements based on review of the literature, synthesized with the expert opinion of the group.

Methods. An expert panel, selected from membership of the AHNS, constructed the manuscript and recommendations for management of DTC with invasion of recurrent laryngeal nerve, trachea, esophagus, larynx, and major vessels based on current best evidence. A Modified Delphi survey was then constructed by another expert panelist utilizing 9 anchor points, 1 = strongly disagree to 9 = strongly agree. Results of the survey were utilized to determine which statements achieved consensus, near-consensus, or non-consensus.

Results. After endorsement by the AHNS Endocrine Committee and Quality of Care Committee, it received final approval from the AHNS Council.
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KEY WORDS: invasive thyroid cancer, tracheal invasion, recurrent laryngeal nerve invasion, locally aggressive thyroid cancer, vascular invasion

INTRODUCTION

Locally invasive disease from differentiated thyroid cancer (DTC) occurs in approximately 13% to 15% of patients as a result of extrathyroidal spread of tumor and has important prognostic significance.[1,2] Although this condition is seen frequently, specific guidelines devoted to its management do not currently exist outside of the broader American Thyroid Association (ATA) guidelines.

Papillary thyroid carcinoma (PTC) is the most common type of DTC and is the most common type of DTC associated with extrathyroidal spread. In a Mayo Clinic series of 296 patients with invasive DTC, the histologic types were 262 papillary, 14 follicular, 7 Hurthle cell, 10 medullary, and 2 anaplastic.[3] Extrathyroidal spread occurs with a higher frequency in older patients and with larger tumors. There is a higher incidence of extrathyroid spread in those over 50 to 58 years of age and from tumors larger than 3.7 to 4 cm.[4,5]

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Invasion of local structures most commonly involves the strap muscles, recurrent laryngeal nerve (RLN), and trachea. Extrathyroidal spread may also affect the larynx, esophagus, and major vessels, although this is rare. A locally advanced presentation is often seen among those who ultimately die from disease.[6] Widely invasive follicular thyroid carcinomas (FTCs) and older age are associated with a significantly higher mortality than tumors with minimal invasion.[7] Incomplete surgical excision of the primary DTC also has been shown to be associated with higher mortality.[8,9] Because of this prognostic significance and the expanded surgery that is typically required beyond simple thyroidectomy for this invasive disease, it is important to be aware of preoperative signs and symptoms suggestive of local invasion, and to perform the appropriate evaluation preoperatively to assess for presence and extent of invasion so that residual disease is not left behind. Proper laryngeal examination and advanced radiographic imaging reduce the likelihood of unanticipated surgical findings.

Resection of the strap muscles can easily be performed without the need for reconstruction and is of minimal consequence to the patient. However, management of involvement of the other structures becomes more complicated and should be planned accordingly preoperatively before thyroidectomy whenever possible. Although there are controversies regarding the extent of resection necessary for invasive disease, there is general consensus that macroscopic (gross) tumor removal is important for achieving locoregional control. The morbidity of radical extirpation must be balanced against the issues of tumor control, morbidity of persistent/recurrent local disease, and survival outcome benefit.

Despite the fact that invasive DTC is relatively frequent and has great clinical impact, there is a paucity of high-level studies that evaluate its management in a controlled fashion with long-term follow-up. Thus, it is difficult to draw definitive conclusions regarding best practice management of this condition based on the published body of literature alone. Given that the topic of invasive DTC does not have a robust enough evidence base to support the development of recommendations in the format of a formal clinical practice guideline according to standardized methods, the American Head and Neck Society (AHNS) convened a panel to provide a clinical consensus statement (CCS) based on a review of the data that are available, synthesized with the expert opinion of the group.

This CCS focuses on the evaluation and treatment of locally invasive DTC in adults. More specifically, the panel was charged with determining whether a consensus could be achieved in key management decisions regarding DTC, specifically invasion of the RLN, trachea, esophagus, larynx, and major vessels. This document describes the procedure and results of the consensus panel of the AHNS, which is the principal United States professional organization dedicated to head and neck surgical cancer. This initial construct focuses primarily on standard techniques in evaluation and treatment of invasive thyroid malignancy. Through this work, we seek to reduce the unnecessary variation in the management of invasive thyroid malignancy, to clarify the limitations in the current best evidence, and to help identify those areas in which additional research is necessary.

METHODS

Expert panel and manuscript approval process

Members of the panel were selected from the membership of the AHNS. Both otolaryngologists and general surgeons with expertise in head and neck endocrine surgery were included. The specific goals of the CCS were reviewed with the entire group. The initial 5 panel members (M.S., E.K., J.M., J.P., and S.C.) discussed the contents and controversial points of the proposed statements using email communications. Draft statements and relevant text were circulated among these members, and edits were incorporated by the lead author (M.S.). When this iterative process was complete, a draft was then sent to the wider panel for commentary. Based on the feedback received, a Modified Delphi survey (described in a section below) was constructed for distribution throughout the group. The survey, draft, and relevant references were then sent to the complete panel. Once the survey data was analyzed and results confirmed that a consensus was reached for each recommendation statement, the manuscript was then distributed to members of the AHNS Endocrine Committee for further feedback. After endorsement by the Endocrine Committee, it was reviewed by the AHNS Quality of Care Committee. Once the recommendations from the Quality of Care Committee were incorporated into the manuscript, it received final approval from the AHNS Council.

Literature review

Relevant systematic reviews of the literature were undertaken to provide critical reference material for the panel members to access before and at the time of completing the Modified Delphi survey. Computerized and manual searches were performed to identify relevant data. Computerized searches were performed using PubMed (1966 to December 2012). First, an overarching search was performed. Articles that mapped to the medical subject heading "thyroid neoplasms" were cross-referenced with those containing "papillary," "follicular," "differentiated," or "well-differentiated," in the title or abstract. This group was then cross-referenced with those containing the text words "invasive," "invasion," "extrathyroidal," "extrathyroid," "aggressive," or "advanced." Articles were limited to those studying humans and reported in the English language. Afterward, searches were conducted specific to the proposed consensus statements. For statement 1 (preoperative examination of the larynx), articles that mapped to the medical subject heading "thyroid neoplasms" were cross-referenced with those containing "papillary," "follicular," "differentiated," or "well-differentiated," in the title or abstract. This group was combined with those mapping the subject heading "thyroidectomy." The combined collection was then cross-referenced with those articles mapping to the terms "laryngoscopy" or "preoperative" or the medical subject headings "preoperative care" or "preoperative period." For statements 2 to 4 (RLN involvement), articles obtained through the overarching search described above were cross-referenced with those mapping to the medical subject headings "recurrent laryngeal nerve," "recurrent laryngeal nerve injuries," and "vocal cord paralysis." For statements 5 to 6 (tracheal invasion) and statement 7 (esophageal invasion), the overarching search was cross-referenced with articles under the respective subject headings "trachea," "bronchoscopy," and "esophagus." For statement 8 (laryngeal invasion), "laryngeal diseases" was utilized as the medical subject heading cross-reference term. For statements 9 to 10 (vascular invasion), the subject headings "carotid arteries" or "jugular veins" were used, along with the text words "internal jugular" and "superior vena cava." For statement 11 (radiation therapy), the medical subject heading "radiotherapy" and text words "external" or "beam" were utilized. Content experts were also contacted with an invitation to supplement the reference lists.

Modified Delphi method and data analysis

The modified Delphi method, a previously described and established method to systematically establish consensus, was utilized to determine which statements achieved consensus, near-consensus, or non-consensus.[10,11] A recent example of the method's use is reported by Setzen et al.[12] Through this method, each expert on the panel expressed his or her opinion for each proposed statement using a Modified Delphi survey. Survey content was developed based on edits to the initial statement drafts and vetted by 3 members of the panel (G.W.R., D.J.T., and J.J.S.). The survey was delivered to the group electronically, via separate entry forms, so as to blind panelists to the responses of other members of the group. One primary mailing was utilized, followed by subsequent mailings for panel members who had missing values or had difficulty with question interpretation. Converse statements were included within the survey to serve as internal controls for participant responses.

Responses for the modified Delphi survey were collected electronically and a dataset stripped of panel member names was created. These masked results were analyzed using a Likert scale with numerical interpretations of 1 to 9, utilizing the following anchor points: 1 (strongly disagree); 3 (disagree); 5 (neutral); 7 (agree); and 9 (strongly agree). Statements were defined as achieving consensus if there was a mean score of 7.00 or greater and 1 or fewer outlier responses were returned. Near-consensus was defined as statements with a mean of 6.50 to 6.99 with 2 or fewer outliers. Non-consensus was the default if these criteria were not met. Outliers were defined as any rating at least 2 Likert points away from the mean. Statistical analysis was performed utilizing Stata 12.0 (College Station, TX). Mean, SD, median, and interquartile range were calculated according to their standard definitions.

RESULTS

Systematic review

The overarching topic review returned 2506 articles. There were no previously published consensus statements or clinical practice guidelines with the same goals. Statement-specific reviews yielded 204 relevant references, which were distributed to panel members.

Modified Delphi results

The finalized survey included 56 statements and 2 algorithms, developed from the initial iterative draft process. Response rates to the survey were 100% ($n = 10$ of 10). Consensus was achieved in 41 of the statements and in 2 of the algorithms. Near-consensus was achieved in $n = 2$ of the statements. The non-consensus default was assigned to 13 statements.

Preoperative examination of the larynx

Statement 1-A. Preoperative examination of the larynx is recommended in the management of DTC (consensus).

Statement 1-B. Fiberoptic examination is the preferred method to examine the larynx preoperatively in DTC (consensus).

Preoperative examination of vocal fold function is essential when evaluating patients with thyroid malignancy, because vocal fold paresis or paralysis may not always manifest with apparent change in voice quality, particularly in cases with well-compensated vocal fold paresis and selective abductor vocal cord paralysis. There is controversy in the endocrine community regarding this because there is a paucity of data. Recent studies suggest that the sensitivity of voice change in predicting vocal fold paralysis ranges from 33% to 68%.[13,14] Randolph and Kamani[13] demonstrated that 70% of patients with preoperative vocal fold paralysis were found to have invasive thyroid cancer. Preoperative vocal fold paralysis is an important predictor of invasive thyroid malignancy, and, therefore, all patients with thyroid malignancy may benefit from preoperative laryngoscopy.

In addition, an examination finding of vocal fold paralysis may prompt advanced radiographic imaging to help determine the extent of surgery. For example, a contrast-enhanced CT scan may be used to assess for tracheal or laryngeal invasion, and endoscopy may be pursued at the time of thyroidectomy to evaluate for intraluminal invasive disease. Such preoperative evaluation allows both the patient and surgeon to be prepared for possible airway resection and reconstruction at the time of thyroidectomy.

Management of the RLN found to be invaded by tumor at the time of surgery in part depends on the functional status of both the ipsilateral and contralateral vocal fold, which can best be determined by preoperative laryngeal examination.[3] A recent American Academy of Otolaryngology–Head and Neck Surgery Foundation clinical practice guideline has recommended preoperative laryngoscopy in all patients undergoing thyroid surgery when the voice is abnormal, if there is a history of surgery in which the vagus or RLN was at risk, or if there is preoperative suggestion of malignancy with extrathyroidal extension. Guidelines from professional bodies vary widely on this topic. The ATA clinical guidelines on thyroid nodules and differentiated thyroid cancer make no reference to this issue.[15] However, the recently published ATA guidelines regarding anaplastic thyroid cancer strongly recommend that every patient undergo initial evaluation of the vocal folds.[16] The British Thyroid Association currently recommends laryngeal examination for patients with preoperative voice changes and for those undergoing thyroid cancer surgery. A recent consensus statement of the British Association of Endocrine and Thyroid Surgeons states that all patients undergoing thyroid surgery should have preoperative and postoperative laryngeal examination (www.baets.org, 2010). The German Association of Endocrine Surgeons practice guidelines recommend preoperative and postoperative laryngeal examination in all cases of thyroid surgery.[17] The National Comprehensive Cancer Network guidelines describe preoperative vocal fold paralysis as a "highly suspicious factor" for cancer and the need for surgery. These guidelines recommend a preoperative laryngeal examination for all patients with papillary, follicular, Hurthle cell, and medullary cancers (www.NCCN.org).

The optimal method for examining the larynx is using a flexible fiberoptic scope videolaryngoscopy, which provides documentation for review and comparison of function before versus after surgery, if needed. Recent work has suggested that an average of 6 attempts for novices are necessary in order to become technically competent in performing flexible laryngoscopy.[18] Interpretation of all laryngeal findings may take greater clinical experience. Nevertheless, in a patient with appropriate anatomy and no or minimal gag reflex, and when instrumentation may not be available, indirect examination with a laryngeal mirror may also provide adequate visualization.

Recurrent laryngeal nerve resection or preservation

Statement 2-A. If the RLN is encased by tumor, and ipsilateral vocal fold paresis or paralysis is present preoperatively, resection of the RLN is indicated (consensus).

Statement 2-B. If the RLN is encased by tumor, and bilateral vocal fold function is normal preoperatively, the tumor may be shaved off to spare the RLN, as long as all gross disease is removed (consensus).

Statement 2-C. If the RLN is encased by tumor, and the contralateral vocal fold is paretic or paralyzed, the tumor may be shaved off so that the RLN is spared (consensus).

Statement 2-D. If the RLN is encased by tumor and the RLN is spared intraoperatively, then adjuvant therapy is indicated (consensus).

Statement 2-E. When only the contralateral vocal fold is paralyzed, shaving the tumor off the ipsilateral nerve followed by adjuvant may be justified to avoid bilateral paralysis and the need for a tracheostomy (consensus).

Statement 2-F. If intraoperatively the tumor is found to be minimally adherent to the RLN (not encasing it) then the RLN should be preserved (consensus).

The RLN is involved in 33% to 61% of invasive thyroid cancers.[1,9,19] RLN invasion may be due to direct invasion by the primary tumor or from paratracheal lymph node metastasis. The degree of involvement by tumor can vary from adherence to the nerve to complete encasement.

The decision to resect or preserve the RLN in the presence of invasive DTC has been controversial. This is because earlier studies reported that invasion of the RLN did not independently impact survival rates, but invasion of other structures, such as the trachea and esophagus, independently decreased survival.[1] Likewise, others have shown that complete resection of the nerve does not necessarily provide a survival benefit,[3,19] prompting some to favor incomplete excision and adjuvant radioactive iodine or external beam radiation therapy (EBRT). However, Chan et al[20] reported an indepth analysis of 20 patients with RLN involvement; 13 of these underwent near-total removal with shave procedures, whereas 5 underwent complete resection, and 2 had debulking. There was no difference in survival between the shave and complete resection groups; however, those who were only debulked required extensive re-resection, including laryngectomy and sternotomy. In this series in which 75% of their patients had "incomplete" resection followed by radioactive iodine treatment and EBRT, the 10-year disease-specific mortality was 42%. Curative resection should therefore generally be the goal unless the patient has widespread distant metastasis or radical complete tumor resection would result in unacceptable risk of perioperative morbidity and mortality.

The surgical decisions regarding nerve management in the setting of unequivocal nerve invasion at the time of surgery should balance several important factors including: (1) preoperative functional status of the ipsilateral and contralateral vocal folds; (2) whether tumor is found to be adherent to or to encase the nerve at the time of surgery (in the latter case, resection of the nerve is indicated); (3) tumor histology; and (4) overall disease status as it relates to distant metastasis or other locoregional disease that is not resectable. Leaving gross disease behind may result in ineffective local control; postoperative radioactive iodine treatment is less likely to achieve complete tumor response in the setting of a gross residual tumor. Intraoperative electromyography data may also be helpful in neural management decision-making when neural monitoring is used.

Several studies have reported that in cases in which nerve dysfunction is caused by compression rather than infiltration, vocal fold mobility may return after peeling the tumor off of the nerve.[3,20,21] Chiang et al[22] showed that extensive dissection of the RLN can be performed with relatively low rates of temporary nerve palsy; in their study, there were no cases of permanent palsy. Therefore, in patients with confirmed thyroid carcinoma histology and intact preoperative vocal fold function, nerve resection should only be performed if unequivocal neural invasion is found and the tumor completely encases the nerve or a plane of dissection cannot be achieved between nerve and tumor. Given that survival benefits have not been clearly demonstrated with complete nerve resection, a near-complete removal or shaving the tumor off of the nerve is reasonable, when possible. In rare cases of known preoperative paralysis of the contralateral vocal fold, the potential morbidity from sacrificing the ipsilateral nerve and resulting bilateral vocal fold paralysis (with subsequent need for tracheostomy) may justify dissection of tumor off the nerve rather than resection, and then treating with adjuvant therapy.

Management algorithms

Two algorithms that incorporated multiple concepts related to a number of the above recommendations were presented to the panel for assessment (Figures 1A and 1B). Both achieved the criteria for consensus. Figure 1A (management algorithm for preoperative RLN paralysis) describes a potential management strategy in the setting in which fiberoptic examination has identified RLN paralysis. Given the strong relationship between preoperative RLN paralysis and invasive disease, it suggests axial imaging to assess for the degree of local invasion. If found, then an endoscopy can be recommended at the initial surgery and the patient and surgeon can be prepared for possible concurrent airway surgery. Resection of the nerve would come only after carcinoma invasion has been identified. Figure 1B (management algorithm for RLN infiltration found at surgery) describes that nerve resection would be recommended only with carcinoma invasion; whereas paralysis associated with lymphoma or benign disease would be managed without nerve resection. Further knowledge of preoperative laryngeal function is an important consideration in managing the invaded nerve. Normal preoperative function would lead one to attempt to preserve the RLN (with removal of gross disease, if possible) and to consider postoperative adjuvant therapy, such as T4 suppression, radioactive iodine, and/or EBRT. A nerve that is preoperatively paralyzed, however, generally can be resected. Preoperative

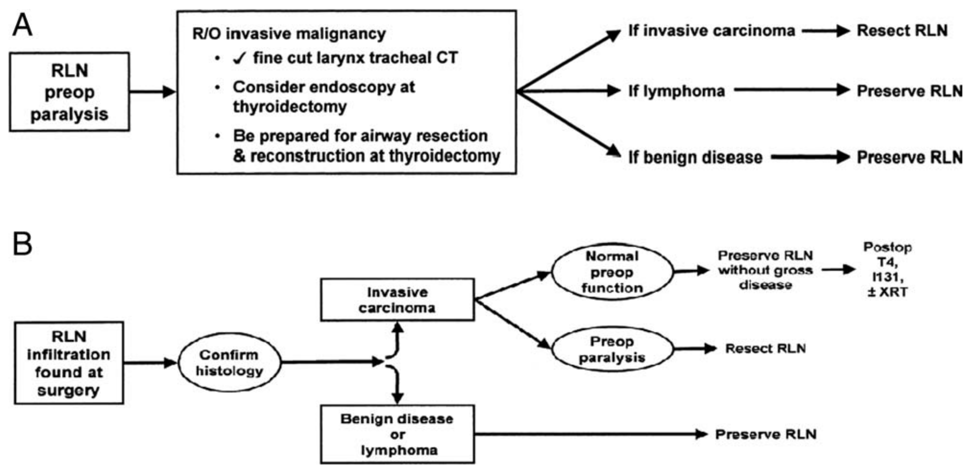

FIGURE 1. (A) Algorithm for preoperative recurrent laryngeal nerve (RLN) paralysis. (B) Algorithm for RLN infiltration found at surgery. Reprinted with permission of G. W. Randolph, editor. Surgery of the thyroid and parathyroid glands. 2nd ed. Philadelphia, PA: Elsevier–Saunders, 2012.

laryngeal examination is critical in this situation to ensure normal contralateral vocal fold function.

Recurrent laryngeal nerve reinnervation

Statement 3-A. If feasible, immediate reinnervation should be performed when the RLN is resected during surgery for invasive DTC (consensus).

Laryngeal reinnervation after RLN resection is an important rehabilitative option when resection of the RLN is necessary. Reinnervation can restore muscle tone, ultimately achieving a good voice outcome. A prospective study of phonatory function after laryngeal nerve resection was undertaken in which 3 groups were compared – immediate reinnervation, no reinnervation, and delayed static framework surgery. The reinnervated group had a smaller or no glottic gap as well as better maximum phonation time, mean air flow rate, and harmonic-to-noise ratio compared to the other 2 groups.[23] Immediate reinnervation may not always be achievable. One prerequisite is the surgical skill required to perform microneural anastomosis. Therefore, if the patient has preoperative vocal fold paralysis and RLN resection is anticipated, the surgeon should be prepared to perform a reinnervation procedure or elicit the help of another surgeon with such skills. The second requirement is presence of disease-free stumps of the RLN; this status may be confirmed with frozen section, at the discretion of the attending surgeon. The requisite nature of such a frozen section did not achieve the threshold for formal consensus among this panel. Reinnervation can be achieved by placing a nerve graft between the resected nerve stumps or suturing the ansa hypoglossi to the distal stump of the RLN.[24]

Recurrent laryngeal nerve monitoring

Statement 4-A. Intraoperative monitoring of the RLN during thyroidectomy for invasive DTC may provide prognostic information regarding the functional status of the nerve during the procedure (consensus).

Statement 4-B. Intraoperative monitoring of the RLN during thyroidectomy for invasive DTC provides prognostic information regarding the functional status of the nerve at the conclusion of the procedure (consensus).

Statement 4-C. Laryngeal nerve monitoring may be considered during the performance of thyroid cancer surgery, especially when preoperative nerve dysfunction is observed (consensus).

Intraoperative RLN monitoring can provide prognostic information regarding the functional status of the nerve during and at the end of resection.[25–28] Laryngeal nerve monitoring may be beneficial when performing surgery for thyroid malignancy when preoperative nerve dysfunction is present.

Information gained from such information may be helpful in providing guidance for the extent and timing of contralateral surgery.[29,30] Electrophysiologic information may also be helpful in making intraoperative decisions as to whether or not to preserve or sacrifice the nerve. In a setting in which the contralateral RLN is paralyzed, electrophysiologic information from the involved side may guide the decision for performing elective tracheostomy.[31] Further research will be helpful to fully establish the utility of RLN monitoring under these circumstances.

Assessment of tracheal invasion

Statement 5-A. If the clinical presentation raises concern for tracheal invasion, CT is an acceptable means to assess for the status of the trachea, and is superior to ultrasound when assessing for tracheal invasion (consensus).

Statement 5-B. If the clinical presentation or imaging raises concern for tracheal invasion, then a bronchoscopy should be performed before or at the time of the initial tumor resection and the operative team and patient should be prepared to proceed with tracheal resection at the time of the initial resection (consensus).

Extrathyroidal invasion into the trachea is often identified at the time of operation. It is frequently associated with loss of tumor differentiation and a reduction in long-term survival compared to thyroid tumors limited to the gland. Thyroid cancer-related deaths are rare; however, over half of the deaths are related to airway obstruction and bleeding. Comparative studies are lacking.

Tracheal or laryngeal invasion has been reported in 3.6% to 22.9% of patients undergoing thyroid surgery.[31,32] A recent report from Honings et al[32] represented a review of 20 studies; among 10,251 patients with thyroid cancer, 595 (5.8%) had airway invasion. Adherence of thyroid tumor to the tracheal and or esophageal wall was noted in 10.9% of patients in 1 series; however, the most advanced stage of tracheal invasion is endoluminal, which occurs in only 0.5% to 1.5% of cases.[33]

Preoperative symptoms suggestive of airway invasion may include hoarseness (22%), hemoptysis (11% to 79%), and dyspnea (5%); however, preoperative symptoms are usually not predictive of the depth of tracheal invasion, unless thyroid fixation is present on neck examination.[34,35] Preoperative laryngoscopy is recommended in all patients undergoing thyroid surgery to identify patients with otherwise unsuspected invasive thyroid cancer and vocal cord fold paralysis preoperatively.[13] In some centers, in-office fiberoptic tracheobronchoscopy can be performed in patients where there is suspicion for tracheal invasion.

Preoperative cervical ultrasound in experienced hands may be helpful in anticipating tracheal invasion (Figure 2), although this is highly operator dependent. In 1 study, ultrasound had a reported sensitivity of 91%, a specificity of 93%, a positive predictive value of 25%, and a negative predictive value of 99%; the overall accuracy was 93% relative to surgical findings.[36] However, in another study, the sensitivity was 42.9% for tracheal invasion and 28.6% for esophageal invasion.[37] A CT scan may also provide important information regarding tracheal invasion (Figure 3A–3D). In a study by Seo et al,[38] the mean sensitivity, specificity, and accuracy of CT for tracheal invasion was 59.1%, 91.4%, and 83.2%, respectively.

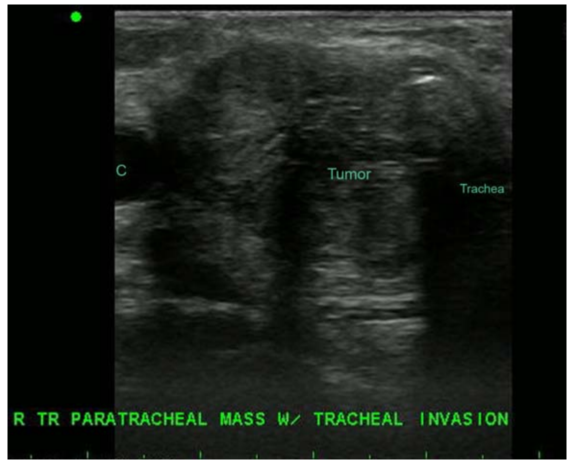

FIGURE 2. Ultrasound showing right-sided papillary thyroid cancer invading trachea. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Tracheal resection

Statement 6-A. If a short segment of the trachea is invaded and there is minimal cartilage invasion, a tracheal shave excision is appropriate (consensus).

Statement 6-B. If there is intraluminal tracheal invasion or significant cartilage invasion, circumferential sleeve resection of the trachea is appropriate (consensus).

Statement 6-C. If the surgeon performing the thyroidectomy is not experienced in performing tracheal resections and a head and neck or thoracic surgeon with such expertise is not available, referral to a tertiary center should be considered and may be preferable to staging the operation and performing tracheal resection after thyroid surgery (consensus).

The extent of tracheal resection is, in part, determined by the nature of tumor invasion. Tangential shave excision of tumor (shaving) is commonly performed for tumors with minimal invasion of the trachea. The technique consists of sharp separation of the tumor from the wall of the airway, leaving the mucosa intact. Although possible, complete resection is difficult with shave excision for several reasons: (1) it is difficult to confirm negative margins intraoperatively; (2) the peritracheal fascia is continuous with dense fibrous tissue between the tracheal rings, resulting in a lack of a continuous plane underneath the "external perichondrium" to tangentially shave off the tumor completely[39]; and (3) tumor can spread into the tracheal lumen via lymphatics that communicate in the intercartilaginous spaces.[40] Ozaki et al[41] showed in their circumferential tracheal resection specimens that the disease extended beyond the tracheal adventitia in 18 of 21 cases. Park et al[41] reported recurrence in 12 of 16 shave procedures, 10 of which recurred in the trachea or in the paratracheal soft tissue. McCarty et al[34] also reported 17% local recurrence with 35 tracheal shave procedures in which microscopic disease was left. Therefore, shave excision for extensive tumors is likely to result in incomplete resection because of the high reported rate of microscopically positive margins, which may increase the risk of local recurrence. Nevertheless, local control rates as high as 95% can be achieved with the shave procedure if the tumor does not penetrate beyond the perichondrium.[42]

Tracheal circumferential en bloc sleeve resection with the thyroid gland is the preferred approach for intraluminal tracheal invasion given the propensity for circumferential cartilaginous ring involvement.[43–46] The mortality rate from tracheal or laryngotracheal resection has been reported to be as high as 5% to 9% in some series,[42,44] prompting some to advocate the use of tracheal window resections in selected cases.[48] Window resection is limited by the length and circumference of the trachea that can be safely resected while still maintaining the stability of the trachea. Primary closure of the window defect is rarely possible and needs to be reconstructed with a muscle or myoperichondrial flap.[48] In a small series of 6 window resections, 1 death occurred from tracheoinnominate fistula, and 50% were tracheostomy tube dependent.[49] Some authors report very low mortality and morbidity with segmental resection and, therefore, advocate segmental resection instead of window resection for tumors that transgress the cartilage.[36,40,49,50] Complications associated with tracheal sleeve resection include anastomotic dehiscence, laryngeal stenosis, and anastomotic stricture.

When deciding on the extent of tracheal resection for tracheal invasion, the morbidity of resection needs to be

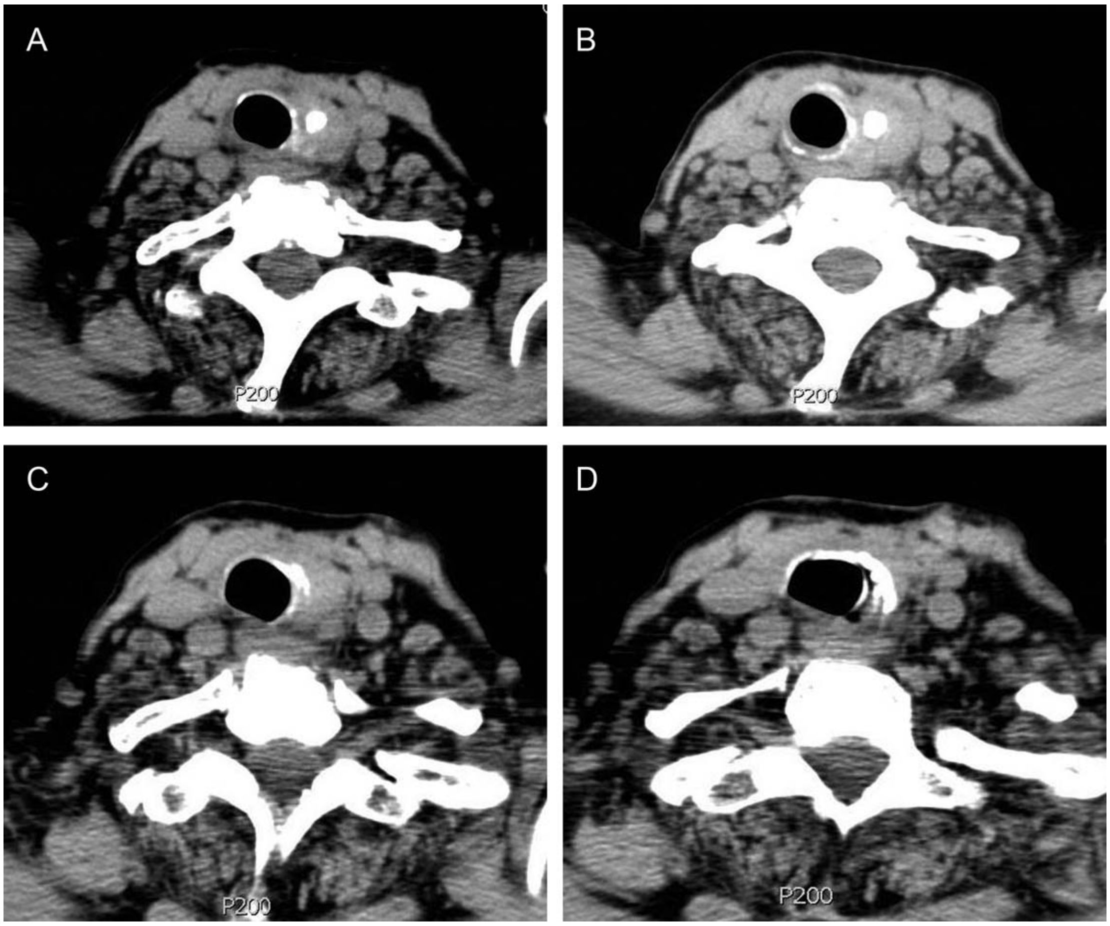

FIGURE 3. (A–D) CT scans showing left papillary thyroid carcinoma. The patient presented with preoperative vocal cord paralysis. CT demonstrates tumor in the area of the tracheoesophageal groove and suspicious for lateral tracheal wall invasion.

weighed against the need for tumor extirpation to achieve microscopic negative margins. Several series have reported 5-year survival rates >80% with segmental resection.[1,50–54] At the same time, similar excellent local control rates have been reported with just a shave procedure. Tsukahara[42] reported results of 22 patients with PTC who underwent tracheal shave excisions in which local control was achieved in 21 patients (95%); the 5-year and 10-year survival rates were 93% and 41%, respectively. Survival rates from segmental resection have been reported to be similar for segmental and shave procedures.[1,42,48] However, complication rates are higher and survival rates are low when salvage surgery is performed for recurrence after shave procedures.[45,54] Although it is true that a survival benefit may not be demonstrable with tracheal sleeve resection, those undergoing shave resection have a higher incidence of positive margin and local recurrence.[34,40,41,55] Residual or recurrent disease in the trachea or central neck can present difficult management problems with great morbidity including hemoptysis, dyspnea, and dysphagia, which ultimately adversely affects quality of life.

Most invasive thyroid tumors are resistant to adjuvant radioiodine therapy. EBRT may improve local control in patients with residual disease, however, DTCs are not always radiosensitive (see the section on EBRT). Therefore, recurrent or persistent disease may ultimately require extensive salvage surgery, such as laryngectomy, laryngopharyngectomy, or esophagectomy, which are associated with significant morbidity and can significantly affect quality of life (see subsequent sections on laryngeal and esophageal resection). Therefore, segmental resection is preferred over shave procedure for tumors extending beyond the tracheal cartilage into the mucosa to achieve long-term local control, provided it can be done with low morbidity. It is important to suspect intraluminal extension preoperatively so that the patient can be referred to an appropriate center for tracheal resection. However, if a thyroidectomy has been accomplished with only a tangential shave excision and there is known residual endoluminal disease, tracheal resection may then be performed after referral to a center with experience in airways.[29,31] The decision to refer is best made before the initial surgery through appropriate staging workup rather than aborting the procedure and then referring the patient.

There are few long-term follow-up studies on large numbers of patients with tracheal invasion assessing prognosis and predictors of survival. Depth of invasion is thought to be a predictor of reduced survival in patients with endoluminal tumor.[39,56] Other studies have suggested that aerodigestive tract invasion is an important negative prognostic factor.[57,58] Thyroid surgeons should endeavor to perform thorough resections when possible to decrease the incidence of postoperative recurrence, and to collect long-term follow-up data to evaluate for survival benefit.

Esophageal invasion

Statement 7-A. Tumors without intraluminal esophageal invasion can be managed with resection of the involved muscularis layer, avoiding esophageal entry (consensus).

Statement 7-B. Tumors with full-thickness involvement should undergo composite tumor excision (consensus).

Statement 7-C. If a small full-thickness esophageal defect is necessary for complete tumor excision, primary tension-free multilayer closure may be performed if the tissue is healthy (consensus).

Statement 7-D. Extensive defects of the esophagus should be reconstructed with a myofascial/myocutaneous pedicled or free flap (consensus).

Esophageal invasion can occur with posteriorly located tumors or extracapsular spread from paratracheal lymph node metastasis. Direct aerodigestive tract ("cervicovisceral axis") invasion occurs more often from the primary tumor than from central compartment nodal metastasis.[59] An MRI is excellent for evaluation of esophageal invasion, with predictive values of 82% and 100% for outer layer and inner layer invasion, respectively.[60] Invasion is seen as isointense or hypointense areas on unenhanced T1-weighted images and isointense or hyperintense T2-weighted images.[60] CT with contrast is not very sensitive for detecting esophageal invasion (28.6%) but is highly specific (96.2%). Intraoperative esophagoscopy can be performed but the yield is generally low, because intraluminal extension is rare. Esophageal invasion is usually confined to the muscularis layer and spares the mucosa and submucosa, which are resistant to direct invasion by tumor.[1]

When full-thickness involvement of the esophagus is evident, full-thickness resection is undertaken. Repair of small esophageal defects should be a multilayered closure to prevent salivary leak. A salivary bypass tube may be used during the healing phase. With more extensive resections, reconstruction with a myofascial/myocutaneous pedicled flap (ie, pectoralis major or sternocleidomastoid muscle) or microvascular free tissue transfer of a fasciocutaneous flap or jejunum should be considered. For inoperable tumors, a gastrostomy tube or esophageal stent may be considered for palliation.

Laryngeal invasion

Statement 8-A. In cases of partial thickness invasion of the larynx, shave excision of gross disease is favored over organ-sacrificing procedures (consensus).

Statement 8-B. In cases of gross endolaryngeal invasion of the larynx, partial or total laryngectomy is indicated, depending on tumor extent (consensus).

Statement 8-C. If partial or total laryngectomy is indicated and the thyroid surgeon is not well-versed in performing the procedure, then the assistance of an experienced surgeon should be sought (consensus).

Intraluminal invasion of the larynx by DTC is uncommon, but, when it occurs, it may be associated with significant morbidity and, in some cases, mortality related to airway obstruction.[61] Because of the intimate association of the thyroid gland with the underlying airway, there are several possible direct pathways of cancer spread into the larynx. Anterior invasion occurs through the cricothyroid membrane; laterally, spread from the superior poles of the gland can extend through the thyroid cartilage into the underlying paraglottic space. For tumors that grow postero-superiorly behind the thyroid cartilage, extension into the pyriform fossa may occur.[62] As with the trachea, it is critical to make the distinction between more superficial extraluminal invasion and deeper transcartilaginous true intraluminal invasion, as these variations have significant implications for treatment.[31] Extraluminal invasion or partial-thickness wall invasion is often not recognized preoperatively and is associated with very few symptoms. However, subtle signs may be recognized on physical examination (laryngeal fixation – ie, failure of the gland to move independent of the airway on palpation and deformation or discoloration; ecchymosis of the paraglottic space, false cord, or pyriform sinus region during laryngoscopy) or with imaging techniques, such as ultrasound or contrast-enhanced CT scan.

Intraluminal invasion of the larynx by DTC is usually manifested preoperatively by symptoms and signs, including severe hoarseness and hemoptysis, paraglottic mucosal thickening and discoloration may be seen on office laryngeal fiberoptic examination along with true vocal fold paralysis. Tumor may be seen growing along the mucosal surfaces of the true or false vocal folds or ventricles often manifested as studding of tumor in multiple friable nests, or gross invasion may be demonstrated into the pyriform sinus.[62,63] Most intraluminal invasion is recognized preoperatively by history and office laryngeal fiberoptic examination, demonstrated on imaging techniques (usually contrast-enhanced CT scan), and confirmed by intraoperative endoscopy performed to assess areas of involvement for surgical planning.

When extraluminal invasion is recognized at surgery, partial thickness or "shave" excision to clear gross tumor can be performed.[9,41] This may require partial removal of the external wall of the cricoid or thyroid cartilage or shave excision of the cricothyroid joint, occasionally with sacrifice of the RLN to obtain negative margins where the nerve enters the larynx at the posterior-lateral aspect of the cricoid cartilage. Shave excision may leave microscopic disease behind, which may be controlled with radioactive iodine or EBRT. In contrast, however, full-thickness invasion with gross intraluminal disease requires a composite resection. Therefore, familiarity with conservative partial laryngeal surgery approaches is necessary.[64] Invasion into the paraglottic space may be amenable to hemilaryngectomy with reconstruction by strap muscle flaps if they have not been resected with the thyroid. If the cricoid, hyoid, and a single functioning arytenoid can be preserved, the defect can be reconstructed with cricohyoidopexy or cricohyoidoepiglottopexy techniques and vocal function can be preserved.[46] In some cases, patients can be decannulated and retain normal swallowing function. Wedge excisions of the cricoid cartilage can also be accomplished up to approximately 25% to 30% of the total cricoid circumference; the defect can be reconstructed by local muscle flaps, bone, or rib grafts, maintaining airway stability. When larger portions of the cricoid are involved on its intraluminal surface, total laryngectomy may be required and offers good long-term survival.[35,65]

When shave excision was compared to complete margin-negative excision, which often included entire organ removal (ie, total laryngectomy, partial pharyngectomy, etc.), there was no difference in either local control or long-term survival.[31,42,51,56] Therefore, it is recommended that less invasive shave excision of gross disease (with its lower associated morbidity) may be favored over organ-sacrificing procedures when oncologically feasible. Long-term disease recurrence usually requires more aggressive reoperative surgery.[32,35,43,62]

Preoperative vascular assessment

Statement 9-A. When vascular involvement is suspected, preoperative imaging should be performed to assess for invasion and resectability (consensus).

Statement 9-B. Either CT angiogram or MR angiogram (MRA) are appropriate means to evaluate for vascular invasion and provide adequate information when planning for safe vascular control and/or resection (consensus).

Statement 9-C. If carotid resection is planned, the extent of collateral intracranial blood flow and integrity of Circle of Willis should be assessed with MRA or conventional angiography to determine whether the carotid is shunted or not (consensus).

DTC is rarely complicated by substantial vascular invasion, vessel encasement, or thrombosis (Figure 4).[66] Fortunately, some of these tumors remain resectable.[67–69] The unexpected intraoperative discovery of massive vascular involvement should cause the unprepared surgeon great concern. With the very common nature of thyroid surgery and the relatively simple workup of basic laboratory studies and thyroid ultrasound, the inexperienced surgeon may miss the subtle physical findings that can portend a potential operative catastrophe. A thoughtful history should therefore be elicited, and a careful, complete examination of the head and neck is essential.

The most common major vascular structure affected by tumor invasion or occlusion is the internal jugular vein. It is most frequently involved by bulky matted metastatic lymph nodes and less likely to be from direct primary.[69] These patients may report swelling, facial flushing, a sense of heaviness, or varicose veins over the upper body surface. There may also be accompanying globus sensation or dysphagia because of vascular engorgement and collateral vessels cephalad to the mass.[70] The involvement of the neck base and upper mediastinal venous structures may lead to superior vena cava syndrome. Less commonly, the carotid artery may be invaded or encased by tumor. Unfortunately, arterial invasion usually is asymptomatic, and when symptoms are present they may have been discounted as incidental transient ischemic attacks, migraines, or dementia.

It is important for the surgeon to assess for involuntary restriction of neck mobility, changes in skin color, edema, hoarseness, or the presence of distended neck and facial veins. DTC more commonly invades the anterior musculature of the neck and there may be reduced cervical mobility. Typically, when the internal jugular vein and or the carotid artery are invaded or encased, the mass often feels essentially fused to the bony structures of the thoracic inlet or vertebral column.

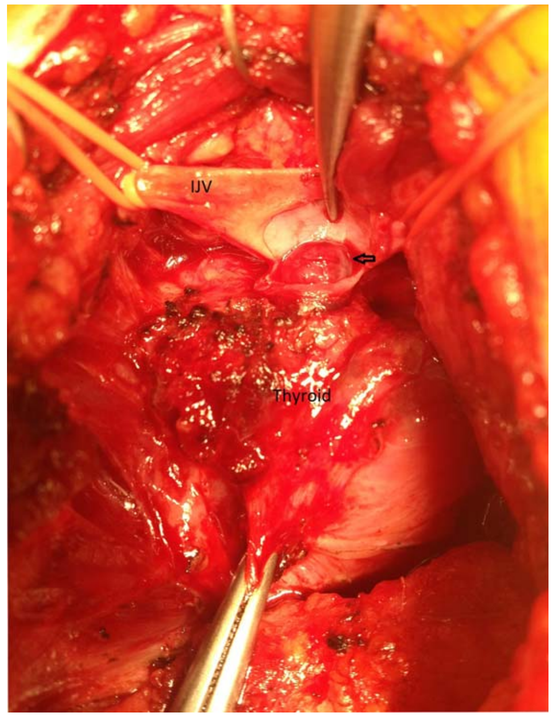

FIGURE 4. Follicular thyroid carcinoma with invasion of the middle thyroid vein and tumor extending partially into the lateral wall of the internal jugular vein (IJV; arrow). A venotomy has been performed. The wall of the IJV was resected and repaired. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

When vascular involvement is suspected, the usual imaging evaluation should be expanded to determine resectability and/or extent of surgery. A neck ultrasound may be considered with particular attention directed at the great vessels but in isolation is not sufficient for full vascular evaluation. A cervical and thoracic 3-phase CT angiogram may be the most appropriate next study as it provides a high-resolution road map for assessment of operative exposure, vascular control, and resection margins.[69] Conventional angiography may be needed to distinguish between external vascular compression and endoluminal tumor or thrombus, and can help to confirm the patency of the Circle of Willis. MRI and MRA may be considered as they are effective in predicting the commonly accompanying invasion of the larynx, esophagus, and mediastinal structures.[69] If carotid resection is contemplated, consultation with vascular surgery would also be prudent.

Vascular reconstruction

Statement 10-A. One internal jugular vein may be excised without reconstruction when the contralateral internal jugular vein is patent (consensus).

Statement 10-B. In the event that both internal jugular veins are resected simultaneously, at least one should be reconstructed, preferably with autologous vein graft (consensus).

Statement 10-C. In the case of focal vascular invasion, the vessel wall may be excised after appropriate proximal and distal control and reconstructed with patch angioplasty (near-consensus).

The most important factor in any planned en bloc resection with vascular reconstruction is a thorough understanding of the contralateral cerebral flow and intraoperative management of ischemia time. The operative exposure is dictated by the vascular access needed, which may require a full median sternotomy. The resection should achieve grossly frozen section negative margins with a segment of normal vessel.[67] In the case of a small area of venous or arterial invasion, either vascular wall may be excised after appropriate proximal and distal control, and repaired by patch angioplasty with either autologous saphenous vein or biologic versus synthetic patch. However, more commonly, when significant vascular invasion is present, segmental venous or arterial resection is necessary. The ipsilateral internal jugular vein may be excised without reconstruction when the contralateral internal jugular vein is patent. In the event that the contralateral internal jugular vein has been previously resected or is similarly involved by bilateral cervical metastasis, one or both internal jugular veins should be reconstructed as bilateral internal jugular occlusion carries at least a 2% mortality.[68] The neck dissections can also be staged if it was anticipated that both jugular veins may need to be sacrificed and/or reconstructed (Figure 2).

The best option for major venous reconstruction is an autologous vein graft, which provides the most durable patency with the fewest thrombotic and infectious complications.[70] If autologous vein is unavailable ringed expanded polytetrafluoroethylene grafts are suitable for venous reconstruction. Arterial reconstruction should restore the vessels to their anatomic flow and this may require a branched "Y" graft, particularly on the right where the carotid-subclavian junction may require reconstruction.[68] The majority of case reports of arterial reconstruction are with expanded polytetrafluoroethylene grafts that have been fashioned before resection to limit ischemia time. When the carotid is encased but not occluded, it may be necessary to place a temporary arterial shunt depending on the anticipated length of clamp time and the patency of the Circle of Willis.[69,71,72]

External beam radiation therapy

Statement 11-A. EBRT is considered postoperatively in cases in which DTC has high-grade histology (consensus).

Statement 11-B. EBRT is considered postoperatively in cases in which there is unresectable gross disease (consensus).

Statement 11-C. In cases of extensive extracapsular nodal extension, EBRT may be considered, balancing the relative effectiveness and morbidity of the EBRT (consensus).

The value of EBRT for poorly differentiated thyroid cancer, including anaplastic thyroid cancer, has been shown in a number of studies.[73–75] All data on the role of EBRT in DTC is derived from retrospective reviews, as no prospective trial on this subject has ever been published. The limitations of early studies reporting on this topic were non-uniformity in patient selection, surgery performed, and radiation dosing, and universal inclusion of other adjuvant therapy, such as radioactive iodine and thyroid hormone suppression.[73,76,77] More recently, however, several studies have shown a statistically significant improvement in patient outcomes for patients with PTC, lymph node-positive disease, pT4 status, and gross residual disease after resection.[78–80] Improvements in locoregional disease control rates from adjuvant EBRT are best demonstrated in patients with PTC. Clear benefits of EBRT have yet to be demonstrated for invasive FTC and Hurthle cell cancers.

In a retrospective review of 1297 patients, Chow et al[78] reported a significant benefit of combined radioactive iodine and 60 Gy of EBRT in patients with pT4 PTC compared to radioactive iodine alone or no radiation therapy. Failure-free survival, locoregional recurrence rates, and disease-specific survival were all improved with the addition of EBRT for patients with pT4 disease, extensive nodal metastasis, and gross disease left at the primary site. Others have also reported benefit of EBRT in patients with unresectable disease and gross positive margins.[79,81] The case for EBRT with microscopically positive margins was not well demonstrated in this report. Conventional treatment such as radioactive iodine and additional surgery may be less morbid and equally effective. In 1996, Farahati et al[79] reported a retrospective case-control study on patients with PTC and FTC with locally advanced stage without distant metastasis at presentation who were treated with total thyroidectomy, thyroid-stimulating hormone suppression, and postoperative radioactive iodine. EBRT was administered to 99 patients, whereas 70 patients had radioactive iodine alone. The authors observed a reduction in local recurrence in the EBRT group (7% vs 30%). A multivariate analysis established that patients with PTC, pT4, node positive disease, and age >60 years had statistically significant improvement in locoregional recurrence. A benefit of EBRT for patients with FTC or age <45 years was not demonstrated.

Keum et al,[80] reported on a series of 68 patients with T4 PTC who had tracheal invasion. In that study, all patients underwent shave excision for tracheal involvement. The degree of tracheal invasion was stratified by whether the tumor invaded through the cartilage or involved the perichondrium only. Margin status was also subclassified to adjust for complete ($n = 12$), microscopically incomplete ($n = 43$), and grossly incomplete resection ($n = 13$). Twenty-five patients received postoperative EBRT with or without radioactive iodine, and 43 patients did not receive EBRT (control group). Radiotracer was concentrated adequately in 14 patients, 12 of whom got therapeutic doses of radioactive iodine. Twenty-five patients who did not concentrate radiotracer to an adequate degree were given EBRT to a total dose of 53 to 63 Gy. After an average of 8.5 years of follow-up, comparison of the 2 groups revealed that, despite a greater disease burden in the EBRT group, a statistically significant reduction in locoregional recurrence was detected (51% in the control group vs 8% in the EBRT group; $p < .01$). When assessed as a function of margin status (microscopic and macroscopic positive margins), a statistically significant reduction in locoregional recurrence was again demonstrated in the EBRT group ($p < .004$). No difference was noted between the EBRT and control groups in the margin-negative patients. The EBRT group had significant progression-free survival as compared to the control group (38% in the control group and 89% in the EBRT group; $p < .0004$).

Intensity modulated radiation therapy (IMRT) affords the ability to give relatively high doses of radiation to the involved target area while partially sparing important uninvolved structures.[73,76,82] This gives a theoretical advantage to IMRT over conventional EBRT in that tumor volumes can be more specifically targeted and higher radiation doses given to the tumor with less adverse effects to the surrounding structures. The role of IMRT in the treatment of DTC has not been well studied. In 2009, The MD Anderson group reported their experience with the use of postoperative EBRT in 131 consecutive patients who had non-anaplastic thyroid cancer.[83] Indications for EBRT were pT4, gross residual disease left at operation, Hurthle cell or tall cell histology, and recurrent disease. Forty-four percent of these patients had IMRT. The study had a short follow-up and no control group, but high local control with EBRT was achieved relative to historical expected recurrence rates after surgery alone. Treatment-related toxicity resulted in a tracheotomy in 11%, percutaneous endoscopic gastrostomy placement in 29%, and 5% had a percutaneous endoscopic gastrostomy tube long term.

The Memorial Sloan–Kettering group published their experience with EBRT in 76 consecutive patients with high-risk and recurrent disease; 63% were treated using IMRT.[84] The predominant histology was PTC but there were substantial numbers of other non-anaplastic carcinomas treated in this study. Ninety-three percent were post-surgical and 15% were considered unresectable. Two-year and 4-year local control rates were significantly improved for patients who underwent EBRT compared to historical disease control rates (86% and 72%, respectively). Acceptable rates of toxicity were reported in this series. Temporary tracheotomy was required in 8, and remained permanent in 3; a temporary gastrostomy tube was required in 22 patients but only 4 patients required it long term.

CONCLUSIONS

Only with proper preoperative evaluation, a high index of suspicion for invasion, and the surgical expertise for complete resection with low morbidity, patients with invasive well-differentiated thyroid cancer are likely to be given the best opportunity for survival and low risk of recurrence. Gross disease resection is an underlying theme throughout the literature for thyroid cancer in general and for invasive disease specifically, which is reflected in the statements offered here for which consensus was achieved. For invasive disease, complete resection can result in a plethora of important functional deficits, which must be considered as the surgical plan is engaged, especially as it relates to the commonly affected recurrent nerve and airway. Such decision-making is best formatted by an experienced surgeon in the context of a multidisciplinary team including endocrinology, laryngology, radiology, nuclear medicine, radiation oncology, medical oncology, and, most importantly, the patient and their family. In these discussions, oncologic completeness is balanced with surgical morbidity, with an understanding of the patient's disease status, distant progression, comorbidities, and wishes.

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