Review Article

Modern surgery for advanced thyroid cancer: a tailored approach

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Abstract: Surgical treatment of advanced thyroid malignancy can be morbid, compromising normal functions of the upper aerodigestive tract. There is a paucity of guidelines dedicated to the management of advanced disease. In fact, there is not even a uniform definition for advanced thyroid cancer currently. The presence of local invasion, bulky cervical nodes, distant metastases or recurrent disease should prompt careful preoperative evaluation and planning. Surgical strategy should evolve from multidisciplinary discussion that integrates individual disease characteristics and patient preference. Intraoperative neuromonitoring has important applications in surgery for advanced disease and should be used to guide surgical strategy and intraoperative decision-making. Recent paradigm shifts, including staged surgery and use of neoadjuvant targeted therapy hold potential for decreasing surgical morbidity and improving clinical outcomes. Modern surgical planning provides optimal treatment for each patient through a tailored approach based on exact extent and type of disease as well as incorporating appreciation of surgical complications, patient preferences and intraoperative findings.

Keywords: Advanced thyroid cancer; neoadjuvant therapy; staged surgery; intraoperative neuromonitoring; tailored approach

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Introduction

The incidence of thyroid cancer has risen dramatically over the last few decades in the USA and other developed countries (1,2). While much of this rise is attributed to increased detection of small (<2 cm) papillary thyroid carcinomas (PTCs), the incidence of larger tumors (>4 cm) has been noted to more than double in the last three decades (3,4). Though the majority of differentiated thyroid carcinoma (DTC) carries an excellent prognosis, locally invasive disease portends a worse prognosis and is relatively common, representing 13% to 15% of DTC (5,6). Medullary thyroid carcinoma (MTC) accounts for only 2–4% of all thyroid carcinomas but presents more frequently at an advanced stage, with 30% of tumors demonstrating extrathyroidal extension, 50–70% of patients presenting with regional metastasis and 10–15% presenting with distant metastasis (7-10). Anaplastic thyroid carcinoma (ATC) comprises less than 1% of cases but carries a dismal prognosis with a 5-year survival rate of 7% and disease-specific mortality approaching 100% (11-13).

Surgical management of advanced thyroid cancer is

complex and challenging. While surgery represents the mainstay of initial treatment, the benefits of surgery must be carefully weighed against the potential for harm (14,15). Traditional paradigms for primary surgical management, including extensive resection of extrathyroidal tissues, can be surgically morbid and associated with decreased quality of life (16-18).

At present, there are few guidelines dedicated to optimal management of advanced thyroid cancer. The American Thyroid Association (ATA) has published recommendations for treatment of advanced disease within its broader guidelines on management of nodules and DTC and has published separate guidelines for management of MTC and ATC (14,15,19). The American Head and Neck Society (AHNS) has published a consensus statement on the surgical management of invasive DTC and addresses surgical management of recurrent disease in a separate consensus statement (20,21). The purpose of this review is to provide a comprehensive assessment of current and evolving management strategies for treatment of advanced thyroid cancer with emphasis on a tailored approach based on disease characteristics, oncologic resection, potential for complications, and an appreciation of patient preferences.

Defining advanced thyroid cancer

While the features of advanced thyroid cancer are intuitively recognized by clinicians who treat this condition, a standard definition for advanced disease does not presently exist in the literature. Certainly, size, extent and spread of disease are central features, as reflected in the AJCC TNM staging system (12). However, staging systems are designed to predict disease-related mortality and may not adequately capture the morbidity of disease or the variable nature of surgical risk that it presents. In advanced thyroid cancer, the benefits of surgical tumor extirpation with regards to local control, risk of persistence/recurrence and overall survival must be carefully weighed against the morbidity of surgery, which may require aggressive resection of extrathyroidal tissues in order to achieve microscopically negative margins (20).

The rate of R0 resection in primary surgical treatment of advanced thyroid cancer is not well known. In an older series of patients with locally advanced PTC, clearance of gross disease was reported to be successful in only 56% (5). More recently, Ibrahimpasic *et al.* reported on a series of 27 patients with advanced poorly differentiated thyroid cancer, 22% of whom had preoperative radiation. The R0 resection rate was 7% and the R1/R2 resection rate was 89%, with margin status unknown in 4% (22).

The issue of surgically "unresectable" disease is worth noting, as no standard definition currently exists for this as well. Importantly, the designation of disease as inoperable must not only account for technical surgical challenges or limitations, but also account for the morbidity associated with surgical resection, especially as it relates to upper aero-digestive tract function and the patient's willingness to undergo such procedures. Surgical treatment of disease invading the trachea, esophagus or larynx may be especially morbid, impacting airway, voice and swallowing functions. In this context, patient's acceptance of the proposed surgical procedure and its attendant morbidity is paramount to establishing the "resectability" of advanced disease.

Locally advanced disease

Clinicopathologic factors associated with local invasion in DTC include older age, larger tumor size, presence of lymph node metastases and aggressive histologic type, including tall cell and diffuse sclerosing variants (23). *BRAF V600E* mutation has also been associated with invasive disease (24).

Involvement of the airway has been reported in 6% to 21% of patients undergoing thyroid surgery (25-28); among patients with invasive DTC, 37% demonstrate tracheal invasion, 21% demonstrate esophageal invasion, and 12% demonstrate laryngeal invasion (5); intraluminal tracheal involvement is less frequent, occurring in 0.5% to 1.5% (29,30). The recurrent laryngeal nerve (RLN) represents one of the most frequent sites of local invasion, occurring in 33–61% of cases (5,31,32). While esophageal and tracheal invasion have been shown to impact survival, RLN invasion does not independently influence survival (5).

Locally advanced DTC is associated with an increased incidence of local recurrence, regional and distant metastasis, and mortality; when death occurs from DTC, it commonly involves complications of local invasion, including airway obstruction and hemorrhage (33-35). MTC frequently presents at an advanced stage, and large tumor size or locally invasive disease is associated with worse prognosis (36-38). Roman *et al.* conducted a study of the SEER database with over 1,200 cases and showed poorer overall survival with locally advanced tumors (9); in a national study from Ireland, advanced T stage was shown to be independently associated with decreased survival (39).

Advanced regional disease

Regional lymph node metastases are present at the time of diagnosis for the majority of patients with PTC, though with controversial clinical significance (14). In a large SEER database study of DTC, 14-year overall survival was 82% for patients without regional nodal metastases and 79% for patients with regional nodal metastases (P<0.05) (40). In another large SEER study of DTC, the presence of lymph node metastases was found to adversely impact survival for patients only with follicular carcinoma or age >45 years old (41). Increased nodal burden and extranodal extension have been shown to be associated with increased risk of recurrence in DTC (42-44).

MTC frequently presents with advanced nodal metastases; the work of Machens and others has shown that nodal metastases occur at presentation in 50% of asymptomatic patients and over 70% of symptomatic patients (45,46). In a series of 73 patients with MTC, Moley identified nodal disease in 80% of central neck dissection specimens, 75% of ipsilateral and 47% of contralateral lateral neck dissections, respectively (47). Importantly, mediastinal nodal disease at presentation has been noted by Machens *et al.* to have prognostic significance equivalent to the presence of distant metastatic disease (48). This group has also noted that when preoperative calcitonin is greater than 1,000 IU, biochemical cure after neck surgery, however extensive, is rare (49). As such, surgical treatment for locoregionally advanced MTC is problematic. In a study reviewing the California cancer registry, the hazard ratio for disease-specific survival in the setting of regional lymphadenopathy (as compared with localized disease) was 9.44 (CI, 1.62–56) (50).

In surgical treatment of nodal disease, completeness of resection is critical to preventing disease persistence or recurrence (51-53). In advanced disease, widely distributed or invasive adenopathy may be problematic, as surgical extirpation of bulky or extensive bilateral central and lateral neck disease has been associated with increased risk of complications, including RLN injury, hypoparathyroidism, and injury to other critical neurovascular structures (54-57).

Distant disease

While the presence of distant metastases signifies advanced disease, patients with metastatic DTC frequently achieve long-term favorable outcomes (58). On the other hand, for patients with metastatic MTC, 10-year survival with distant disease is only 40%, compared with 75% for patients with regional disease and 96% when tumor is confined to the thyroid (59). Where feasible, surgical extirpation of locoregional disease in metastatic thyroid cancer is generally considered to be warranted in order to prevent the complications of locoregional progression. Importantly for DTC, surgical treatment of locoregional disease also permits the administration of radioactive iodine (RAI) to facilitate treatment of distant metastases (14). For MTC, it is suggested that, in the presence of metastatic disease, less aggressive surgery or palliative debulking be considered in order to mitigate surgical morbidity with respect to speech, swallowing and parathyroid function (15). For treatment of metastatic ATC, the ATA recommends that surgical resection of neck disease should be performed whenever feasible, except in the setting of imminently life-threatening distant metastases (19).

Recurrent disease

Recurrent or persistent thyroid cancer warrants special consideration as advanced disease. While the impact of locoregional recurrence in DTC is debatable, especially for low-volume disease, surgical management is inherently more complex and challenging (60). In reoperative thyroid bed surgery, the presence of scar tissue or altered anatomy may pose additional risk of complications, with rates of permanent RLN injury and permanent hypoparathyroidism as reported high as 6.4% and 9.5%, respectively (61-63). Still, in experienced hands, reoperative thyroid bed surgery has been shown to be safe and effective (64,65). The decision to perform reoperative thyroid surgery should be made carefully, with consideration of observation or non-surgical treatment methods where appropriate.

Preoperative evaluation of advanced disease

Preoperative detection of locoregionally advanced disease is critical to formulating an appropriate surgical plan and obtaining informed consent. The surgeon should not be caught by surprise when encountering invasive disease intraoperatively, as this may potentially preclude execution of the appropriate surgical procedure at the time of initial surgery. Incomplete resection of advanced thyroid cancer has been associated with increased mortality (66,67). In a series of 82 patients undergoing segmental tracheal resection for invasive disease, Gaissert *et al.* demonstrated that 10-year survival was better with complete resection

compared with incomplete initial resection followed by subsequent salvage surgery (40% *vs.* 10%, P<0.0001) (68).

Thorough clinical evaluation is needed to assess for advanced disease. While signs and symptoms such as hoarseness, dysphagia, hemoptysis or pain may suggest invasive disease, up to 12% of patients presenting with invasive thyroid cancer may be asymptomatic (68). As such, several preoperative measures are important for the detection of advanced thyroid cancer and planning of surgical treatment.

Preoperative imaging

Accurate mapping of tumor is essential to safe and effective surgery for advanced disease. While ultrasound (US) is recommended for all patients receiving thyroidectomy, the ATA recommends cross-sectional neck imaging including axial computed tomography (CT) with contrast be obtained in cases of DTC where there is clinical suspicion for advanced disease, including a large primary tumor, bulky lymphadenopathy or clinical evidence of invasion (14). Similarly, imaging is recommended in MTC where there is extensive neck disease, evidence of distant metastases, or where calcitonin is >500 pg/mL (15). Cross-sectional imaging of the neck is imperative in ATC to assess for regional disease and extent of local invasion (19).

In recurrent neck disease, US should be used as a first-line modality for detection of recurrence; however, there should be a low threshold for use of cross-sectional imaging to map and characterize areas of disease. Lesnik *et al.* have demonstrated that a combined approach utilizing preoperative US and CT provides a reliable, objective and complete preoperative macroscopic nodal metastasis map that can be used to frame nodal surgery in primary/revision PTC patients (69). While US is a sensitive tool for detection of recurrence, it is limited by operator dependence and less effective in visualizing critical areas of potential disease, including the tracheoesophageal groove, retropharynx or upper mediastinum (21).

Laryngoscopy

Laryngeal evaluation is an important component of preoperative assessment for advanced thyroid cancer. Preoperative vocal cord paralysis (VCP) is a robust marker for invasive disease, as demonstrated by Randolph and Kamani who identified VCP in 70% of patients with invasive thyroid cancer *vs.* 0.3% in benign or noninvasive disease (70). Importantly, 30% of patients with unilateral VCP are asymptomatic with normal voice production. (70,71). It is therefore incumbent upon the treating team to assess for vocal cord dysfunction, especially when advanced disease is present.

Preoperative laryngeal examination is currently not uniformly performed, however, clinical findings suggestive of RLN invasion should prompt evaluation. The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), AHNS and ATA all recommend preoperative laryngeal evaluation for patients at risk of RLN compromise, including those with preoperative voice abnormalities or malignancy with evidence of posterior or extrathyroidal spread or extensive central neck adenopathy (14,72,73). Other groups have published more stringent recommendations. The British Thyroid Association recommends preoperative laryngeal evaluation for all patients receiving thyroid surgery for cancer (74). The German Association of Endocrine Surgeons has recommended both preoperative and postoperative laryngoscopic examination for all patients undergoing thyroid surgery, and the International Neural Monitoring Study Group (INMSG) recommends preoperative and postoperative laryngoscopy for all patients undergoing thyroid surgery with intraoperative neural monitoring (IONM) (75,76).

It is important to recognize that an invaded RLN may still have preserved function without VCP. Kamani *et al.* demonstrated that 45% of invaded RLNs present with normal preoperative laryngeal function (77). Factors such as tumor histology, posterior location, and radiographic features of invasion or bulky central neck adenopathy should be considered when assessing risk to the RLN and counseling a patient about expected surgical outcome.

Considerations in surgical management of locally advanced disease

IONM and management of the invaded RLN

IONM has important applications in surgery for invasive thyroid cancer. Guidelines recently published by the INMSG outline the application and benefits of IONM and offer evidence-based algorithms to guide surgical decision-making, especially as it relates to intraoperative loss of signal (LOS) as well as invaded RLN management (78,79). Integral to neuromonitoring strategy is the detection of impending neurologic injury and neural prognostication

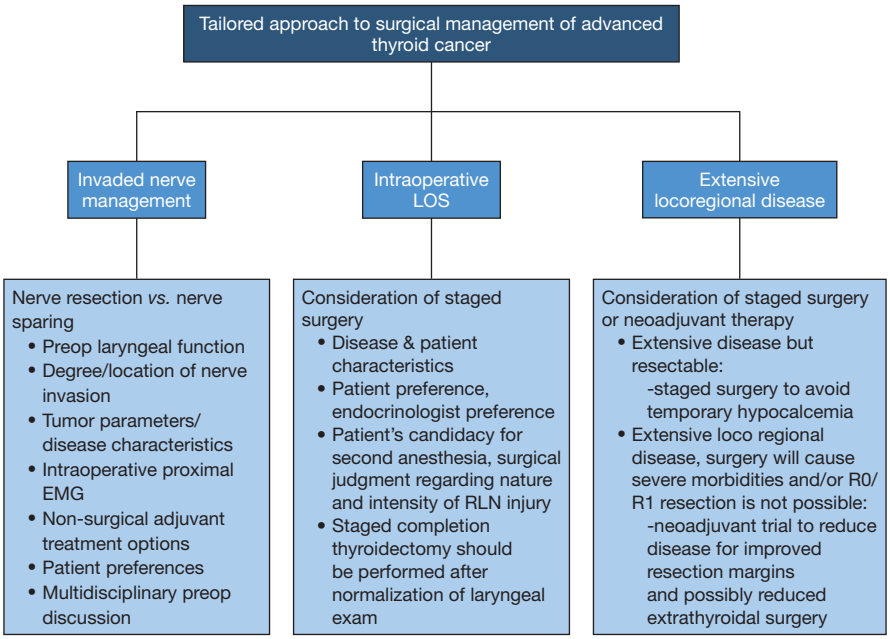

Figure 1 Tailored approach to surgical management of advanced thyroid cancer: in cases with invaded nerve management, intraoperative LOS or extensive loco-regional disease. LOS, loss of signal; EMG, electromyography; RLN, recurrent laryngeal nerve.

at the termination of surgery. Adverse electromyography (EMG) changes associated with surgical manipulation of the RLN can predict impending neuropraxia, allowing opportunity to modify or cease injurious maneuvers (80). Evolving EMG changes related to repeated neural insults can result in LOS, defined by the INMSG as EMG response <100 μV. LOS at the termination of surgery indicates a high risk of neuropraxia, with only a ~15–25% likelihood of intraoperative recovery (81). In planned bilateral surgery, when LOS has occurred on the first operative side, the INMSG recommends this information be used to inform the decision of whether to stage contralateral surgery.

For the invaded RLN, intraoperative management is accomplished through integration of intraoperative neuromonitoring data, surgical information and knowledge of preoperative vocal fold function (79) (*Figure 1*). The extent and location of neural invasion, ability to stimulate proximally, and overall disease characteristics, including histologic type and presence of unresectable locoregional or distant metastases, have important bearing on intraoperative decision making (82).

When the RLN is found to be superficially invaded and preoperative vocal cord function is normal, attempts should be made to preserve the structural integrity of the nerve while achieving gross total resection. Though shave/partial layer resection may result in LOS, the majority of nerves subjected to this demonstrate long-term recovery of neural function (81). When extensive RLN invasion is identified, the surgeon must determine whether to resect or preserve the nerve. Importantly, whether an invaded nerve is resected or preserved does not appear to impact prognosis (31,83-86). Rather, the decision should be guided through incorporation of EMG data with patient- and disease-related factors.

The ability to intraoperatively stimulate the proximal segment of an invaded nerve has important bearing on the decision to resect, as it suggests some maintenance of neural function, even when VCP is present. Kamani *et al.* demonstrated that 60% of invaded nerves can be electrically stimulated intraoperatively, including 33% of nerves with preoperative glottic impairment (77). Resection of an invaded RLN with preoperative paralysis but intraoperative stimulability may lead to worsening glottic function (87). The INMSG recommends that proximal stimulability be used as a parameter to assess RLN function and direct intraoperative decision-making (79).

The location and extent of neural invasion should also direct intraoperative decision-making. When tumor invades only the epineurium, macroscopic resection can be achieved with a shave excision (84,85). However, if tumor

infiltrates the perineurium and endoneurium and extends along neural fibers, gross macroscopic resection cannot be readily achieved and neural resection should be considered, especially in cases where adjuvant therapy is expected to be less effective. Notably, resection may be warranted when neural invasion occurs close to the RLN's entry point into the larynx and there is concern that disease may persist or progress. This is because progression along the nerve may result in spread of tumor into the larynx, with subsequent efforts at surgical control requiring laryngectomy.

Disease-and patient-related characteristics should also guide intraoperative management. For high-risk disease where surgical treatment is urgent, completion of planned bilateral surgery in the setting of LOS with possible risk of bilateral VCP should be discussed preoperatively in a multidisciplinary setting and with the patient. Similarly, pre-existing contralateral VCP in the setting of an invaded only-functioning nerve should prompt thoughtful decision-making that incorporates disease characteristics and patient preference. In this setting, careful shave resection of the invaded nerve should be considered along with use of adjuvant treatment in order to avoid bilateral VCP (20,79). For disease with distant metastases or where complete locoregional resection cannot be safely achieved, leaving a small amount of macroscopic tumor on a grossly invaded nerve may be warranted in order to preserve glottic function.

Invasion of visceral structures

When thyroid cancer invades visceral structures and aggressive surgery is aligned with therapeutic goals, the aim of surgery should be to resect all gross disease. Adjuvant therapy, including RAI or external beam radiotherapy (EBRT), is typically required to achieve locoregional control. The requisite surgical procedures should be anticipated preoperatively through careful clinical evaluation.

Extent of tracheal invasion has been classified by Shin as well as others (88,89). The most limited form of involvement includes perichondrial invasion with adherence to the trachea but no requirement for airway resection (stage I); this is followed by cartilaginous invasion but without mucosal involvement (stage II). More advanced disease invades the mucosa (stage III) or extends into the lumen (stage IV). If clinical or imaging findings raise concern for tracheal involvement, bronchoscopy may be performed pre-operatively or at the time of tumor resection to assess for mucosal or intraluminal involvement.

For limited cartilage invasion over a short segment, shave resection of the airway is considered to be appropriate. However, for more extensive invasion including mucosal or intraluminal involvement, full-thickness tracheal resection is recommended (20). Performance of tracheal resection requires an advanced skill set and may be associated with significant functional morbidity. In cases where disease extends into the cartilage but not clearly into the mucosa, shave excision as a less aggressive approach has been favored by some, though remains controversial (90). Invasion of tumor into the laryngeal framework is a particularly ominous element of invasive disease. Shave excision is recommended where possible, however, when tumor extends into the endolarynx, more aggressive resection, including laryngectomy, may be warranted (20).

Esophageal invasion may occur through direct posterior extension of tumor; while involvement of the muscularis is commonly seen in invasive DTC, extension into the lumen is rare. In most cases, resection of the involved layer of muscularis is sufficient. Where there is mucosal involvement, full-thickness resection and appropriate reconstruction should be performed (20).

Invasion of vascular structures in neck or upper mediastinum should be addressed through careful preoperative evaluation and planning. Where vascular invasion is suspected, appropriate imaging should be obtained to determine the extent of invasion and feasibility of resection. Involvement of the internal jugular vein (IJV) by nodal disease is one of the most common sites of invasion and can be readily addressed with unilateral excision of the IJV. Bilateral IJV excision may lead to complications of venous congestion in the head and neck and reconstruction of one side with an autologous graft is recommended. Similarly, if the need for carotid resection is anticipated, imaging studies to ensure patency of the Circle of Willis should be obtained and consultation with vascular surgery may be warranted (20).

Role of multidisciplinary patient-centered decision-making and informed consent

Surgical planning for advanced disease should be multidisciplinary and tailored to patient-specific disease characteristics and patient preferences. Tumor histology and behavior, extent of local invasion and nodal disease, presence of distant metastases, effectiveness of adjuvant therapy, surgical morbidity and overall treatment goals

should all be considered by a multidisciplinary treatment team and should influence the surgical plan, especially as it relates to the timing and extent of surgery. Completeness of surgery for oncologic benefit must be carefully balanced with the goal of preserving function. Ultimately the surgery must be acceptable to the patient.

It is imperative to have direct and detailed conversations with patients preoperatively in order to understand their preferences regarding treatment. Some patients may prefer less aggressive surgical resection in favor of preserving voice or swallowing function while others may prefer a more aggressive surgical approach to maximize chances of cure or avoid future need for active surveillance. During preoperative discussion, anticipated intraoperative decision-making should be discussed, especially as it relates to management of the RLN and airway. Care should be taken to review the impact of various surgical decisions on both function and oncologic outcome so that the patient's stated preference is appropriately informed.

In neuromonitored surgery, RLN injury with intraoperative LOS has important implications for staging of contralateral surgery to avoid potential bilateral VCP. If initial LOS occurs, clinical factors and patient preference must figure into the decision to complete or stage contralateral surgery. These types of considerations should be addressed preoperatively to facilitate patient-centered decision-making and manage patient expectations with regard to surgical outcome.

Staged bilateral surgery

Staging of bilateral thyroid surgery may be based on intraoperative LOS or may be planned as two-stage surgical management for extensive disease; both exemplify integration of a tailored approach in modern thyroid surgery (*Figure 1*).

IONM and staged surgery

Staging of bilateral surgery is a core feature of surgical strategy in neuromonitored modern thyroid surgery. The effectiveness of staging to avoid bilateral VCP has been readily demonstrated. Goretzki *et al.* showed that the rate of bilateral VCP was 0% when intraoperative neuromonitoring data was used to stage surgery after LOS, *vs.* 17% where unrecognized neural injury occurred on the first side and surgery proceeded to the second side (91). Several additional studies have demonstrated a zero rate of bilateral vocal fold paralysis (VCP) when surgery is staged after initial LOS (81,92,93).

Staging of surgery in the setting of LOS has largely gained acceptance among the surgical community. In a survey distributed to over 1,200 surgical departments in Germany, 94% of respondents indicated they would be willing to modify their surgical strategy after initial LOS (94). Still, the intraoperative decision to stage surgery may be fraught for some when it deviates from the intended plan. In the setting of LOS, the INMSG encourages the surgeon to prioritize the benefits of staging over concerns about altering the surgical course (81). Indeed, preoperative discussion should be held with the patient in order to manage expectations about this potential outcome. Most patients will accept the idea of staging in order to avoid the potential morbidity of bilateral VCP. Melin *et al.* demonstrated that there was no difference in patient satisfaction for patients receiving single- *vs.* two-stage surgery (95).

Planned staging of bilateral surgery

Planned staging of surgery for bulky or extensive locoregional disease represents an important paradigm shift in surgical strategy. Resection of nodal metastases in advanced malignancy may require extensive dissection of the bilateral central and lateral neck compartments to clear disease. In the central neck, performance of nodal dissection in addition to thyroidectomy is associated with increased risk of complications, especially hypoparathyroidism. Giordono *et al.* performed a retrospective review of 1,087 patients with PTC and clinically negative neck nodes who underwent total thyroidectomy with or without central neck dissection. These authors showed increased risk of temporary hypoparathyroidism for both unilateral and bilateral central neck dissection compared with no neck dissection (36.1% *vs.* 27.7%, P=0.014 for unilateral *vs.* none; 51.9% *vs.* 27.7%, P<0.001 for bilateral *vs.* none). Increased risk of permanent hypoparathyroidism was significant in patients who underwent bilateral central neck dissection (16.2% *vs.* 6.3%, P<0.001) (96). These findings are consistent with other reported series in the literature (97-99). Studies have also reported increased rates of temporary and permanent hypoparathyroidism with the addition of bilateral lateral neck dissections to central neck procedures (56,99). Complications associated with the simultaneous performance of bilateral lateral neck dissection may also include vascular injury, chyle leak, spinal accessory nerve

injury, and Horner syndrome (56).

When multicompartment surgery is required, staging of contralateral surgery can mitigate complications of extensive dissection. Just as staged surgery prevents risk of bilateral RLN injury by allowing recovery of neural function, staged surgery may decrease risk of hypoparathyroidism by allowing recovery of ischemic or congested parathyroid gland or autotransplanted parathyroid tissue. A retrospective study by Merchavy *et al.* comparing 146 cases of total thyroidectomy with 68 cases of completion thyroidectomy found a significantly lower incidence of temporary hypocalcemia in the completion thyroidectomy group, suggesting some recovery of parathyroid function with staged procedures (100). Furthermore, staged surgery may have benefit for surgeons in preventing muscular fatigue by decreasing operative length (101).

Staged bilateral surgery for advanced thyroid cancer has been shown to be both safe and effective. Salari *et al.* reported on a series of 35 patients with advanced DTC and MTC who underwent planned staging of bilateral procedures, for a total of 70 neck operations. There were no cases of unintentional RLN injury. Temporary hypoparathyroidism occurred in 16 patients (45.7%); only one patient developed permanent hypoparathyroidism (2.9%). For patients with PTC, oncologic outcomes were shown to be favorable, with a median postoperative stimulated thyroglobulin level of 0.75 ng/mL. Locoregional recurrence occurred in 5.7% of patients with a median follow-up of 28 months (102).

Role of neoadjuvant therapy for advanced disease

Recent advances in understanding the genetic alterations driving thyroid tumorigenesis and the subsequent advent of targeted systemic therapies have shifted the landscape of advanced thyroid cancer management. Molecular characterization of PTC and identification of genomic alterations along the mitogen-activated protein kinase (MAPK) signaling pathway, including *BRAF V600* and RAS, has led to the development of targeted tyrosine kinase inhibitors, with several agents being used clinically to treat progressive disease (103-106). Two of these agents, lenvatinib and sorafenib, are now FDA-approved for use in advanced, recurrent, and RAI-refractory DTC. Lenvatinib showed robust clinical activity in the phase III trial, with a median progression-free survival (PFS) of 18.3 *vs.* 3.6 months for placebo (P<0.001). Treatment with lenvatinib also resulted in a highly statistically significant effect on response rate compared with placebo (64.8% *vs.* 1.5%, P<0.0001); among those treated with lenvatinib, there were four complete responses, a remarkable finding for an anti-angiogenic agent (107).

Targeted therapy for *RET*-altered tumors is an area of rapid advancement. Germline *RET* mutation is present in all inherited MTC; somatic *RET* mutations are present in up to 40% of sporadic cases of MTC and have been associated with more aggressive disease (108,109). *RET*-PTC rearrangements are reported to be present in 20% to 70% of PTC, with a higher prevalence in the pediatric population and radiation-induced thyroid cancers (110,111). Several studies have demonstrated variable relationships between these rearrangements and clinicopathologic characteristics; *RET/PTC3* in particular has been associated with a short post-radiation latency period as well as de-differentiation and aggressive behavior (111-113).

Multikinase inhibitors cabozantinib and vandetanib have been approved for use in *RET*-mediated metastatic or locally advanced MTC, however these agents inhibit other targets more potently then *RET* and have significant side effect profiles (114,115). Newly developed selective *RET*-inhibitors, BLU-667 and LOXO-292 hold promise for treatment of *RET*-altered tumors. LOXO-292 has shown potent and selective anti-*RET* activity in pre-clinical human cancer *RET*-altered lines and patient xenograft studies. (116,117). Reporting of phase I trial results for 82 patients with *RET*-altered cancers treated with LOXO-292 and studied with the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 endpoint shows confirmed overall response rate of 56% for *RET*-mutant (MTC) tumors and 78% for *RET*-fusion tumors. For those remaining on treatment, the response rate was 94% for *RET*-mutant tumors and 100% for *RET*-fusion tumors with a median follow-up of 8.4 and 8.5 months, respectively. Dramatic reductions in calcitonin and CEA were also observed. Importantly, owing to its highly selective activity, LOXO-292 was noted to be well tolerated, with only 10% of patients experiencing adverse events, the majority of which were grade 1 and judged to be unrelated to LOXO-292 (118).

Recent advances in targeted therapy for *BRAF V600*-mutated ATC have also been reported. Genetic analyses reveal *BRAF V600E* mutation to be present in up to 45% of ATCs (119-121). Treatment of locally advanced or metastatic *BRAF V600*-mutant ATC with dabrafenib (*BRAF* inhibitor) and trametinib (MEK inhibitor) was studied in 16 patients using RECIST 1.1 criteria with an investigator-assessed overall response rate of 69% (median follow-up

duration of 47 weeks). One patient exhibited a complete response. Estimated 12-month PFS and overall survival were 79% and 80%, respectively. The regimen was well-tolerated, with the most common adverse events including fatigue (44%), pyrexia (31%), and nausea (31%) (122). FDA approval for use of this regimen in *BRAF V600*-mutant locally advanced or metastatic ATC was granted based on the results of this phase II trial.

The robust activity of targeted therapies in treatment of progressive disease suggests opportunity for use in the neoadjuvant setting where gross resection of disease might be otherwise morbid or difficult to achieve. Neoadjuvant treatment in patients presenting with extrathyroidal locally invasive disease may allow for more oncologically secure margins and perhaps less aggressive and less morbid initial surgical management. Such improved initial therapeutic efficacy could also decrease rates of locoregional recurrence and potentially, in turn, impact long-term survival in patients presenting with advanced disease.

In the literature, very limited experience exists with neoadjuvant cytotoxic therapy for thyroid carcinoma. Besic *et al.* treated 13 patients with poorly differentiated thyroid cancer with a mean tumor diameter of 9 cm, with 61% staged as T4. Cytotoxic neoadjuvant treatment was combined with external beam radiation in 15%. Some degree of tumor regression was seen in all patients, and 38% experienced >30% decrease in tumor diameter. Pathologic R0 resection was possible in 38% and R1 resection in 60% (123). This same group treated 29 patients presenting with advanced T3 or T4 follicular and Hürthle cell cancers with a mean tumor size of 7.3cm with neoadjuvant vinblastine; 13% were also treated with EBRT. Tumor size reduced by >50% in 45% of patients. R0 resections were achieved in 51% and R1 in 34%, with local long-term control obtained in 97% (124). This same cytotoxic regimen with or without radiation was investigated when given preoperatively to 16 patients with locally advanced papillary thyroid cancer, 43% of whom had T4 tumors, and mean tumor size was 9.6 cm. Tumor reduction of >50% occurred in 44% of patients, with an R0 resection rate of 12% and R1 resection rate of 62% (125). Notably, cytotoxic chemotherapy has shown poor performance in treating distant metastatic MTC and to the best of our knowledge has not been studied the neoadjuvant setting (126).

At present, there is no large data set available regarding experience with targeted therapies (TKI or *RET* inhibition) in the neoadjuvant setting. Wang *et al.* reported on a series of 6 patients with locoregionally advanced unresectable *BRAF V600*-mutated ATC treated with neoadjuvant dabrafenib and trametinib, with 5 patients receiving 1–4 months and 1 patient receiving 12 months of neoadjuvant treatment; 3 of these patients also received neoadjuvant immune-directed therapy (pembrolizumab). Trametinib was discontinued 3–7 days before surgery and dabrafenib was discontinued the day before surgery. In each case, complete surgical resection was achieved without requiring tracheal, laryngeal or full-thickness esophageal resection. Histopathology of the resected specimens showed reduced viability of tumor cells. All patients received postoperative adjuvant chemoradiation, with 5 patients resuming maintenance dabrafenib/trametinib and 4 receiving pembrolizumab. Overall survival was reported to be 100% at 6 months and 83% at 1 year, with all patients demonstrating locoregional control (127). Stewart *et al.* reported a case of a 73-year-old patient with PTC invading the tracheal lumen, deemed unresectable due to medical comorbidities; lenvatinib treatment for 14 months facilitated successful conservative resection without need for tracheal resection (128). Similarly, Tsuboi *et al.* reported on the case of a 73-year-old patient with PTC invading the trachea and esophagus with bulky lymphadenopathy; treatment with lenvatinib for 22 weeks resulted in sufficient tumor shrinkage to permit less morbid surgery (129). Milner *et al.* described a case of MTC presenting in a pediatric patient with carotid encasement and pulmonary metastasis. Treatment with vandetanib resulted in a 68% decrease in primary tumor size and resolution of pulmonary metastases, facilitating surgical resection. At 6 years of follow-up, the patient remained alive and well on maintenance vandetanib therapy (130).

There is limited data regarding the safety of neoadjuvant kinase inhibitor therapy as it relates to perioperative complications in thyroid surgery. Many of the TKIs inhibit VEGFR pathways with resultant anti-angiogenic activity, raising concerns for bleeding and postoperative wound healing, among other complications (131). No major perioperative complications have been reported in the small amount of data available for thyroid surgery. Patel *et al.* examined surgical complications in patients with metastatic renal cell carcinoma receiving neoadjuvant sunitinib and cytoreductive nephrectomy versus primary surgery with adjuvant therapy; 21 patients received 4 weeks of neoadjuvant treatment, with 2 weeks off therapy prior to surgery. This group had more high-grade surgical complications compared with the group receiving primary surgical treatment (28.6% *vs.* 0%), with advanced age being an independent risk factor

for development of surgical complications (132). By contrast, Harshman *et al.* studied 14 renal cell carcinoma patients treated with TKI for 17 weeks with 2 weeks off prior to cytoreductive nephrectomy and found no difference in overall perioperative complications (50% *vs.* 40%) or perioperative bleeding (36% *vs.* 34%), but an increased rate of surgical field adhesions (86% *vs.* 58%) (133).

Conclusions

Surgical treatment of advanced thyroid cancer is complex and may be associated with significant morbidity. Thoughtful multidisciplinary planning should be tailored to balance oncologic and functional outcomes. Shifts in treatment paradigms, including staging of surgery and neoadjuvant therapy, may mitigate the morbidity associated with surgical treatment of invasive disease, as well as provide opportunity to frame the approach based on the disease characteristics and patient preferences. Neoadjuvant use of targeted therapy holds significant promise for improving clinical outcomes and warrants further investigation. Additional studies are needed to define clinical indications, establish optimal timing for treatment, and evaluate clinical outcomes.

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Footnote

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