Annals of Otolaryngology Head and Neck Surgery
Review Article (ISSN 2835-7132)

# Surgical Management of Locally Advanced Differentiated Thyroid Cancer: A Structure- and Depth-Based Review

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**Citation:** Rodrigo Arrangoiz, Susana Barreiro Sacco, Aradhya Nigam, Fernando Cordera. Surgical Management of Locally Advanced Differentiated Thyroid Cancer: A Structure- and Depth-Based Review. Annals of Otolaryngology Head and Neck Surgery. 2026;5(5):1-63.

**Received Date:** 17 October, 2026; **Accepted Date:** 20 October, 2026; **Published Date:** 24 October, 2026

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## ABSTRACT

**Background:** Locally advanced differentiated thyroid cancer presents significant challenges in diagnosis, surgical management, and multidisciplinary treatment, particularly when tumors invade critical structures such as the recurrent laryngeal nerve, trachea, larynx, esophagus, or major cervical vessels. Advances in molecular profiling, targeted systemic therapies, and surgical techniques have substantially expanded treatment options, creating opportunities to improve oncologic outcomes while preserving organ function and quality of life.

**Methods:** A comprehensive narrative review of the literature was conducted, focusing on contemporary evidence regarding the evaluation and management of locally advanced thyroid cancer. Relevant clinical studies, systematic reviews, consensus statements, and international guidelines were examined, with particular emphasis on the American Thyroid Association and National Comprehensive Cancer Network recommendations. The review evaluated prognostic factors, imaging modalities, molecular alterations, surgical approaches, neoadjuvant therapies, and multidisciplinary treatment strategies.

**Results:** The extent and anatomical location of gross extrathyroidal extension, completeness of surgical resection, histologic subtype, and molecular characteristics are major determinants of prognosis and treatment selection. Complete macroscopic resection remains a central therapeutic objective when technically feasible, although surgical aggressiveness must be balanced against functional morbidity. Advances in preoperative imaging and intraoperative techniques have improved surgical planning and the management of invasion involving the aerodigestive tract and recurrent laryngeal nerve. Molecularly targeted therapies, particularly inhibitors directed against BRAF, RET, and NTRK alterations, have demonstrated clinically meaningful responses in selected patients. Emerging evidence also supports the potential role of neoadjuvant systemic therapy in reducing tumor burden and facilitating resection of

initially unresectable or borderline resectable disease, although long-term oncologic outcomes remain insufficiently established.

**Conclusions:** The management of locally advanced thyroid cancer has evolved from a predominantly surgery-centered approach toward an individualized, multidisciplinary strategy integrating anatomical assessment, molecular characterization, advanced surgical techniques, and selective systemic therapies. Achieving optimal oncologic control while preserving function requires careful patient selection and coordinated treatment planning. The incorporation of molecularly guided neoadjuvant therapy represents a promising development that may expand surgical opportunities in selected patients. Future prospective studies are essential to define optimal treatment sequencing, establish standardized selection criteria, and determine long-term survival and functional outcomes.

**Keywords:** Locally advanced thyroid cancer; Extrathyroidal extension; Differentiated thyroid carcinoma; Surgical management; Recurrent laryngeal nerve invasion; Tracheal invasion; Molecular targeted therapy; Neoadjuvant therapy; Multidisciplinary management

## INTRODUCTION

Differentiated thyroid cancer (DTC) accounts for roughly 90% to 95% of all thyroid malignancies and, under current World Health Organization (WHO) and American Thyroid Association (ATA) classifications, encompasses papillary thyroid carcinoma (PTC) (the dominant subtype), follicular thyroid carcinoma (FTC), invasive encapsulated follicular variant of papillary thyroid carcinoma, and oncocytic carcinoma (OC). It is generally associated with an excellent prognosis, with 5-year relative survival approaching 98% overall and 10-year survival of approximately 93% for PTC [1-5]. Nevertheless, a small but clinically important subset of patients presents with locally advanced disease characterized by gross extrathyroidal extension (gETE) into the structures surrounding the thyroid gland. Locally invasive DTC with gETE involving adjacent cervical structures is reported in approximately 5% to 15% of patients at diagnosis, with aerodigestive tract invasion specifically accounting for roughly 5% to 13% of cases [4,6,7]. It represents one of the most challenging manifestations of the disease because treatment must balance complete oncologic resection against preservation of voice, airway, swallowing, and vascular function, a balance made more critical by the fact that gETE carries a substantially higher recurrence risk, 23% to 40%, than microscopic ETE (mETE), and progressive aerodigestive invasion accounts for approximately half of disease-specific mortality [8].

For the purposes of this review, locally advanced DTC refers primarily to gross macroscopic extension beyond the thyroid gland into adjacent cervical structures, including the strap muscles, recurrent laryngeal nerve (RLN), larynx, trachea, pharynx or esophagus, subcutaneous soft tissues, prevertebral fascia, or major cervical and mediastinal vessels [9,10]. Among these structures, the strap muscles and RLN are most frequently involved, followed by the trachea, laryngotracheal junction, pharyngoesophageal tract, and major vessels [9]. The clinical significance of ETE, however, is heterogeneous and is strongly influenced by the extent of invasion, the specific structure involved, the presence of regional or distant metastatic disease, tumor biology, and the ability to achieve complete gross resection (Figure 1) [10-12].

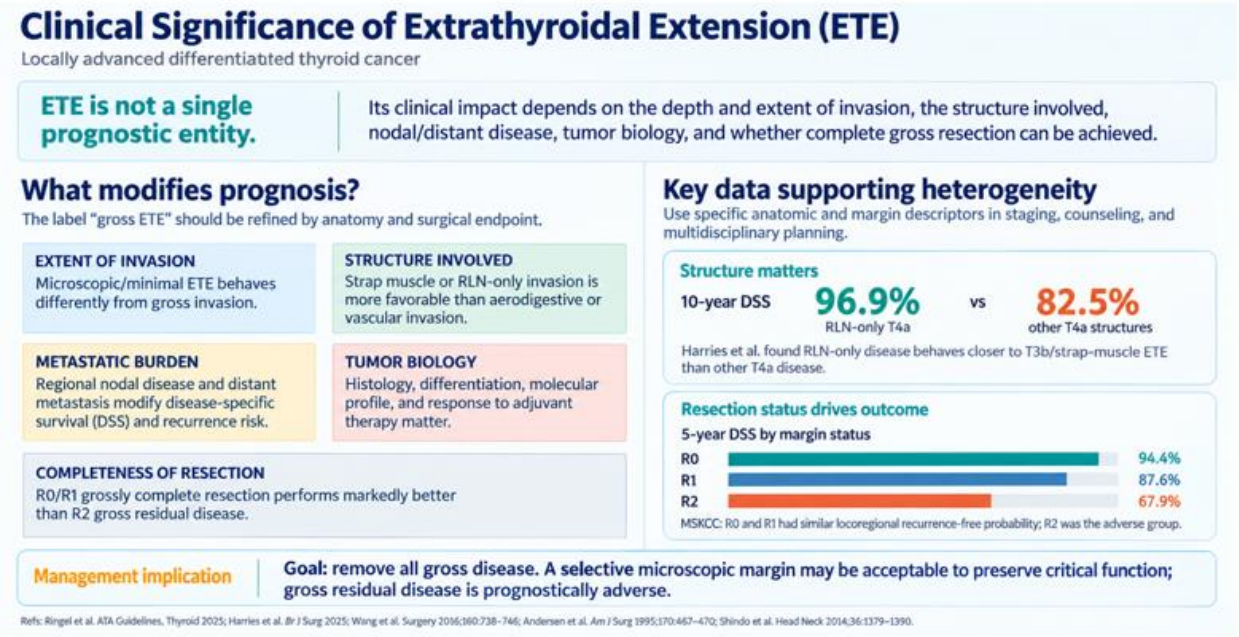



**Figure 1:** Clinical Significance of Extrathyroidal Extension (ETE) [10-12].

## METHODS

### Literature Search and Evidence Synthesis

This narrative review synthesizes contemporary evidence on the evaluation and management of locally advanced DTC, with emphasis on gETE and invasion of adjacent aerodigestive, neurovascular, and prevertebral structures. The review was conducted in a manner informed by the Scale for the Assessment of Narrative Review Articles (SANRA) to support transparency in rationale, aims, search reporting, referencing, and presentation of evidence [13].

PubMed / MEDLINE and Google Scholar were searched from database inception through 2026, supplemented by professional society and guideline resources. Searches combined terms including differentiated thyroid carcinoma, locally advanced thyroid cancer, gross extrathyroidal extension, T3b / T4 thyroid cancer, and structure-specific terms (RLN, tracheal, laryngeal, esophageal, carotid, and mediastinal invasion), together with surgical, radioactive iodine, external-beam radiation, targeted / systemic therapy, and neoadjuvant therapy terms, and related terminology. Reference lists of key publications were hand-searched. English-language sources were included.

Priority was given to current clinical practice guidelines and consensus statements, including the 2025 ATA guidelines for adult patients with DTC [4], the NCCN Thyroid Carcinoma guidelines [14], the 2026 ASCO guideline on systemic treatment of thyroid cancer [15], and recommendations from the American Head and Neck Society [16].

Staging terminology follows the AJCC / UICC 8th edition, under which mETE no longer upstages tumors and T-category is defined by gETE (T3b, strap muscles; T4a, subcutaneous tissue / larynx / trachea / esophagus / RLN; T4b, prevertebral fascia / carotid / mediastinal vessels). Seminal historical studies were retained when they established enduring principles of staging, prognosis, patterns of invasion, or surgical management.

Studies were selected on the basis of clinical relevance, methodological quality, cohort size, length of follow-up, and contribution to understanding of prognosis or management, with particular attention to mETE versus gETE; invasion of the strap muscles, RLN, larynx, trachea, esophagus, major vessels, and prevertebral structures; completeness of resection and organ-preserving techniques; postoperative radioactive iodine and external-beam radiation therapy; molecularly targeted therapy; and emerging neoadjuvant strategies. Given substantial heterogeneity in populations, definitions of locally advanced disease, surgical techniques, treatment eras, and outcomes, a quantitative meta-analysis was not performed, and evidence was synthesized narratively.

Generative artificial intelligence tools (ChatGPT, OpenAI; OpenEvidence) were used only to assist with literature discovery, topic organization, and language refinement. AI output was not treated as a source of scientific evidence; all clinically relevant statements, data, guideline recommendations, and references were verified by the authors against the original publications. All decisions regarding study inclusion, interpretation, and conclusions were made by the authors, who assume full responsibility for the accuracy and integrity of the work.

## DISCUSSION

The adverse prognostic significance of tumor extension beyond the thyroid gland has been recognized for decades. Remarkably, local tumor extent or invasion appears repeatedly in nearly every major historical prognostic system developed for DTC, despite these systems originating independently at different institutions and during different eras. These observations established the principle that ETE is not simply an anatomic descriptor but a marker of more aggressive thyroid cancer biology.

At Memorial Sloan Kettering Cancer Center (MSKCC), Shah and colleagues analyzed 931 previously untreated patients with DTC treated over a 50-year period. Adverse prognostic factors on univariable analysis included age > 45 years, follicular histology, tumor size > 4 cm, ETE, and distant metastases. Importantly, age, histology, tumor size, ETE, and distant metastases retained prognostic significance on multivariable analysis [17].

These observations contributed to the MSKCC GAMES risk-stratification framework, Grade, Age, distant Metastases, Extrathyroidal extension, and Size, which categorized patients into low-, intermediate-, and high-risk groups according to risk of thyroid cancer–specific mortality [12,17].

Thus, extrathyroidal invasion was recognized early in the MSKCC experience as one of the principal features distinguishing favorable intrathyroidal tumors from biologically aggressive disease.

Similar observations emerged from the Mayo Clinic. In 1987, Hay and colleagues developed the AGES prognostic system from their experience with PTC. The model incorporated Age, histologic Grade, tumor Extent, and Size and was specifically designed to identify patients at increased risk of PTC mortality [18].

The inclusion of tumor extent again demonstrated the prognostic importance of invasion beyond the thyroid gland. The Mayo Clinic subsequently developed the MACIS system in 1993. Because histologic grade was not consistently available, Hay and colleagues evaluated 1,779 patients with PTC treated between 1940 and 1989 and developed a prognostic model incorporating distant Metastases, Age, Completeness of resection, local Invasion, and tumor Size [19]. The original formula was:

MACIS = age component + 0.3 × tumor size (cm) + 1 if incompletely resected + 1 if locally invasive + 3 if distant metastases are present

Where the age component is 3.1 for patients ≤ 39 years and 0.08 × age for patients ≥ 40 years [19]. The model demonstrated striking separation in long-term outcome, with 20-year cause-specific survival rates of 99%, 89%, 56%, and 24% for MACIS scores < 6, 6 to 6.99, 7 to 7.99, and ≥ 8, respectively [19]. Of particular relevance to locally advanced thyroid cancer, both local invasion and incomplete tumor resection independently contributed to worsening prognosis.

At the Lahey Clinic, Cady and Rossi developed the AMES classification based on Age, distant Metastases, Extent, and Size [20]. This deliberately simple clinical classification separated patients into low- and high-risk groups according to the probability of thyroid cancer mortality. In the original analysis, approximately 89% of patients were classified as low risk, with a disease-related mortality of only 1.8%, whereas the high-risk group constituted approximately 11% of patients and experienced a mortality rate of approximately 46% [20]. A subsequent analysis of 1,019 patients confirmed the durability of the AMES classification: across successive treatment eras, survival among low-risk patients was approximately 96% to 98%, compared with only 47% to 62% in high-risk patients [21]. Importantly, extrathyroidal tumor extent was one of the defining criteria separating these prognostic groups.

The DAMES classification developed at the Karolinska Institute further modified AMES by incorporating tumor DNA ploidy. Pasieka and colleagues prospectively evaluated 73 patients with PTC and classified patients with euploid / AMES-low tumors as low risk, euploid / AMES-high tumors as intermediate risk, and aneuploid / AMES-high tumors as high risk [22].

Residual, recurrent, or metastatic disease occurred in 8% of low-risk patients and 55% of intermediate-risk patients, while all three patients classified as DAMES high risk developed distant metastases and died of thyroid cancer within 24 months [22]. Although the small cohort limits its contemporary clinical applicability, DAMES reinforced the concept that anatomic extent and tumor biology interact to determine prognosis.

Collectively, the GAMES, AGES, MACIS, AMES, and DAMES systems (Figure 2) reached a remarkably consistent conclusion: local invasion beyond the thyroid gland is a major adverse prognostic feature in differentiated thyroid cancer [12, 17, 20-22].

Nevertheless, contemporary evidence has refined this concept by demonstrating that not all forms of extrathyroidal extension carry equivalent prognostic weight. This distinction became particularly important with modern staging systems.

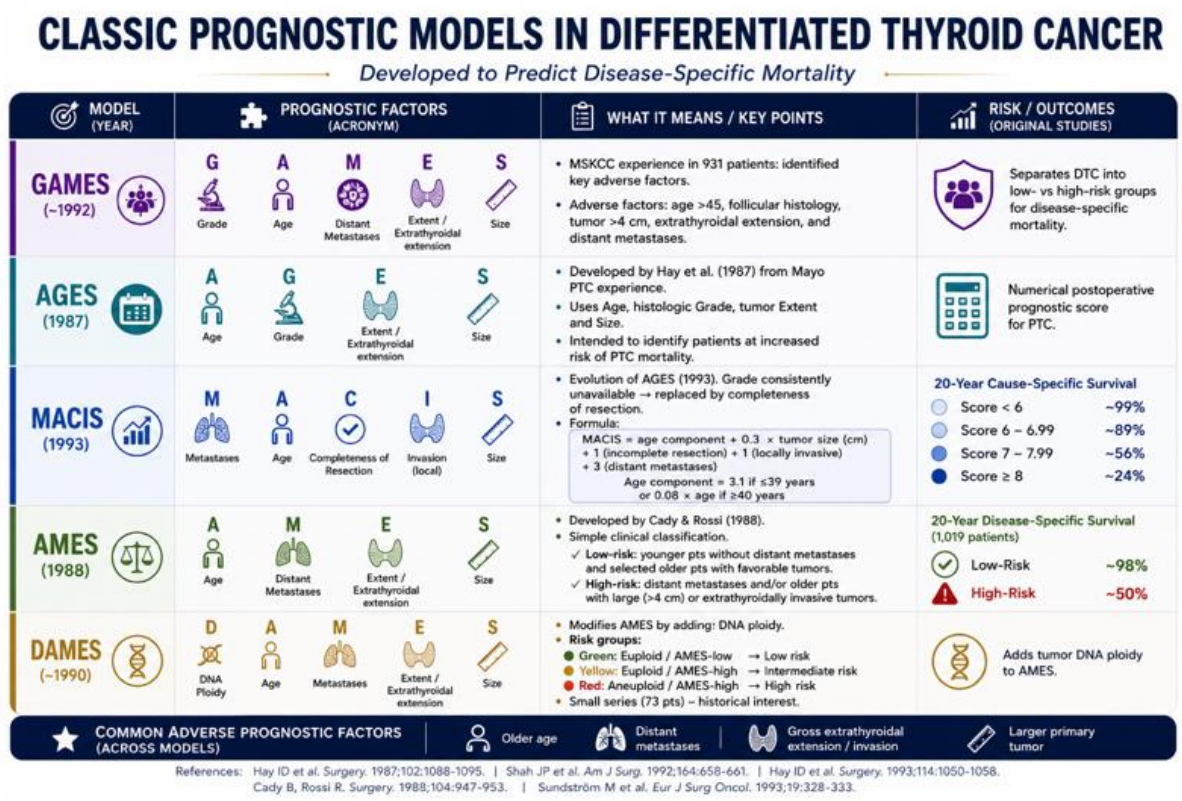



**Figure 2:** Classic Prognostic Models in Differentiated Thyroid Cancer [12,17,20-22].

Microscopic ETE (mETE) has a substantially weaker association with clinically meaningful outcomes than gross invasion and was therefore removed as a determinant of T category in the AJCC 8th edition [23].

Gross ETE (gETE) confined to the strap muscles is categorized as T3b, whereas gross invasion of the subcutaneous soft tissues, larynx, trachea, esophagus, or RLN constitutes T4a disease. Invasion of the prevertebral fascia or encasement of the carotid artery or mediastinal vessels constitutes T4b disease [23].

Contemporary outcome studies support this biologic gradient. In a series of 3,174 patients with DTC, the 10-year cancer-specific survival rates were 98.6% in patients without ETE, 98.3% with mETE, and 98.9% with gETE confined to the strap muscles, with no significant difference among groups [24]. Although gross strap-muscle invasion was associated with inferior recurrence-free survival on univariable analysis, it was not an independent predictor of recurrence after multivariable adjustment [24]. Similarly, an MD Anderson series of 2,084 patients demonstrated 10-year disease-free survival rates of 90%, 82%, and 83% for tumors with no ETE, perithyroidal soft-tissue extension, and gross strap-muscle invasion, respectively; neither perithyroidal soft-tissue extension nor gross strap-muscle invasion independently predicted disease-free survival, and disease-specific survival (DSS) was not significantly different among the groups [25]. They did find a significant difference in locoregional recurrence-free survival between the no ETE and perithyroidal soft-tissue groups (HR 2.02, 95% CI 1.06–3.94) [25].

In contrast, gross invasion of major aerodigestive, neural, or vascular structures represents a substantially more aggressive phenotype. In the MSKCC experience reported by Wang and colleagues, 153 of 3,664 previously untreated patients undergoing surgery for DTC had gross invasion of structures including the subcutaneous tissues, RLN, larynx, trachea, or esophagus [10]. The RLN was involved in 51%, the trachea in 46.4%, and the esophagus in 39.2% of patients. Five-year DSS was 94.4% after an R0 resection, 87.6% after an R1 resection, and 67.9% when gross residual disease remained after an R2 resection (P=0.030) [10]. Importantly, there was no statistically significant difference in DSS between R0 and R1 resections (P=0.222), and 5-year locoregional recurrence-free probability was nearly identical after R0 and R1 resection (85.8% versus 85.5%; P=0.593) [10]. These findings emphasize that, in selected locally advanced DTC, complete gross tumor removal may be more clinically consequential than sacrificing critical structures solely to convert a microscopic positive margin to a negative margin. However, the apparent oncologic equivalence of R0 and R1 resection is not universally accepted and should not be interpreted as evidence that margin status is unimportant.

Brauckhoff and colleagues reported a significant DSS advantage among patients in whom histologically clear margins were achieved, supporting complete microscopic resection whenever this can be accomplished without disproportionate morbidity [26]. Similarly, McCaffrey and colleagues demonstrated the adverse prognostic significance of locally invasive disease, particularly laryngotracheal involvement and residual gross tumor, emphasizing the importance of the extent of local invasion and completeness of resection in determining outcome [27].

Thus, the contemporary organ-preservation approach supported by the MSKCC experience and similar data from MD Anderson, that an intentional or unavoidable R1 margin may be oncologically acceptable when obtaining an R0 resection would require major functional sacrifice, should not be regarded as definitively established equivalence between R0 and R1 resection. Rather, R0 resection remains the preferred oncologic objective when achievable with acceptable morbidity; R1 resection may represent an appropriate compromise in carefully selected patients when more radical surgery would require sacrifice of a functioning RLN or major laryngotracheal or esophageal structures, whereas R2 resection with gross residual disease is consistently associated with substantially inferior oncologic outcomes [10].

The 2025 ATA guidelines further emphasize this distinction and incorporate the extent of local invasion into contemporary recurrence-risk assessment and surgical decision-making [4]. Grossly invasive disease is recognized as a high-risk feature, while treatment recommendations emphasize individualized surgical planning based on disease extent, anticipated morbidity, postoperative risk, and the likelihood of obtaining meaningful locoregional control [4]. This represents an evolution from historical staging systems based predominantly on mortality toward modern risk-adapted management that incorporates both risk of recurrence and DSS. Therefore, the clinically relevant question in locally advanced DTC is no longer simply whether tumor extends beyond the thyroid capsule. Rather, prognosis and treatment are determined by whether the extension is microscopic or gross, which structure is invaded, the depth of invasion, whether distant metastatic disease is present, whether complete gross resection can be achieved, and what functional morbidity is required to achieve that resection. Gross invasion of the RLN, larynx, trachea, esophagus,

prevertebral fascia, or major vascular structures represents the most clinically consequential form of ETE and forms the basis for the surgical challenges addressed in this review.

**Extrathyroidal Extension: Definition, Classification, and Prognostic Significance**

Extrathyroidal extension (ETE) is defined as extension of a primary thyroid carcinoma beyond the thyroid parenchyma into the surrounding perithyroidal soft tissues or adjacent anatomic structures. Because the thyroid gland does not have a complete and uniformly identifiable fibrous capsule, ETE is more appropriately defined by invasion into tissues outside the thyroid rather than simply by penetration of the thyroid capsule.

ETE is broadly classified as minimal (microscopic) ETE or gross (macroscopic) ETE, a distinction that is clinically important because these entities differ substantially in their staging implications, risk of recurrence, prognostic significance, and impact on surgical management [4,23,28,29].

Minimal or microscopic ETE (mETE) refers to tumor extension into the immediate perithyroidal soft tissues, with or without microscopic involvement of adjacent skeletal muscle, that is identified only on histopathologic examination and is not evident clinically, radiographically, or grossly during surgery [4,23,28,29].

In the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging system, microscopic invasion into perithyroidal soft tissues or the sternothyroid muscle was sufficient to classify a DTC as T3, regardless of tumor size [30]. This classification was substantially revised in the AJCC eighth edition, in which mETE was removed from the definition of T3 disease and therefore no longer affects the T category or overall AJCC stage [23,28,29]. This change reflected accumulating evidence demonstrating that mETE has little or no independent effect on DSS and is associated with, at most, a modest increase in the risk of structural recurrence [4,31].

The prognostic significance of mETE has been evaluated extensively. A systematic review and meta-analysis by Diker-Cohen et al. demonstrated a modest increase in recurrence among patients with mETE compared with those without ETE. Among patients without lymph-node metastases recurrence occurred in approximately 3.5% of patients with mETE compared with 2.2% of those without ETE, importantly, mETE was not associated with an increase in disease-specific mortality [31]. The 2025 ATA guidelines similarly recognize mETE as a relatively low-risk pathologic feature, with reported structural recurrence rates generally in the range of approximately 3% to 9%, depending on associated clinicopathologic factors [4]. Furthermore, histologic assessment of mETE is limited by substantial interobserver variability, reflecting the absence of a complete thyroid capsule and the difficulty in consistently distinguishing true invasion from normal anatomic relationships at the thyroid–soft tissue interface [4]. Consequently, the presence of isolated mETE should not be considered synonymous with locally advanced thyroid cancer.

In contrast, gross or macroscopic ETE (gETE) refers to tumor invasion beyond the thyroid that is evident clinically, radiographically, or intraoperatively. Gross ETE represents a substantially more important prognostic and therapeutic finding than mETE and directly influences AJCC T classification and surgical management [4,23,28,29]. Importantly, gETE encompasses a spectrum of disease ranging from invasion limited to the strap muscles to extensive involvement of the aerodigestive tract, RLN, prevertebral fascia, or major vascular structures.

The AJCC eighth edition stratifies gETE according to the structures involved. T3b disease is defined as a tumor of any size with gross invasion limited to the strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid). T4a

disease includes gross invasion of the subcutaneous soft tissues, larynx, trachea, esophagus, or RLN, whereas T4b disease is characterized by invasion of the prevertebral fascia or encasement of the carotid artery or mediastinal vessels [4,23,28,29].

This anatomic subdivision is clinically relevant because the prognostic consequences of gETE increase substantially with the extent and depth of invasion (Figure 3).

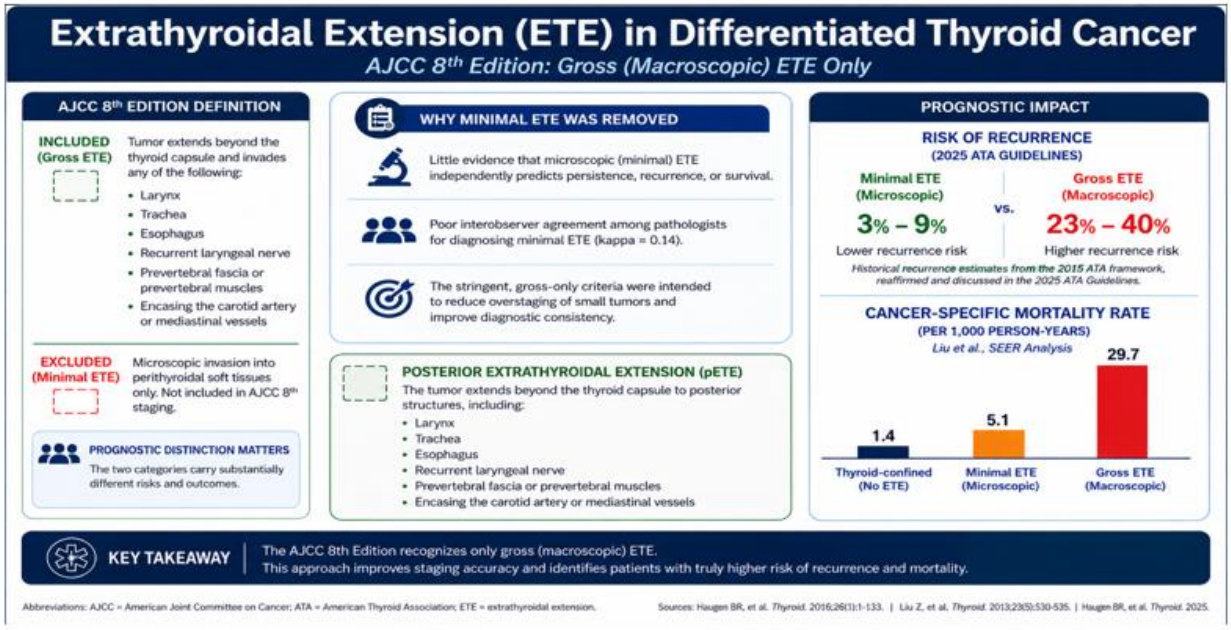



**Figure 3:** Extrathyroidal Extension AJCC 8th Edition Definition [29].

Gross invasion confined to the strap muscles has a more favorable prognosis than invasion of major adjacent structures. Although several retrospective studies and meta-analyses have demonstrated an increased risk of locoregional recurrence in patients with gross strap-muscle invasion compared with patients with intrathyroidal tumors, its independent effect on DSS appears considerably smaller than that associated with T4 disease [23,28,29, 32].

A recent systematic review and meta-analysis demonstrated that gross strap-muscle invasion was associated with increased recurrence and lymph-node metastasis compared with the absence of ETE; however, when tumors ≤ 4 cm were analyzed separately, the adverse effect on recurrence and survival was substantially attenuated [32]. These findings support the current distinction between T3b disease and gross invasion of deeper structures classified as T4 disease.

Gross ETE involving major adjacent structures represents a fundamentally different clinical entity and is one of the most important adverse prognostic factors in DTC. Invasion of the RLN, trachea, larynx, esophagus, prevertebral fascia, or major vascular structures is associated with substantially increased risks of persistent disease, locoregional recurrence, distant metastasis, incomplete surgical resection, and disease-specific mortality [4,23,28,29].

The 2025 ATA guidelines report structural recurrence rates of approximately 23% to 40% for gETE involving major adjacent structures, compared with approximately 3% to 9% for mETE, emphasizing the marked prognostic difference between microscopic and clinically apparent invasive disease [4]. The prognosis also varies according to the specific structure involved and the depth of invasion; superficial involvement of an adjacent structure should therefore not necessarily be considered biologically equivalent to deep transmural aerodigestive invasion or encasement of major vascular structures.

Recent MSKCC data argue that gETE to the RLN alone behaves prognostically more like T3b than like other T4a disease. Harries et al., in an analysis of 8,030 patients with T4a differentiated thyroid carcinoma, demonstrated that the prognostic impact of gETE varies according to the structure involved (Figure 4). Patients with isolated RLN invasion had significantly more favorable outcomes, with a 10-year DSS of 96.9%, compared with 82.5% among patients with invasion of other T4a structures [8]. Based on these findings, the authors proposed that RLN-only invasion may warrant downstaging from T4a to T3b. Similarly, Song et al. reported that isolated RLN invasion was associated with more favorable DSS than invasion of aerodigestive structures, supporting the concept that the prognosis of gETE is strongly influenced by the specific anatomic structure involved [33].

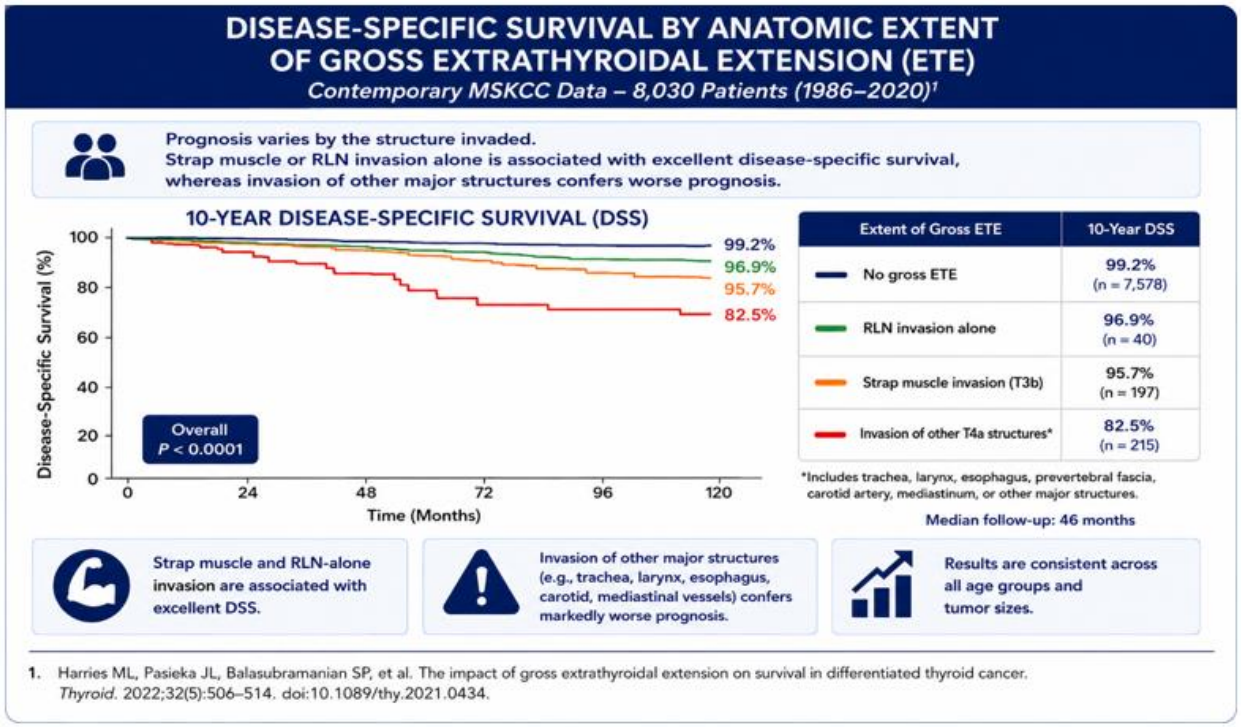



**Figure 4:** Disease-Specific Survival by Anatomic Extent of Gross Extrathyroidal Disease [8].

The distinction between mETE and gETE is therefore essential when evaluating locally advanced thyroid cancer. Microscopic ETE is predominantly a histopathologic finding that no longer influences AJCC staging and has only a limited independent effect on recurrence and essentially no consistent independent impact on DSS. In contrast, gETE is a clinically meaningful manifestation of invasive disease whose prognostic impact increases according to the structures involved. Gross invasion limited to the strap muscles (T3b) carries an intermediate risk, whereas invasion of the RLN, larynx, trachea, esophagus, prevertebral fascia, or major vessels (T4a to T4b) defines truly locally advanced disease and has important implications for prognosis, surgical planning, and the use of multimodality therapy [4,23,28,29,32].

**Survival and Treatment Failure in Locally Advanced Differentiated Thyroid Cancer**

Gross extrathyroidal extension (gETE) is an important adverse prognostic feature in DTC; however, its prognostic significance is heterogeneous and is influenced by the anatomic extent of invasion and the ability to achieve complete gross tumor resection. Historical data from MSKCC demonstrated a substantially greater risk of treatment failure among patients with ETE. Andersen et al. reported treatment failure in 77% of patients with ETE compared with 34% of patients without ETE [34]. Local (48% vs 9%), regional (41% vs 16%), and distant failure (37% vs 11%) were all significantly more frequent in patients with ETE ($P < 0.0001$), **establishing extension beyond the thyroid as an important predictor of both locoregional and distant recurrence** (Figure 5) [34].

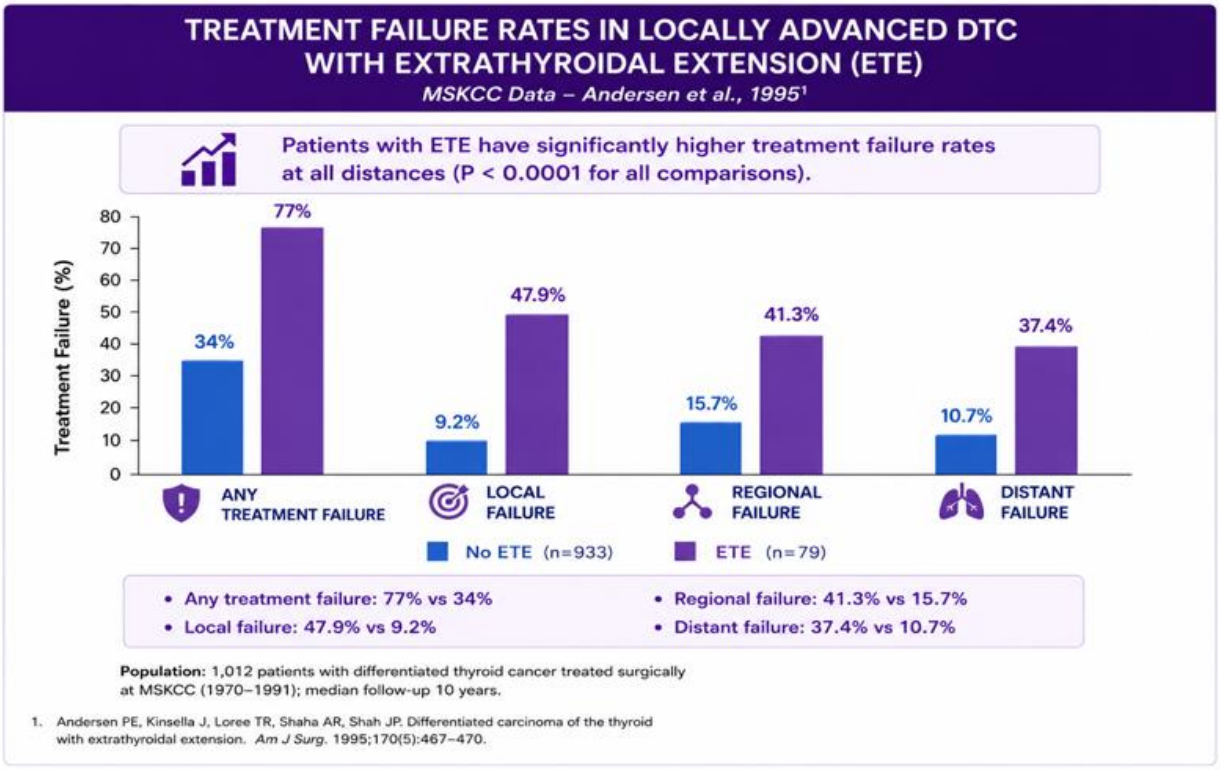



**Figure 5:** Treatment Failure Rates in Locally Advanced DTC with ETE [34].

Contemporary data indicate that gETE should not be treated as a single prognostic entity; rather, long-term DSS varies substantially according to both the structure invaded and the age of the patient. In a large MSKCC cohort (n=8,030), 10-year DSS was 99.2% in patients without gETE, 95.7% for gross invasion limited to the strap muscles (T3b), and 96.9% for isolated RLN involvement, whereas invasion of other T4a structures, trachea, larynx, or esophagus, was associated with a markedly lower 10-year DSS of 82.5% (P<0.0001) [8]. After adjustment for age, nodal and distant disease stage, RLN-only T4a disease behaved similarly to T3b disease (hazard ratios 2.91 and 2.28, respectively), leading the authors to propose downstaging isolated RLN involvement to the T3b category [8]. Importantly, this relatively favorable prognosis attenuates with age: in the ≥ 55-year cohort, 10-year DSS fell to 89.4% for T3b and 90.9% for RLN-only involvement, versus 67.6% for other T4a structures, so the characterization of strap-muscle or RLN-only invasion as a "favorable" form of gETE is most robust in younger patients [8].

The completeness of surgical resection further modifies outcome in locally advanced DTC (Figure 6). In the MSKCC series reported by Wang et al. (n=153 with invasion beyond the thyroid capsule), 5-year DSS was 94.4% following R0 resection, 87.6% following R1 resection, and 67.9% in patients left with gross residual disease (R2) (P=0.030) [10].

No statistically significant difference in DSS or locoregional recurrence-free survival was detected between R0 and R1 resections (P=0.222 and P=0.593, respectively) [10]. These retrospective findings should not be interpreted as establishing equivalence between R0 and R1 resection; rather, they identify gross residual (R2) disease as the dominant adverse surgical factor and underscore the importance of achieving complete gross tumor removal, while preserving function whenever oncologically appropriate, as a fundamental objective of surgery for resectable locally advanced DTC [10].

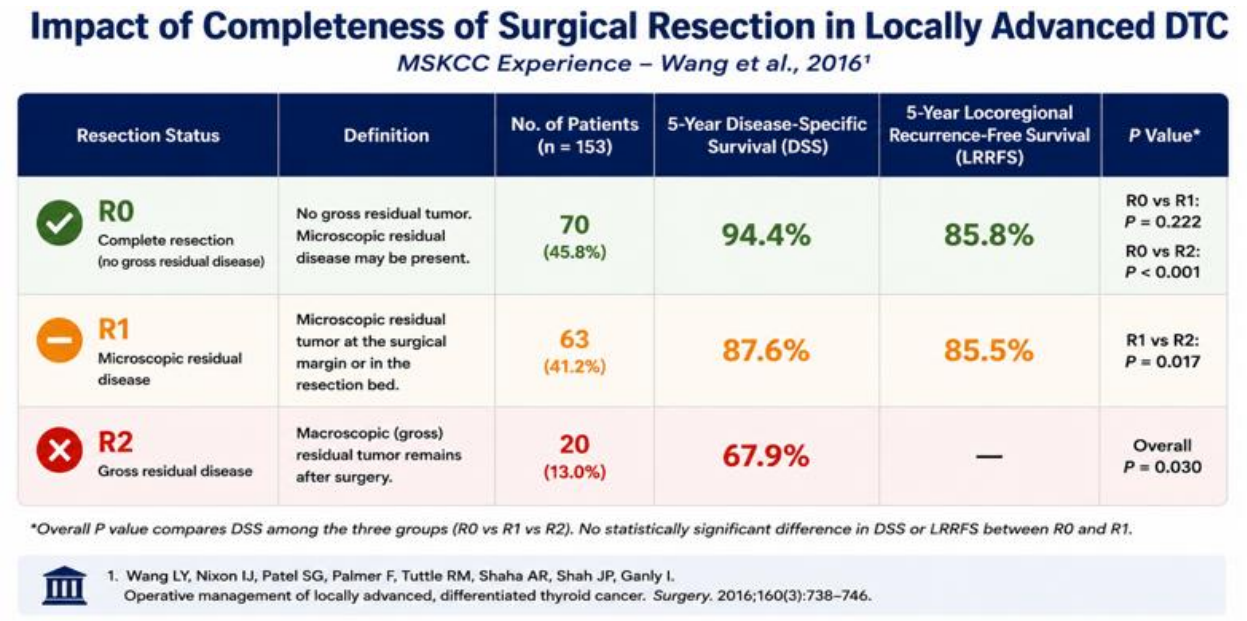



**Figure 6:** Impact of Completeness of Surgical Resection in Locally Advanced DTC [10].

**Frequency and Patterns of Invasion of Adjacent Structures in Locally Advanced DTC**

Gross invasion of adjacent structures is uncommon in DTC, although its reported frequency varies according to the definition of locally advanced disease and the population studied. In the large MSKCC surgical series, 153 of 3,664 previously untreated patients (4.2%) demonstrated gETE, supporting an incidence of approximately 4% to 5% in unselected surgical populations [10]. Among patients with locally advanced disease, however, involvement of more than one adjacent structure is common; consequently, reported site-specific percentages are not mutually exclusive (Figure 7).

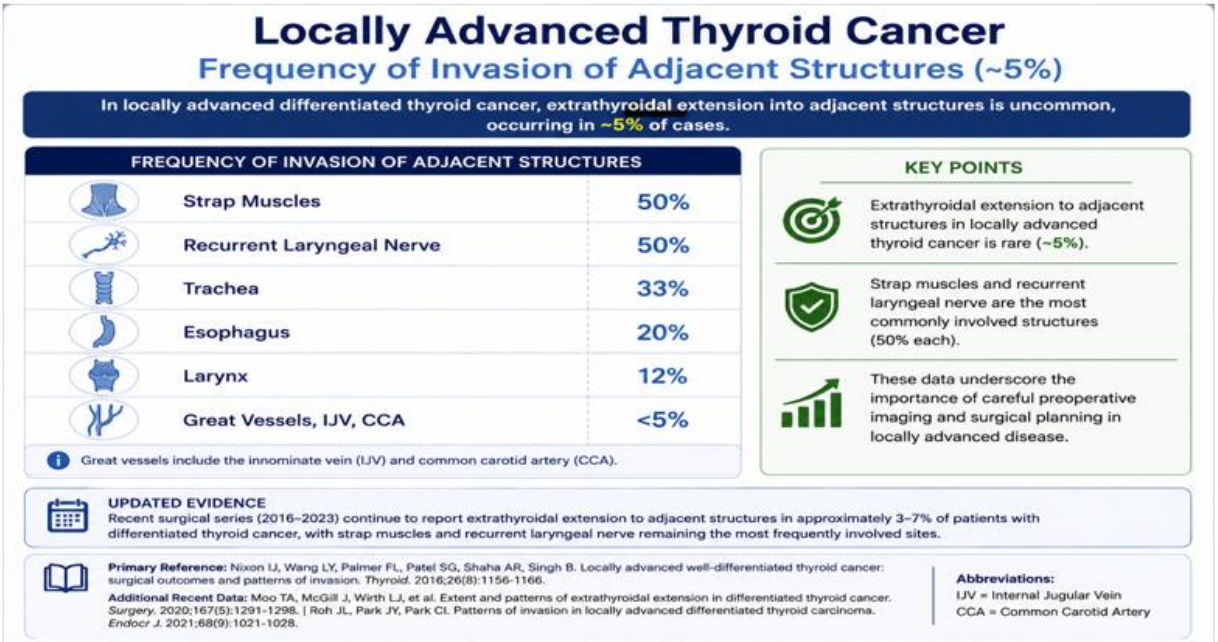



**Figure 7:** Frequency of Invasion of Adjacent Structures [10,35].

Historically, the most frequently involved structures have been the strap muscles (roughly 50% to 53%), RLN (47% to 51%), and trachea (approximately 30% to 46%), followed by the esophagus (roughly 20% to 21%) and larynx (approximately 12%), while invasion of the carotid artery, internal jugular vein, and other major vascular structures is considerably less frequent [10,35]. In the MSKCC series specifically, the RLN was involved in 51.0%, the trachea in 46.4%, and the esophagus in 39.2% of patients with gross locally invasive DTC [10].

More contemporary series confirm the predominance of RLN involvement but demonstrate substantial variability in the frequency of invasion of other structures. In a recent series of 60 patients with pT4a DTC, representing 1.25% of 4,775 surgically treated DTCs, invasion involved the RLN in 75.0%, trachea in 23.3%, pharyngoesophageal junction in 18.3%, internal jugular vein in 10.0%, and larynx in 3.3% [36]. Population-based SEER data similarly identify the trachea (26.3%) and esophagus / larynx (21.0%) as the predominant sites of invasion in locally advanced PTC, while confirming that follicular and oncocytic carcinomas preferentially invade major vessels (31.3%) [37].

Taken together, contemporary evidence indicates that the RLN is the most consistently involved critical structure in locally advanced DTC, with reported involvement of approximately 50% to 75% of T4 tumors, whereas tracheal

invasion occurs in approximately 23% to 46%, esophageal / pharyngoesophageal invasion in approximately 18% to 39%, major vascular invasion in approximately 9% to 10%, and laryngeal invasion in approximately 3% to 12% [10, 35,38].

Differences between series largely reflect patient selection, referral patterns, tumor histology, and whether gross strap-muscle invasion (T3b) is included within the definition of locally advanced disease.

**Surgical Management of Locally Advanced Differentiated Thyroid Carcinoma**

Surgery remains the cornerstone of treatment for resectable locally advanced DTC (Figure 8). The principal objective is complete removal of all gross disease while preserving, whenever oncologically appropriate, critical neural, aerodigestive, and vascular function. This concept is emphasized in the 2025 ATA guidelines, and contemporary surgical guidelines for locally invasive DTC [4,9]. The 2025 ATA guidelines specifically recommend that patients with tumors of any size demonstrating gETE (cT3b or cT4a) undergo total thyroidectomy with gross removal of all primary tumor, together with therapeutic compartment-oriented lymph-node dissection when clinically apparent nodal disease is present [4].

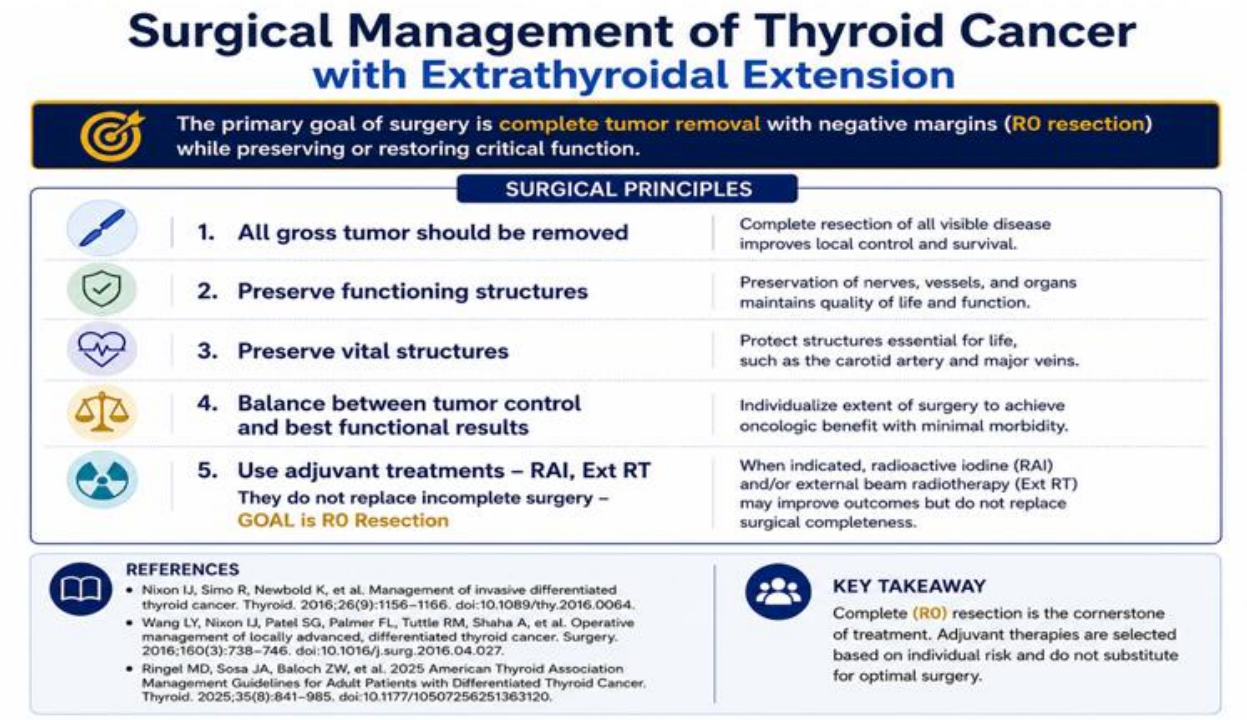



**Figure 8:** Surgical Management of DTC with ETE [4,9,38].

**Preoperative assessment and surgical planning**

Preoperative evaluation of locally advanced DTC should be directed toward three objectives: accurate definition of the extent of local disease, assessment of resectability, and anticipation of the functional consequences of surgery. This evaluation is particularly important when gETE is suspected because the operative strategy may require resection or reconstruction of the RLN, larynx, trachea, esophagus, or major cervical vessels. Contemporary guidelines therefore emphasize a structured assessment incorporating history and physical examination, preoperative evaluation of vocal-

fold function, high-resolution cervical ultrasonography, and selective cross-sectional imaging [4,9,39]. The recently published 2025 ATA guidelines remain the most current comprehensive guideline for adult DTC and specifically incorporate preoperative evaluation and surgical planning into the initial management pathway.

A careful history should assess voice change (dysphonia), dysphagia, odynophagia, aspiration, hemoptysis, dyspnea, stridor, and positional respiratory symptoms, as these may indicate invasion of the RLN or aerodigestive tract. Physical examination should assess cervical lymphadenopathy and fixation of the thyroid mass to adjacent structures. A firm or immobile tumor, particularly in the posterior or central compartment, should raise suspicion for invasion of the RLN, trachea, cricoid or thyroid cartilage, or esophagus. Although physical findings cannot reliably establish the depth of invasion, they provide important information regarding the likelihood of gETE and the need for more detailed imaging [9].

Preoperative assessment of vocal-fold mobility is particularly important when gETE is suspected. Flexible fiberoptic laryngoscopy establishes baseline vocal-fold function and may identify an occult preoperative RLN palsy that substantially alters surgical planning. Knowledge of contralateral vocal-fold function is critical when the involved RLN may require sacrifice and reconstruction, and preoperative paralysis in the setting of an ipsilateral invasive thyroid tumor strongly raises the likelihood of RLN invasion [9].

High-resolution neck ultrasonography remains the first-line imaging study for assessment of the primary thyroid tumor and cervical lymph-node compartments. Ultrasound should document tumor size, location, relationship to the thyroid capsule, suspicious nodal disease, and features suggesting gETE. Suspicious cervical lymph nodes should undergo ultrasound-guided fine-needle aspiration when confirmation would alter the planned extent of surgery; thyroglobulin measurement in needle washout may provide additional diagnostic information in appropriate cases [4,40]. The ATA surgical imaging statement continues to support routine preoperative ultrasound of the thyroid and cervical nodal basins and selective FNA of suspicious nodes to guide compartment-oriented neck dissection.

Ultrasound, however, has important limitations in locally advanced disease. It may underestimate posterior extension, substernal disease, deep central-compartment lymphadenopathy, and invasion of the aerodigestive tract or major vessels.

For these reasons, contrast-enhanced CT of the neck and upper mediastinum should be strongly considered when gETE, bulky nodal disease, posteriorly located disease, airway involvement, mediastinal extension, or vascular invasion is suspected [4,9,40].

Cross-sectional imaging can define the circumferential relationship of the tumor to the trachea and esophagus, identify cartilage destruction, characterize carotid or jugular involvement, and delineate nodal disease that may be inaccessible to ultrasound. The ATA imaging statement specifically identifies suspected tumor invasion and bulky, posterior, or inferiorly located nodal disease as settings in which CT or MRI provides information beyond ultrasound [4].

The potential impact of iodinated contrast on subsequent radioactive iodine (RAI) therapy should not preclude its use when contrast-enhanced imaging is necessary for accurate preoperative assessment. The American Thyroid Association (ATA) notes that iodine from intravenous contrast is generally cleared within 4 to 6 weeks and that concern regarding clinically meaningful delays in RAI administration is unfounded for most patients [4]. Similarly, the National Comprehensive Cancer Network (NCCN) emphasizes that a short delay in RAI related to iodinated

contrast exposure is unlikely to adversely affect oncologic outcomes [14]. Nevertheless, an appropriate washout interval should be observed before RAI administration, generally approximately 1 to 2 months after contrast exposure (at least 1 month according to ATA guidance and approximately 2 months in the NCCN pathway) [4,14]. When uncertainty regarding iodine clearance exists, spot or 24-hour urinary iodine measurement may be used to confirm adequate clearance. Thus, in patients with suspected locally advanced thyroid carcinoma, the need for comprehensive anatomic delineation and optimal surgical planning generally outweighs the disadvantage of a temporary delay in RAI therapy.

MRI is complementary rather than routinely superior to CT. Its principal advantage is improved soft tissue contrast and multiplanar characterization of tumor relationships to the larynx, tracheoesophageal groove, esophageal wall, prevertebral musculature, neural structures, and major vessels. MRI is particularly useful when CT findings are equivocal regarding soft-tissue planes or when iodinated contrast cannot be administered. CT generally remains more informative for calcification, cortical cartilage destruction, airway anatomy, and thoracic extension, whereas MRI may provide better distinction between tumor and adjacent soft tissues.

When there is concern for intraluminal laryngotracheal or esophageal disease, direct endoscopic evaluation may be required. Flexible laryngoscopy defines vocal-fold mobility and can demonstrate laryngeal or subglottic extension. Bronchoscopy is useful when imaging suggests tracheal mucosal penetration or significant luminal compromise, while esophagoscopy may be considered when there is suspected mucosal involvement of the esophagus. Endoscopy is not required for every patient with ETE; it should be targeted to situations in which the findings would change the surgical approach or confirm transmural invasion [9,39,40].

The information obtained from these studies should be integrated into a structure-specific operative plan before incision. The surgeon should determine whether gross tumor clearance is likely to require RLN shaving versus segmental resection, superficial versus full-thickness tracheal resection, partial laryngeal framework resection, esophageal muscularis versus full-thickness resection, or vascular resection and reconstruction. Particular attention should be paid to whether preservation of a functioning structure can be achieved without leaving gross disease. This distinction is central to modern management because the objective is not indiscriminate radical resection but rather complete macroscopic tumor removal while preserving or restoring function whenever oncologically appropriate [4, 9,39].

For patients in whom airway, esophageal, laryngeal, or major vascular reconstruction may be required, multidisciplinary planning should occur before surgery, involving endocrine or head-and-neck surgeons together with thoracic, reconstructive, vascular, anesthesia, speech / swallow, and radiation or medical oncology expertise as appropriate. The preoperative evaluation should therefore ultimately answer four practical questions: What structures are invaded? How deeply are they invaded? Can all gross disease be removed? And what functional price will be required to achieve that clearance? Those questions, rather than ETE as a binary finding, determine the operative strategy.

**Completeness of resection**

The core oncologic principle in locally advanced DTC is removal of all gross tumor, and the most clinically meaningful distinction is between microscopically positive margins (R1) and macroscopic residual disease (R2). In

the MSKCC series reported by Wang and colleagues, 153 patients with locally advanced DTC were identified among 3,664 previously untreated patients [10]. Five-year DSS was 94.4% after R0 resection, 87.6% after R1 resection, and 67.9% in patients with gross residual disease (R2) (P = 0.030). Survival did not differ significantly between R0 and R1 resection (P = 0.222), and the 5-year locoregional recurrence-free probability was nearly identical (85.8% vs 85.5%; P = 0.593) [10]. A companion MSKCC analysis similarly found that, after adjustment for gETE and pT stage, microscopically positive margins were not an independent predictor of local failure [41].

These data support a central surgical principle: gross residual disease (R2) is the dominant adverse resection-related prognostic factor and should be avoided whenever technically and functionally feasible, whereas increasingly morbid surgery undertaken solely to convert an otherwise grossly complete R1 resection into an R0 resection may not always confer proportional oncologic benefit. This conclusion, however, warrants caution. The MSKCC investigators themselves noted that the prognostic impact of R1 status may become apparent only with longer follow-up, and several contemporary series report that microscopic margin positivity is independently associated with recurrence.

Kim and colleagues found R1 resection to be an independent predictor of locoregional recurrence (hazard ratio [HR] 3.16) and total recurrence (HR 3.04), even after adjuvant radioactive iodine or external-beam radiotherapy [42]. More recent data reinforce this signal: in 502 patients with T1 to T2 disease, microscopic margin positivity independently predicted locoregional recurrence (HR 2.72) [43], and in a propensity-matched PTC cohort, a microscopically positive margin increased recurrence risk approximately fivefold (HR 4.96; 5-year recurrence-free survival 90.1% vs 98.2%) [44]. The 2025 ATA guidelines reflect this unresolved tension, citing a meta-analysis of 7,696 patients showing no association between microscopic margins and recurrence while also noting that a positive posterior margin may be an independent risk factor (HR 22.95) and that positive margins have been linked to increased mortality in national database analyses [4]. The anatomic location of a positive margin, anterior versus posterior, may therefore be more informative than margin positivity alone.

Consequently, the extent of surgery should be individualized according to the depth and site of invasion, tumor biology, distant metastatic burden, patient age and comorbidity, expected responsiveness to adjuvant therapy, and the functional consequences of resection. Contemporary population data support this individualized approach: in a SEER analysis of 6,920 patients with T3b disease, surgical extent contributed minimally to survival (10-year overall survival 89.9% for lobectomy vs 89.6% for total thyroidectomy) [45], and incomplete resection remained an independent adverse predictor of DSS in a population-based cohort of 3,330 patients [46]. The optimal operation is therefore not necessarily the most extensive operation, but rather the one that achieves durable gross disease control (R0 or R1) with acceptable functional morbidity, while recognizing that a microscopically positive margin, particularly a posterior margin, should prompt closer surveillance and consideration of adjuvant therapy rather than being regarded as oncologically inconsequential.

**Management of Gross Extrathyroidal Extension Limited to the Strap Muscles**

Gross extrathyroidal extension (gETE) confined to the infrahyoid strap muscles represents the least extensive form of macroscopic local invasion in DTC. Under the AJCC 8th edition, a tumor of any size with gross invasion limited to the sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles is classified as T3b, whereas invasion of the RLN, trachea, larynx, esophagus, or subcutaneous soft tissues constitutes T4a disease [28,29,47]. Importantly, gross strap-muscle invasion should be distinguished from mETE identified only histologically, which no longer affects AJCC T classification [4,29]. Although T3b disease represents gETE, its biological behavior is substantially more favorable than that of invasion into major aerodigestive or neural structures, though, as detailed below, this favorable profile is strongly conditioned by patient age and tumor size, and its designation as an independent prognostic factor remains contested.

**Prognostic Significance**

In a single-institution series of 3,174 patients with DTC reported by Park SY et al. [24], 10-year cancer-specific survival (CSS) was 98.9% for gETE limited to the strap muscles, compared with 98.6% for tumors without ETE and 98.3% for mETE; these differences were not statistically significant (P = 0.375) (Figure 9). Ten-year recurrence-free survival (RFS) was modestly lower with strap-muscle invasion (89.2%) than with no ETE (93.7%; P = 0.016). Although strap-muscle invasion was associated with recurrence on univariable analysis (HR 1.67, 95% CI 1.10–2.55), it was no longer an independent predictor after multivariable adjustment (HR 1.09, 95% CI 0.71–1.69) [24].

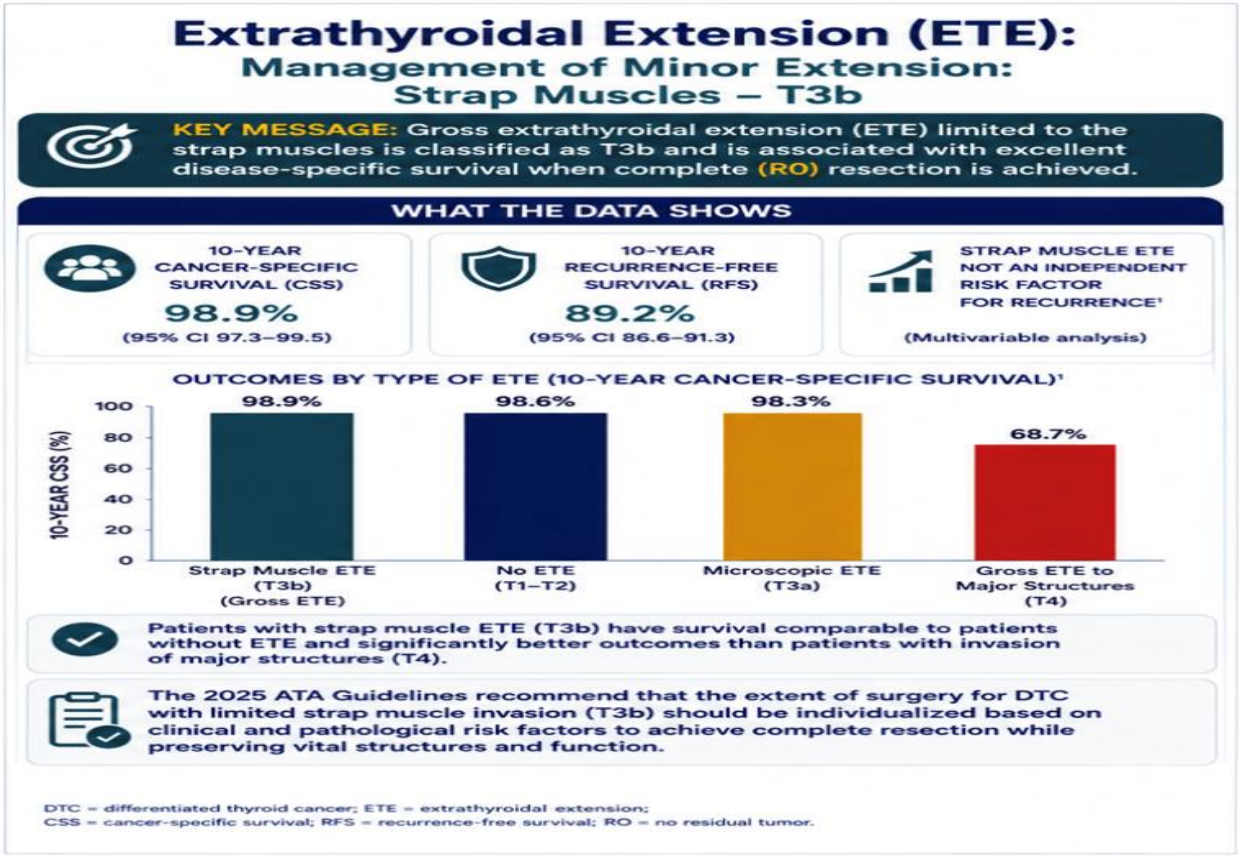



**Figure 9:** Management of Minor Extension into the Strap Muscles [24].

A distinct cohort of 3,104 patients reported by Song E et al. [33], analyzed DSS by direction of invasion. T3b (≤ 4 cm) showed no DSS difference versus T2 (HR 0.81, 95% CI 0.24–2.77) and better DSS than T3a (HR 0.19, 95% CI 0.05–0.72), whereas posterior gETE, even when limited to the RLN, carried markedly worse DSS (HR 7.78, 95% CI 3.41–17.75). On that basis, Song et al. proposed downstaging T3b (≤ 4 cm) to T2 [33].

Consistent with a limited independent effect, Amit et al. [25] found, in 2,084 patients with nonmetastatic DTC ≤ 4 cm, that gross strap-muscle invasion was not independently associated with disease-free, overall, or DSS after adjustment for age, gender, and nodal disease; age ≥ 55 years, male gender, and pathologic N1b were the significant predictors of disease-free survival.

Conflicting Evidence: Age and Tumor Size Modify Prognosis

The favorable interpretation above is not uniform across the literature, and the disagreement should be preserved rather than resolved. Several large analyses indicate that T3b carries genuine prognostic weight, particularly in older patients and larger tumors (Figure 10):

- Xiang et al. [48], analyzing 63,315 SEER patients, found that T3b was associated with significantly worse cancer-specific survival (CSS) than both no ETE and mETE after propensity-score matching, and specifically argued against downstaging T3b (≤ 4 cm) to T2. In their data, T3b (≤ 4 cm) had worse CSS than T2 (HR 2.16), and larger T3b tumors (> 4 cm) fared substantially worse than smaller ones (HR 5.05).
- Harries et al. [49] reported that among patients aged ≥ 55 years, macroscopic strap-only ETE was associated with 10-year DSS of 89.3% versus 97.6% for no ETE, and remained an independent predictor of disease-specific death (HR 3.29, 95% CI 1.08–10.09).
- Ito et al. [50] concluded that T3bN0M0 is appropriately classified as stage II in patients aged ≥55 years but should remain stage I in patients aged <55 years; T3b independently predicted local and distant recurrence but not death from carcinoma.
- Xu et al. [51] similarly found that strap-muscle invasion impaired overall survival specifically or with tumors > 2 cm [52].

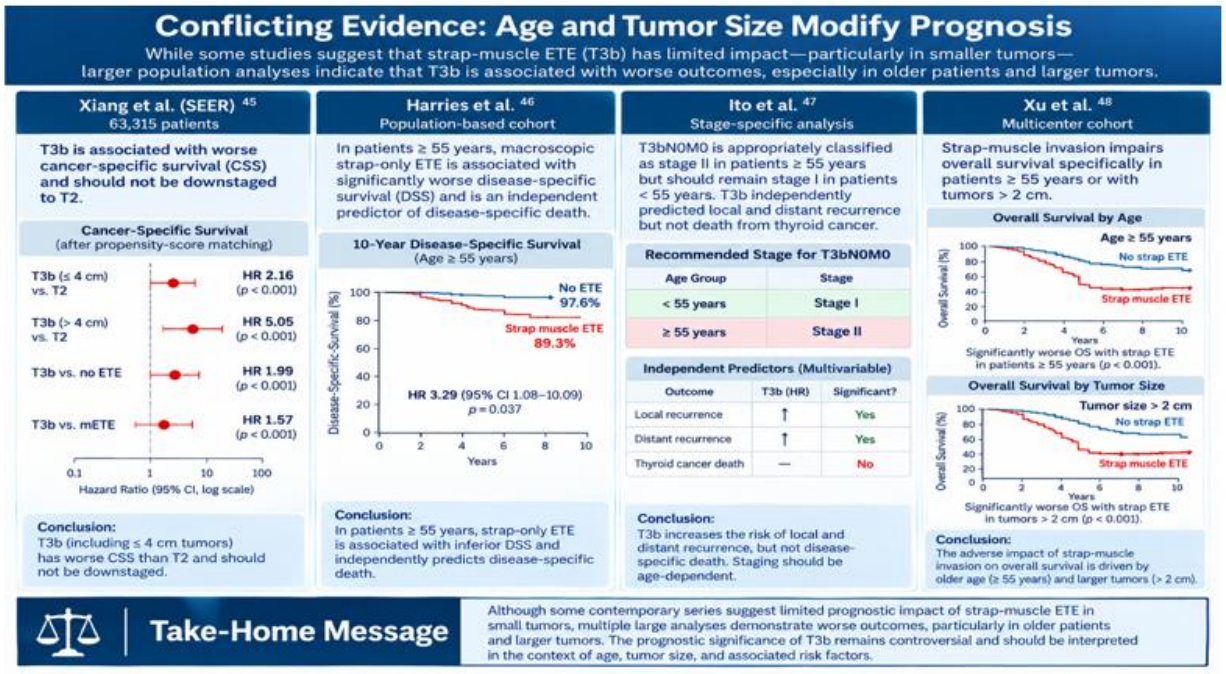



**Figure 10:** Conflicting Evidence: Age and Tumor Size Modify Prognosis.

The size dependence is reinforced by Park et al. (n=6,282), who subdivided T3b into ≤ 2 cm (T3b-1), 2 to 4 cm (T3b-2), and > 4 cm (T3b-3). T3b-1 showed no DSS difference from T1, and a modified classification reclassifying T3b-1 as T1 improved staging performance, supporting size-based downstaging of the smallest T3b tumors. An earlier cohort from the same group [53] (n=634), found a significant recurrence difference between T2 and T3b-2 but not between T2 and T3b-1.

More recent evidence suggests that the prognostic significance of gETE limited to the strap muscles (T3b) is influenced by primary tumor size. In a 2024 systematic review and meta-analysis of 18 observational studies, Won et al. [32], found that gross strap-muscle invasion was associated with significantly increased recurrence (OR 2.50), disease-specific mortality (RR 2.98), overall mortality (RR 1.36), and lymph-node metastasis (OR 5.36) compared with tumors without ETE. Importantly, when the analysis was restricted to tumors ≤ 4 cm, the associations with adverse prognostic outcomes were no longer statistically significant, with the exception of lymph-node metastasis, which remained significantly increased. These findings suggest that the adverse prognostic effect attributed to gross strap-muscle invasion is substantially attenuated in smaller tumors and that T3b status should not be interpreted in isolation as a marker of aggressive disease, particularly in DTC ≤ 4 cm

Taken together, these data indicate that gross strap-muscle invasion should not be interpreted in isolation as a marker of aggressive disease, particularly for smaller primaries in younger patients, but neither should it be dismissed as prognostically neutral, especially in patients ≥ 55 years or with tumors > 2 cm to 4 cm.

*Surgical Management of Gross Extrathyroidal Extension Limited to the Strap Muscles*

The principal surgical objective in T3b disease is complete gross resection while avoiding unnecessary morbidity. When tumor directly invades an adjacent strap muscle, the involved portion of muscle can generally be removed en

bloc with the thyroid specimen, with a limited cuff of grossly uninvolved muscle where necessary to obtain a macroscopically complete resection. Because the sternohyoid, sternothyroid, omohyoid, and thyrohyoid muscles are noncritical structures and partial or even unilateral resection generally produces little functional deficit, aggressive attempts to preserve visibly invaded muscle are rarely justified when doing so would leave gross tumor. Conversely, extensive removal of uninvolved strap musculature provides no demonstrated oncologic advantage. Thus, the extent of muscle resection should be dictated by the actual area of invasion rather than by the T3b designation itself.

The 2025 ATA guidelines recommend that thyroid cancer > 4 cm (cT3a), cancer of any size with gETE (cT3b or cT4), or clinically apparent nodal or distant metastatic disease generally be managed initially with total thyroidectomy, gross removal of all primary tumor, and appropriate nodal dissection, unless contraindications exist. This is a strong recommendation based on moderate-certainty evidence [4]. The NCCN Thyroid Carcinoma guidelines likewise list any ETE as an indication for total thyroidectomy [14]. Accordingly, when gross strap-muscle invasion is recognized preoperatively or intraoperatively, total thyroidectomy remains the guideline-supported standard approach, with en-bloc removal of the directly involved muscle to achieve complete macroscopic resection.

Intraoperative recognition of T3b is, however, imperfect. An et al. [54] (n=4,987), found that among 179 patients judged intraoperatively to have gETE, 21.2% had no muscle invasion on final pathology, underscoring the subjectivity of the assessment. This supports the 2025 ATA suggestion that, when it is unclear whether adherence reflects true extension versus post-biopsy scarring, leaving a cuff of sternothyroid muscle and deferring to final histology is prudent, minimal / microscopic extension into strap muscle with a clearly negative margin does not mandate completion thyroidectomy [4].

There is nevertheless increasing evidence that the extent of thyroid resection may eventually become more individualized in selected T3b tumors, particularly when limited strap-muscle invasion is discovered unexpectedly during lobectomy.

In a cohort of patients with 1 to 4-cm PTC treated initially with lobectomy, gross strap-muscle invasion was associated with structural recurrence (HR 2.54), but recurrence was strongly concentrated among patients who also had intermediate-risk cervical nodal disease [55]. Patients with gross strap-muscle invasion but absent or low-volume nodal disease had substantially better outcomes, leading the investigators to conclude that completion thyroidectomy might be appropriate for selected higher-risk patients rather than automatically for every incidental case of strap-muscle invasion [55]. More recently, Fei et al. [56], reported comparable recurrence-free survival with lobectomy even when ETE was suspected clinically / intraoperatively, and argued for an anterior-versus-posterior ETE distinction not yet formalized in current staging. This evidence is retrospective and does not supersede the current ATA recommendation, but it supports individualized decision-making when T3b disease is an unexpected postoperative finding.

*Central Compartment Management*

An important feature of T3b disease is its association with cervical lymph-node metastasis. A systematic review and meta-analysis by Zhang et al., incorporating six retrospective studies and 13,639 patients, demonstrated significantly more lymph-node metastasis in patients with gross strap-muscle invasion than in patients without ETE (OR 4.19, 95% CI 2.53–6.96). Gross strap-muscle invasion was also associated with increased recurrence (OR 1.46, 95% CI 1.18–

1.80), although mortality and 10-year DSS were not significantly different [57]. Approximately half of cN0 PTC patients with strap-muscle invasion harbor occult central nodal metastasis [51]. Thus, the principal adverse feature of T3b may be its relationship with regional nodal disease rather than an independent effect of muscle invasion on mortality. The more recent 18-study meta-analysis similarly demonstrated a markedly increased prevalence of regional lymph-node metastasis among patients with gross strap-muscle invasion (48.5% vs. 16.0%; OR 5.36, 95% CI 4.22–6.80) [28]. Notably, when analyses were restricted to tumors ≤ 4 cm, lymph-node metastasis remained significantly increased whereas differences in recurrence and survival outcomes were no longer statistically significant.

These findings suggest that, particularly in smaller T3b tumors, the association with regional nodal disease may represent a more prominent adverse clinicopathologic feature than strap-muscle invasion itself [32]. Thus, the principal adverse feature associated with T3b disease may be its relationship with regional nodal disease rather than an independent effect of muscle invasion on mortality.

Therapeutic central neck dissection is clearly indicated when central lymph-node metastases are clinically apparent (cN1a). The 2025 ATA guidelines recommend therapeutic dissection of levels VI and upper VII together with thyroidectomy in this setting. In patients with clinically involved lateral nodes (cN1b), ipsilateral therapeutic central compartment dissection should also accompany thyroidectomy and lateral neck dissection [4].

For cN0 T3b disease, however, prophylactic central neck dissection should not be presented as mandatory. ATA Recommendation 19B states that prophylactic central-compartment dissection may be considered in patients with PTC, clinically uninvolved nodes, and advanced primary tumors (T3 or T4), particularly when the resulting pathologic information is expected to influence subsequent treatment [4]. The recommendation is conditional and supported by low-certainty evidence, and the potential oncologic and staging benefits must be weighed against the risks of RLN injury and hypoparathyroidism [4]. Meta-analyses show that prophylactic dissection reduces locoregional recurrence (e.g., OR 0.65) at the cost of higher rates of transient RLN injury and transient / permanent hypocalcemia, without a demonstrated survival benefit; roughly 31 patients would need prophylactic dissection to prevent one recurrence [4]. Although the high prevalence of occult nodal disease provides a rationale for considering prophylactic dissection, and some data suggest younger male patients with strap-muscle invasion are at particularly high risk of central metastasis [58], current evidence does not establish that routine prophylactic dissection improves survival or should be performed in every cN0 T3b patient.

In practice, the decision should integrate tumor size and location, laterality and extent of muscle invasion, suspicious intraoperative nodes, multifocality, patient age, surgeon experience, the anticipated role of pathologic nodal staging in postoperative radioactive iodine decisions, and the condition of the RLN and parathyroid glands as the operation progresses. The 2025 ATA guidelines specifically emphasize adapting the extent of central dissection to intraoperative circumstances; for example, contralateral prophylactic dissection should be avoided when the first side of surgery has resulted in RLN injury or significant compromise of parathyroid viability [4].

*Contemporary Interpretation*

Current evidence supports viewing gETE limited to the strap muscles as an intermediate local phenotype, more aggressive than intrathyroidal disease but far less so than invasion of major adjacent structures. T3b carries a greater likelihood of nodal metastasis and a modestly increased risk of recurrence, and DSS is generally excellent for smaller

tumors in younger patients. However, the prognostic significance of T3b is genuinely contested: large SEER data [48], and institutional cohorts [49,50], meaningfully worse survival in patients ≥ 55 years and in larger tumors, while size-stratified analyses [52], support downstaging only the smallest (≤ 2 cm) T3b lesions. Newer work also blurs the T3b / T4a boundary posteriorly, with isolated RLN invasion behaving similarly to T3b [8]. The operative goal remains complete macroscopic resection through limited en-bloc removal of involved strap muscle. Total thyroidectomy remains the current ATA- and NCCN- recommended initial operation for known cT3b disease; therapeutic central neck dissection is indicated for clinically involved nodes; and prophylactic central dissection in cN0 disease remains selective rather than routine.

*Management of Recurrent Laryngeal Nerve Invasion*

Invasion of the RLN is one of the most common manifestations of gETE in locally advanced DTC. The nerve may be involved directly by extension of the primary tumor or secondarily by metastatic lymph nodes within the paratracheal or tracheoesophageal groove, patterns illustrated in Figure 11. The RLN is one of the most frequently involved structures in locally invasive DTC, reported in approximately 33% to 61% of cases, and is most susceptible to invasion along the course of the inferior thyroid artery and near its laryngeal entry at the cricothyroid junction, where it is relatively fixed [59].

Importantly, an invaded RLN is not necessarily nonfunctional. In a contemporary series of 65 patients with 66 invaded nerves, preoperative vocal-fold paralysis was documented in only 43.5% of cases despite intraoperative confirmation of RLN involvement; the primary tumor accounted for 59.3% of cases and nodal disease for approximately 30.5% [60]. Electrophysiologic data corroborate this observation, invaded nerves frequently retain recognizable stimulability, and neural invasion is associated with preoperative vocal-fold paralysis in only about half of patients [61]. A 2026 series reproduced this discordance, with nearly 90% of patients demonstrating preserved preoperative vocal-cord mobility despite intraoperatively confirmed nerve invasion [62]. Structural involvement, vocal-fold mobility, and electrophysiologic function therefore provide complementary, and sometimes discordant, information about nerve integrity.

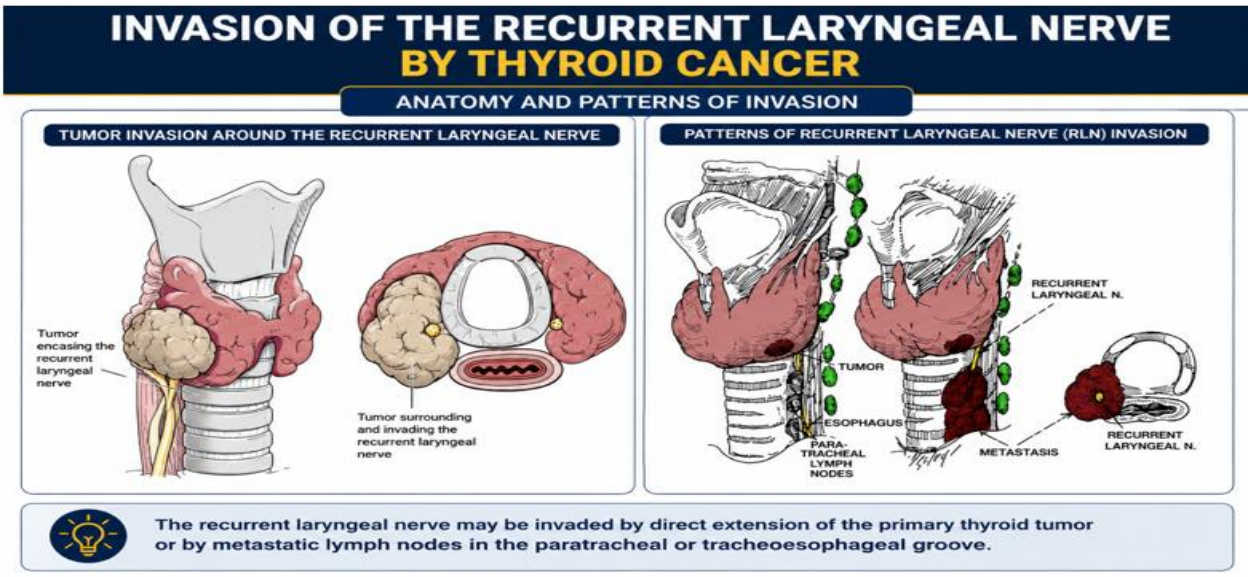



**Figure 11:** Patterns of Invasion of the RLN.

Accordingly, preoperative vocal-fold function should be established before definitive surgical planning whenever RLN involvement is suspected. The 2025 ATA guidelines recommend voice assessment for all patients undergoing thyroid surgery and formal laryngeal examination in patients with dysphonia, posterior gETE, or extensive central or lateral cervical nodal disease [4]. Because correlation between vocal symptoms and objective cord function is poor, up to one-third of patients with paralysis are asymptomatic, laryngoscopy rather than symptom review alone is required in high-risk settings [63,64]. The guidelines further emphasize that management of an invaded nerve should incorporate its preoperative functional status [4].

Intraoperatively, visual identification remains the gold standard for injury prevention, while intraoperative neural monitoring (IONM) provides additional functional information and is particularly useful in advanced, reoperative, or bilateral disease [4]. Meta-analytic and large-registry data show that IONM reduces overall and transient RLN injury, most robustly in cancer and reoperative surgery, with an estimated number-needed-to-monitor of roughly 30 to 70 to prevent one injury [4]. Vagal or proximal RLN stimulation after completing the first side is especially valuable before proceeding with contralateral surgery, the negative predictive value of an intact post-dissection signal for confirming preserved function is on the order of 99%, so preservation of the only functioning RLN may take precedence over an otherwise planned bilateral procedure, and deferring contralateral resection after loss of signal reliably prevents bilateral paralysis [4,58].

When the ipsilateral vocal fold is mobile and the RLN remains functional, preservation of the nerve is generally favored provided that all gross disease can be removed. As depicted in Figure 12, this may be accomplished by meticulous sharp dissection or "shaving" of tumor from the epineurium. When infiltration extends into the superficial layers of the nerve, a partial-layer resection can remove involved tissue while retaining a functional neural trunk. This principle is echoed across specialties, the NCCN Principles of Surgery direct that a functioning nerve be preserved even when otherwise adequate tumor margins are not achieved, provided no gross residual disease is left, with segmental resection reserved for direct invasion or preoperative paralysis [65].

This approach is supported by several retrospective series. Lang and colleagues compared 39 patients undergoing nerve preservation with 38 undergoing RLN resection for PTC involving a functioning nerve; preservation maintained nerve function in more than 90% of patients, while distant metastasis and incomplete resection at sites other than the RLN, not the choice of shaving versus resection, were the independent determinants of cancer-specific survival [66].

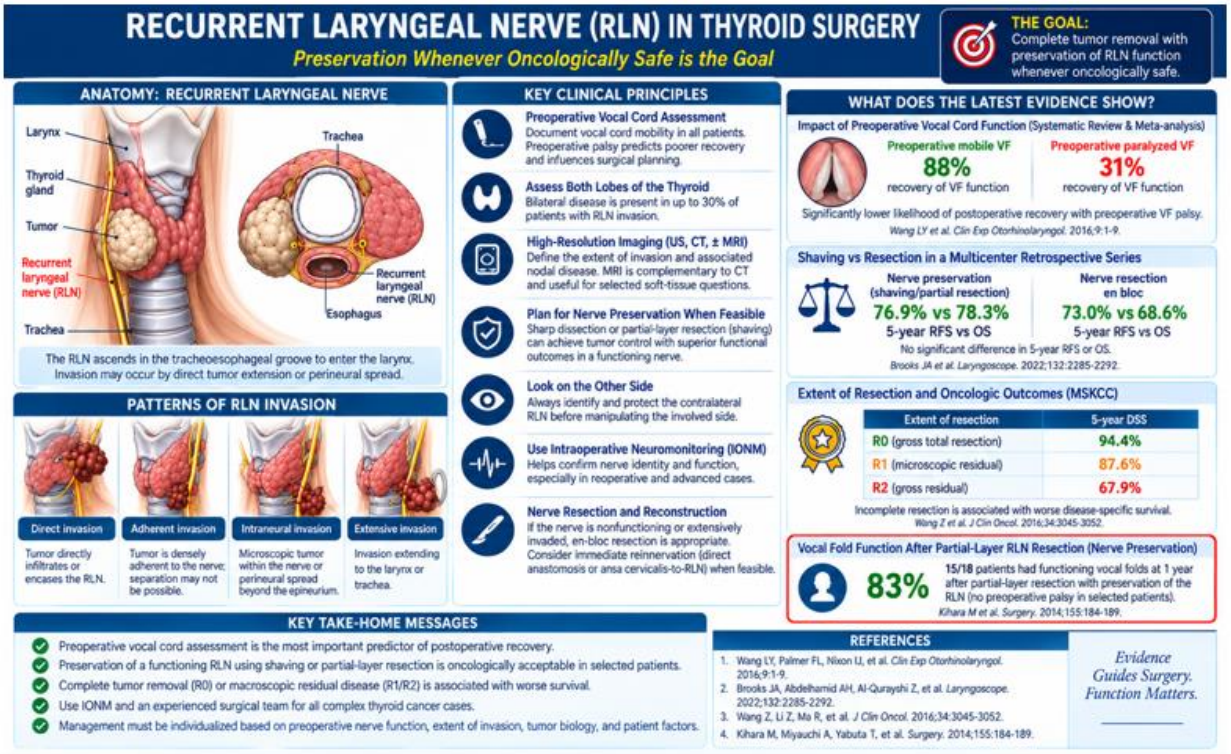



**Figure 12:** Management of RLN Involvement in Locally Advanced Thyroid Cancer.

In the Kuma Hospital experience, vocal-fold function recovered in most patients (83%) after partial-layer resection despite marked thinning of the preserved nerve, aided by IONM to trace the nerve within fibrous or tumor tissue [67]. Miyamaru and colleagues similarly found that postoperative vocal fold function after sharp tumor dissection (shaving) in patients with preoperatively functional folds was favorable and statistically indistinguishable from that achieved by immediate reconstruction, supporting a "shave first, reconstruct if shaving is impossible" hierarchy [67].

More recent evidence has further strengthened the rationale for selective preservation rather than routine sacrifice of every functioning invaded RLN. Lee et al. reported 47 patients with PTC in whom a functioning RLN was shaved despite leaving a very small macroscopic tumor remnant (R2 resection < 1 cm in length and < 4 mm in thickness); after a median follow-up of 93 months, five patients (10.6%) developed cervical recurrence, only one (2.1%) ultimately required RLN resection for progression at the residual-tumor site, and there were no disease-specific deaths, distant metastases, or cases of permanent vocal-fold paralysis [68]. In a large single-institution cohort, voice-quality preservation was significantly higher after shaving than after amputation (93.5% vs 71.0%; P = 0.043), with larger tumor size the only factor associated with amputation [69].

These findings do not establish planned R2 resection as the preferred oncologic approach, and complete gross resection remains the goal whenever it can be achieved without unacceptable morbidity; rather, they demonstrate that in highly selected patients the biologic consequences of leaving a minute amount of disease on a functioning RLN may be substantially less than the functional consequences of obligatory nerve sacrifice.

The most difficult circumstance is therefore a functioning RLN that is deeply or circumferentially invaded and cannot be separated from tumor without leaving gross disease. In this setting, the decision should not be reduced to a simple "preserve versus resect" rule. The potential oncologic advantage of complete gross resection must be weighed against contralateral vocal-fold function, whether the involved nerve is the patient's only functioning nerve, the extent of aerodigestive or vascular invasion, distant metastatic burden, tumor differentiation and biologic aggressiveness, the likelihood of postoperative RAI or other systemic therapy, and the anticipated functional consequences of unilateral or bilateral denervation [4,59]. Some groups have attempted to formalize this judgment, Peng et al. proposed a MACIS-score–based intraoperative phonosurgical algorithm in which, for well-differentiated cancer invading a functioning nerve, a MACIS score > 6.99 favors en bloc resection with immediate ansa cervicalis–RLN anastomosis, whereas lower scores favor preservation by shaving [70].

Intraoperative neural monitoring (IONM) can be particularly informative because an anatomically invaded nerve may retain electrophysiologic activity even when vocal-fold motion is impaired. In the multicenter analysis by Brooks et al., invaded nerves retained variable stimulability and RLN resection itself was not associated with improved 5-year recurrence-free or overall survival, although postoperative RAI was, while interpretation is limited by retrospective design, small sample size, heterogeneous disease extent, and selection bias [60]. Consistent with this, in 72 patients with cT4a PTC and RLN involvement, recurrence was not affected by nerve resection versus shaving, preoperative vocal-fold palsy, or aerodigestive invasion; a positive resection margin was the single most important predictor of recurrence [71]. These data should support individualized preservation, not be interpreted as evidence that gross residual disease is oncologically equivalent to complete resection.

Conversely, when the ipsilateral vocal fold is paralyzed preoperatively and the RLN is grossly encased or extensively infiltrated, nerve sacrifice is usually appropriate when required to obtain gross tumor clearance. This remains consistent with the AHNS consensus, the International Neural Monitoring Study Group recommendations, and the 2025 ATA guidelines [4,16,61].

When resection is required, immediate reconstruction should be considered whenever technically feasible. Direct end-to-end RLN anastomosis is preferred when a tension-free repair is possible; when a segmental defect prevents primary repair, ansa cervicalis–to–distal RLN anastomosis, an interposition nerve graft, or selective vagus-to-RLN anastomosis can be used (Figure 13) [72].

When the peripheral stump is obscured near Berry's ligament, dividing the inferior pharyngeal constrictor muscle along the lateral thyroid cartilage (the "laryngeal approach") can expose the distal RLN for anastomosis [67]. Although reinnervation generally does not restore normal abduction and adduction, it maintains thyroarytenoid tone and bulk, reduces denervation atrophy, improves glottic closure, and can substantially improve voice and swallowing. A systematic review of ansa cervicalis–RLN reinnervation found improvements after both immediate and delayed reconstruction, with practical advantages to reconstruction at the time the nerve is sacrificed [73]. A 237-patient long-term series of delayed ansa cervicalis main-branch–to–RLN anastomosis restored vocal function to near-normal levels, confirming the durability of the technique [74], and a contemporary series showed that immediate ansa cervicalis–RLN anastomosis produced multidimensional acoustic and patient-reported voice recovery to near-baseline by 6 months, including in patients with preexisting unilateral paralysis [75].

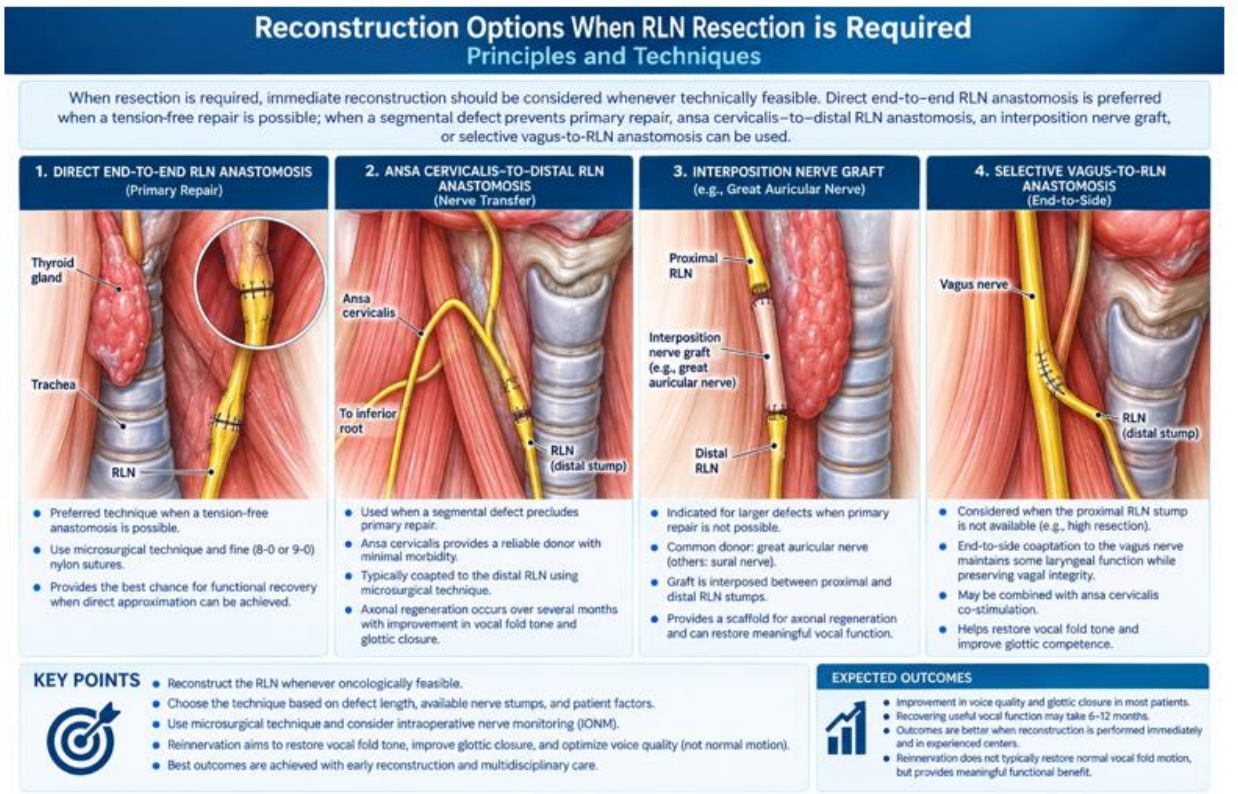



**Figure 13:** Reconstruction Options When RLN Resection Is Required [72].

The most recent surgical series (2026) evaluated 29 patients with DTC invading the RLN: 18 underwent partial-layer preservation and 11 underwent reconstruction after sacrifice. Vocal-fold mobility was preserved in 83.3% of patients undergoing partial-layer resection; among reconstructed patients, vocal-fold tone and glottic closure improved, and no recurrence occurred at the site of nerve preservation or reconstruction, although the cohort remains small and follow-up limits firm oncologic conclusions [62]. The AHNS consensus recommends immediate reinnervation, if feasible, when the RLN is resected during surgery for invasive DTC, as prospective data show smaller glottic gaps and better phonatory measures after immediate reinnervation than after no reinnervation or delayed framework surgery [16].

The oncologic significance of isolated RLN invasion also appears more favorable than historically assumed. Under the AJCC eighth edition, gross invasion of the RLN is categorized as T4a regardless of whether any other aerodigestive structure is involved. However, Harries and colleagues examined 8,030 patients with PTC treated at MSKCC and demonstrated substantial prognostic heterogeneity within this category [8]. Ten-year DSS was 99.2% without gETE, 95.7% with isolated strap-muscle invasion, 96.9% with isolated RLN invasion, and only 82.5% with invasion of other T4a structures. After adjustment for age, nodal status, and distant metastasis, isolated RLN invasion behaved similarly to isolated strap-muscle invasion; among patients ≥ 55 years, corresponding 10-year DSS was 89.4% and 90.9%, respectively. The authors proposed that RLN-only gETE might be more appropriately grouped with T3b rather than other T4a disease [8]. Convergent single-center data support this stratification, in a 602-patient T4a cohort, isolated

RLN invasion carried markedly superior progression-free and DSS compared with multi-organ invasion [76], and a site-based risk-stratification analysis classified nerve invasion as an "extremely low-risk" pattern (15-year cancer-specific survival 88.8%) distinct from tracheal, vascular, and multi-invasion patterns [37].

This favorable characterization is not universal, however. In a cohort of 3,104 patients, posterior-direction gETE conferred significantly worse DSS than T3 disease even when only the RLN was invaded (hazard ratio 7.78, 95% CI 3.41–17.75), with no difference between RLN-only and other posterior-organ invasion [29]. The mechanism of involvement may not mitigate this risk, RLN invasion by extranodal extension of metastatic nodal disease carried DSS as poor as that of direct tumor extension [77], and RLN invasion is itself associated with a high rate of lateral lymph-node metastasis [78]. The prognostic weight of isolated RLN invasion therefore remains debated and is likely modified by patient age, mechanism of invasion, and completeness of resection.

These observations are directly relevant to operative decision-making. The designation of RLN involvement as T4a should not, by itself, mandate sacrifice of a functioning nerve. Rather, the contemporary objective is complete gross tumor removal while preserving neural function whenever this can be accomplished safely.

A functioning nerve with superficial or separable disease should generally be preserved by sharp dissection or partial-layer resection; a nonfunctioning nerve extensively replaced by tumor should generally be resected when required for oncologic clearance and reconstructed when feasible; and a functioning nerve with inseparable circumferential invasion requires individualized judgment integrating tumor biology, disease extent, contralateral laryngeal function, electrophysiologic findings, anticipated adjuvant therapy, and patient priorities. A published intraoperative decision algorithm stratifying management by preoperative vocal-cord mobility and intraoperative neural continuity now provides a practical framework for these decisions [62].

*Management of Invasion of the Larynx by Thyroid Cancer*

Laryngeal invasion by DTC is uncommon but carries important prognostic and functional consequences. Because thyroid carcinoma characteristically invades the larynx from the outside inward, extensive external framework involvement frequently coexists with an intact endolaryngeal mucosa, creating opportunities for organ-preserving resection in appropriately selected patients. In a single-institution series of 60 pT4 DTC cases drawn from 4775 consecutive patients, laryngeal invasion was documented in only two patients, whereas RLN and tracheal involvement predominated [36]. Aerodigestive-tract invasion overall is reported in roughly 10% of DTC case series, with laryngeal luminal involvement being among the rarest patterns [39].

The anatomic pattern of laryngeal invasion by thyroid carcinoma differs fundamentally from that of primary laryngeal malignancy. Primary laryngeal carcinoma arises within the endolarynx and typically progresses outward, whereas thyroid carcinoma approaches the laryngeal framework from outside inward. This distinction is surgically decisive, even tumors with substantial external framework involvement may leave the endolaryngeal or hypopharyngeal mucosa intact, permitting organ-preserving resection in selected patients [16,79].

Three principal routes of laryngeal extension are described (Figure 14) [16, 79]:

- Direct transcartilaginous extension through the thyroid cartilage lamina, progressing from the external perichondrium into the cartilage and potentially the paraglottic space.

- Anterior extension through the cricothyroid membrane, gaining access to the paraglottic compartment without necessarily destroying the thyroid cartilage.
- Posterosuperior extension behind the thyroid cartilage toward the pyriform sinus and adjacent paraglottic tissues.

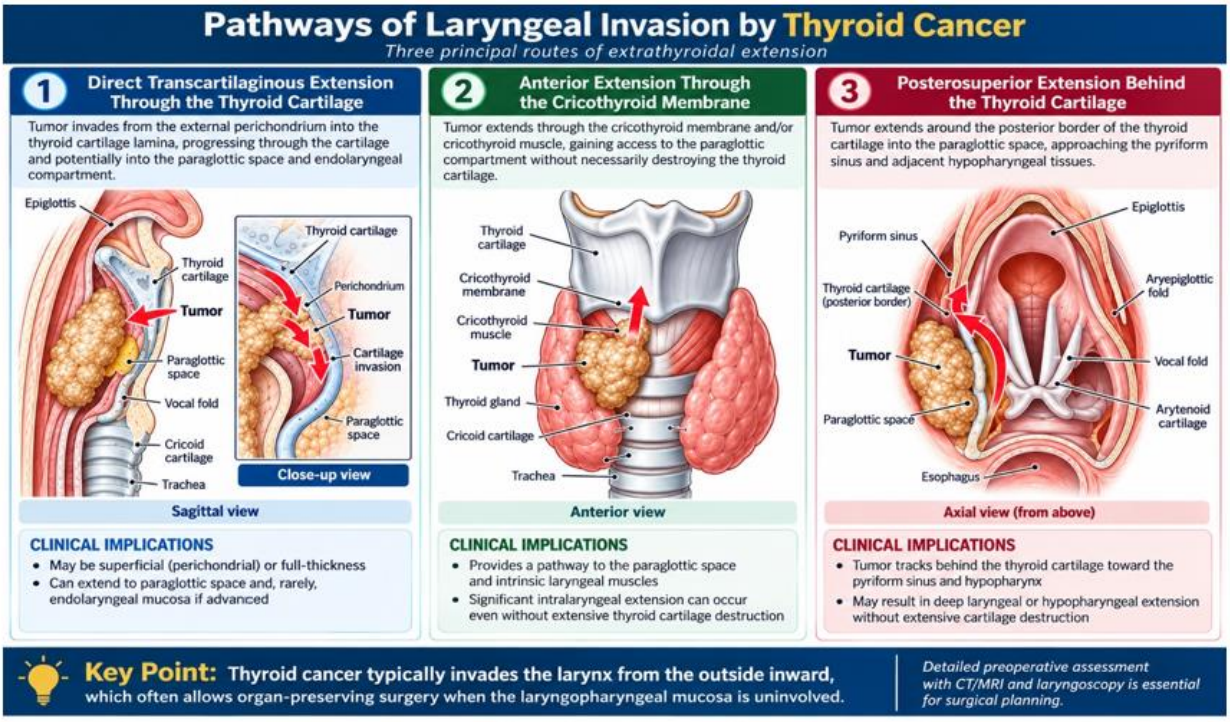



**Figure 14:** Routes of Laryngeal Invasion by Thyroid Cancer [16,79].

The depth of invasion is at least as important as its route. The most widely used depth-based framework is the Shin (Shin–Grillo) classification, developed for airway invasion, which grades involvement in ascending severity (Figure 15) [80-82]:

- Stage 0: tumor confined to the thyroid
- Stage 1: capsular penetration or adherence to the perichondrium / adventitia without invasion
- Stage 2: erosion of cartilage or intercartilaginous tissue
- Stage 3: transmural invasion reaching the submucosa with an intact mucosa
- Stage 4: full-thickness invasion with mucosal penetration or an intraluminal mass

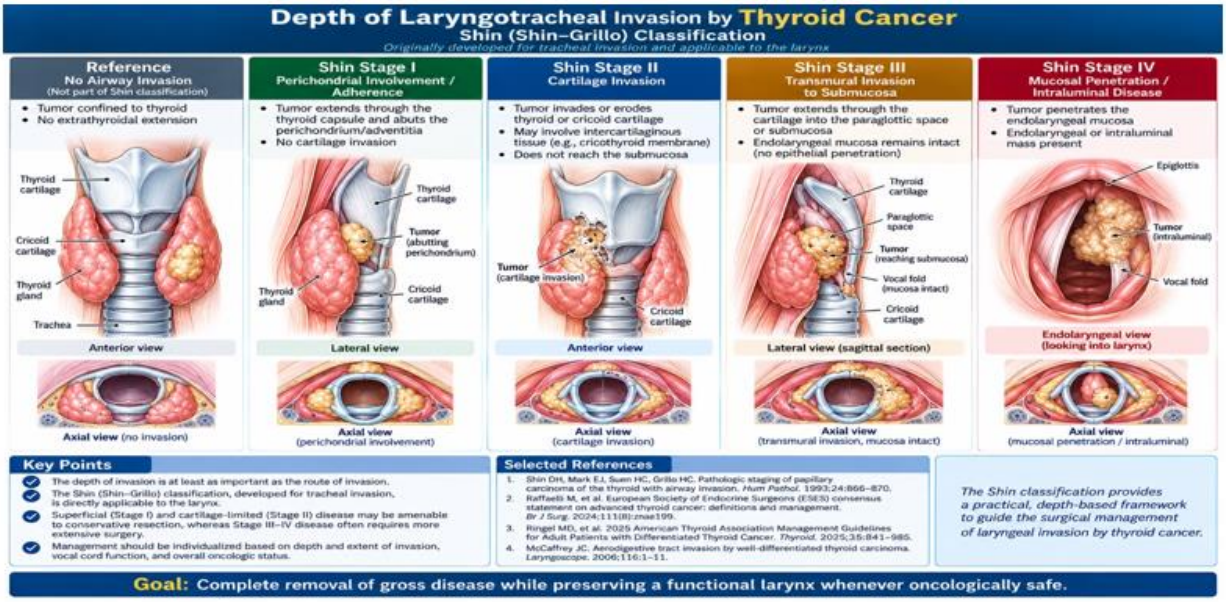



**Figure 15:** Depth of Laryngotracheal Invasion by DTC [80-82].

Although derived principally for the trachea, this depth concept is directly transferable to the larynx and underscores that superficial adherence, transcartilaginous invasion, and intraluminal disease represent distinct surgical problems. The fundamental objective is complete macroscopic removal of disease (R0/R1) while preserving a functional larynx whenever this does not compromise oncologic control. Macroscopically complete resection is consistently associated with improved survival relative to macroscopically incomplete (R2) resection, whereas shave and complete resection yield comparable survival when no gross tumor remains [27,82,83].

Laryngeal invasion should not automatically trigger total laryngectomy. Operative extent should be dictated by the depth and distribution of invasion, mucosal involvement, extent of cricoid involvement, vocal fold / RLN function, the ability to achieve gross clearance, overall disease burden, and anticipated morbidity [4,16,79]. T4a classification defines anatomic extent, not the required procedure; the least morbid operation capable of achieving adequate local control is preferred, and aggressive laryngeal resection should generally not be the index operation unless disease burden mandates it.

The AHNS consensus articulates this graded approach explicitly, in partial-thickness laryngeal invasion, shave excision of gross disease is favored over organ-sacrificing procedures; in gross endolaryngeal invasion, partial or total laryngectomy is indicated depending on tumor extent; and when partial or total laryngectomy is required and the operating surgeon is not well versed in the procedure, an experienced surgeon should be involved [16].

*Superficial Invasion: Shave or Partial-Thickness Resection*

The most common form of laryngeal involvement is extraluminal infiltration rather than luminal penetration. When disease is limited to the external perichondrium or superficial cartilage and complete macroscopic removal is achievable, conservative shave or partial-thickness excision of the involved thyroid or cricoid cartilage is preferred [16,27]. McCaffrey's 45-year laryngotracheal cohort, patients undergoing shave excision had survival comparable to

radical resection provided no gross tumor remained, whereas incomplete resection significantly worsened survival [27].

The goal of a shave procedure is removal of all grossly involved tissue while preserving uninvolved cartilage and the internal mucosal envelope, not indiscriminate debulking. Shave excision may leave microscopic disease, which can be addressed with RAI or external-beam radiotherapy (EBRT) in appropriately selected patients [16,84]. If gross disease cannot be cleared superficially, deeper framework resection is indicated.

*Thyroid Cartilage Invasion and Partial Laryngectomy*

Full-thickness thyroid cartilage invasion does not mandate total laryngectomy. Tumors involving a unilateral thyroid lamina, the cricothyroid membrane, or limited paraglottic tissue may be amenable to partial laryngectomy or partial framework resection when the contralateral larynx and endolaryngeal mucosa are uninvolved [16,79].

The largest contemporary series is that of Hawes et al. at MD Anderson Cancer Center, five patients (four recurrent, one primary) with DTC involving the larynx underwent partial laryngectomy between 2018 and 2024, superseding nine previously reported cases across seven studies [79]. Four patients underwent near-complete resection of the unilateral thyroid ala and one a resection of the inferior (< 50%) thyroid ala; none had cricoid involvement. Cartilage was resected with a 2 to 3 mm cutting burr in a broad plane away from tumor, with the laryngopharyngeal mucosa preserved and reconstructed by rotating sternohyoid or sternocleidomastoid muscle over the exposed mucosa. All achieved complete resection with no perioperative complication attributable to the laryngeal procedure, no speech or swallowing deficit, and no feeding-tube or tracheostomy dependence; patients ate immediately and had a median 1-day hospital stay. Two patients received postoperative RAI; none received EBRT or systemic therapy within two years. At a mean follow-up of 26 months, three remained free of structural disease, one had sub-centimeter contralateral and distant recurrence, and one developed cricoid and distant recurrence [79].

These results demonstrate technical feasibility in highly selected patients but do not establish oncologic equivalence to total laryngectomy, given the small sample and short follow-up.

Larger institutional experience corroborates the broader principle, in Moritani's series of 55 PTC patients with thyroid cartilage invasion, most disease remained confined to the thyroid cartilage or paraglottic space, most patients avoided total laryngectomy, isolated laryngeal recurrence occurred in only 3.6%, and 10-year DSS was 81.0% for superficial versus 61.4% for intraluminal invasion [85].

Hawes et al. offer a practical selection heuristic, partial laryngectomy can generally be performed when less than 50% of the laryngeal framework and cricoid are involved, whereas significant laryngeal or pharyngeal mucosal involvement, contralateral RLN paralysis, and greater than 50% laryngeal or cricoid involvement are contraindications and potential indications for total laryngectomy [79]. This threshold is a technical guide derived from small retrospective experience rather than a prospectively validated oncologic cutoff and should be applied with corresponding caution.

*Cricothyroid Membrane Invasion*

Extension through the cricothyroid membrane permits access to the paraglottic space without obligatory destruction of the thyroid cartilage framework, so selected tumors remain amenable to organ preservation [16,79]. Resection should be tailored to the tissues actually involved and may include the cricothyroid muscle, inferior thyroid lamina,

adjacent intrinsic musculature, and paraglottic tissue, with preservation of uninvolved mucosa and the contralateral functional larynx.

*Cricoid Cartilage Invasion*

Cricoid involvement must be considered separately from thyroid cartilage involvement because the cricoid is the only complete cartilaginous ring of the airway, and extensive resection destabilizes the framework. For superficial involvement, cricoid shaving is appropriate. Resection of small focal segments of the anterolateral hemicricoid can generally be performed without cartilaginous reconstruction, and resection of less than 50% of the cricoid can in selected cases be reconstructed (for example, by rotating and suturing thyroid or tracheal cartilage into the defect); involvement exceeding 50% of the cricoid is a contraindication to partial laryngeal surgery [79]. The operative spectrum for cricoid disease is therefore best conceptualized as:

- Superficial involvement → shave / partial-thickness resection → focal partial cricoid resection with reconstruction when technically appropriate → extensive disease requiring more radical laryngotracheal surgery or total laryngectomy

*Total Laryngectomy and Laryngopharyngectomy*

Total laryngectomy is rarely required for DTC but remains essential when complete macroscopic resection cannot be achieved while maintaining a structurally and functionally acceptable larynx [16,27]. Potential indications include extensive bilateral or transglottic involvement, major framework destruction, extensive intraluminal / mucosal disease, extensive cricoid involvement not amenable to safe reconstruction, or a severely dysfunctional larynx. The status of both RLNs and vocal folds must be incorporated into planning.

Laryngopharyngectomy represents the most extensive end of the spectrum and should be reserved for exceptional cases in which carcinoma extensively involves both larynx and hypopharynx, particularly with pyriform sinus or posterior pharyngeal wall penetration, and gross clearance cannot otherwise be achieved. Multidirectional invasion of larynx, trachea, esophagus / pharynx, and RLN may require multivisceral resection with permanent airway separation and complex reconstruction; such operations carry considerable morbidity and warrant multidisciplinary deliberation weighing oncologic benefit, systemic disease burden, patient preference, functional consequences, and neoadjuvant or systemic alternatives [16,86].

The available evidence supports a depth-directed rather than structure-directed approach. The operative continuum can be conceptualized as: tumor adherence → superficial cartilage invasion → full-thickness framework / paraglottic invasion → mucosal / intraluminal invasion, with a corresponding surgical continuum of sharp dissection / shave → partial-thickness cartilage resection → partial laryngectomy / framework resection → total laryngectomy ± pharyngeal resection (Figure 16). This strategy reflects the outside-in biology of DTC and recognizes that preservation of the mucosal envelope and contralateral functional larynx may permit substantial framework resection without sacrificing the entire organ. Because the supporting evidence for organ-preserving partial laryngectomy derives predominantly from retrospective institutional experience and small case series, these procedures are best undertaken in high-volume centers with expertise in thyroid oncology, head-and-neck surgery, airway reconstruction, and multidisciplinary care [16,79,85].

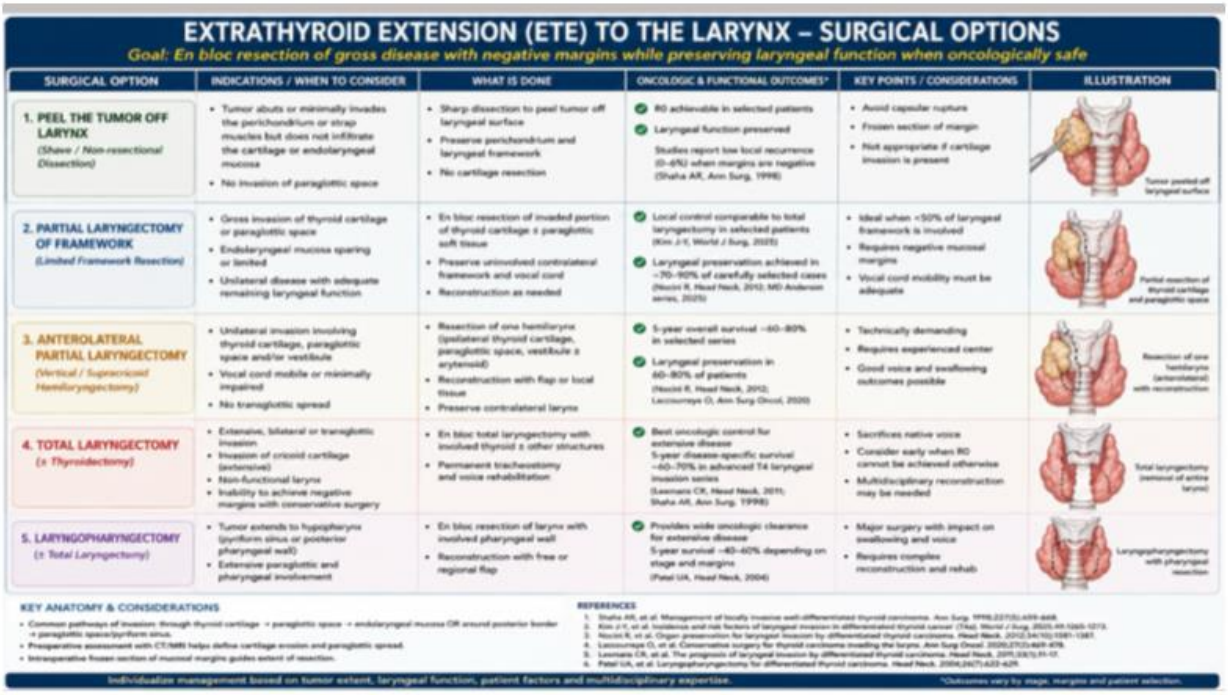



**Figure 16:** Surgical Options for Laryngeal Invasion of DTC.

*Tracheal Invasion Surgical Management*

Tracheal invasion represents one of the most technically challenging manifestations of gETE in DTC. Although uncommon, occurring in approximately 1% to 8% of patients across contemporary surgical series and reviews [87, 88], airway invasion has major implications for local control, functional outcome, and DSS, particularly once tumor penetrates the tracheal cartilage and reaches the submucosa or lumen [89]. Following the strap muscles and RLN, the trachea is the third most commonly involved extrathyroidal structure, reflecting its intimate anatomic relationship with the thyroid gland [81]. Intraluminal disease is a worse prognostic factor than superficial invasion, and in site-based analyses of locally advanced thyroid cancer tracheal invasion carries an intermediate disease-specific mortality risk [88,89].

The 2025 ATA guidelines classify gross invasion of the trachea as T4a disease and recommend total thyroidectomy with gross removal of all primary tumor, together with compartment-oriented therapeutic nodal dissection when clinically involved nodes are present [4]. The central objective of surgery is therefore complete macroscopic tumor removal (R0 / R1) while preserving a functional airway whenever this can be achieved without compromising oncologic clearance; retrospective data consistently show improved survival with macroscopically complete resection compared with macroscopically incomplete (R2 / debulking) surgery [82].

The operative strategy should be established, whenever possible, before entering the operating room. Patients with suspected tracheal invasion should undergo high-resolution cervical ultrasonography supplemented by contrast-enhanced CT of the neck and upper mediastinum to define the longitudinal and circumferential extent of airway involvement and its relationship to the cricoid cartilage, RLNs, esophagus, major vessels, and mediastinum. MRI can provide complementary information in selected cases, particularly when clarification of soft-tissue planes is required.

The 2025 ATA guidelines specifically recommend cross-sectional imaging with intravenous contrast when gETE or aerodigestive tract involvement is suspected, noting that any consequent delay in RAI therapy is not clinically harmful [4,14]. Preoperative laryngoscopy is essential, because baseline vocal-fold function substantially influences management when the RLN and airway are simultaneously involved and is a key determinant of whether a tracheostomy will be required at the time of resection [81].

Bronchoscopy should be considered when imaging or symptoms suggest deep airway invasion. Endoscopic findings such as mucosal irregularity, submucosal bulging, telangiectasia, frank mucosal tumor, or intraluminal disease help establish depth of involvement, and preoperative endoscopic debulking of obstructing intraluminal disease can occasionally avoid an emergency tracheostomy before definitive resection [90]. Nevertheless, because thyroid carcinoma invades the trachea from outside inward, apparently normal mucosa does not exclude significant cartilage or submucosal invasion. Consequently, the definitive depth and extent of involvement frequently remain an intraoperative determination [89]. Because gross tracheal invasion is a contraindication to active surveillance, the 2025 ATA guidelines advise that patients under observation who develop ultrasound evidence of ETE or invasion of the RLN, trachea, or esophagus should promptly return to their surgeon [4].

Depth of Invasion and Selection of the Tracheal Operation

The Shin classification remains the standard conceptual framework for describing depth of tracheal invasion, although the literature applies it in two closely related forms [91]. In its original pathologic description, progression is stepwise from the external perichondrial region, into the cartilage or intercartilaginous tissue, through the cartilage into the lamina propria / submucosa, and finally to the mucosal surface or intraluminal disease (Figure 17). Several contemporary series render the same concept as a five-tier scheme (stages 0 to 4) [80,87]:

- Stage 0: confined to the thyroid
- Stage 1: capsular penetration with adherence to the tracheal adventitia without invasion
- Stage 2: cartilage or intercartilaginous erosion
- Stage 3: invasion of the lumen with intact mucosa
- Stage 4: full-thickness penetration or an intraluminal mass

Surgeons should be aware that stage 3 and stage 4 definitions differ subtly between these renderings; when citing a stage, the operative note should specify the anatomic depth (perichondrium, cartilage, submucosa, or mucosa / lumen) rather than the numeral alone.

Critically, the Shin classification describes depth, not the circumferential or longitudinal extent of invasion. Operative selection therefore requires independent assessment of three dimensions: depth, circumferential extent, and longitudinal (number of rings) extent, because circumferential and longitudinal involvement determine reconstructive feasibility even when depth is identical.

These dimensions provide a practical framework for choosing among three principal operations (Figure 17) [89]:

- Shave resection
- Window resection
- Circumferential (sleeve) resection with primary end-to-end anastomosis

Broadly, shaving is appropriate for Shin stage 1 and selected limited stage 2 disease, whereas disease extending through the cartilage into the submucosa or lumen (Shin stages 3 to 4) generally warrants full-thickness resection when curative surgery is appropriate [80,81].

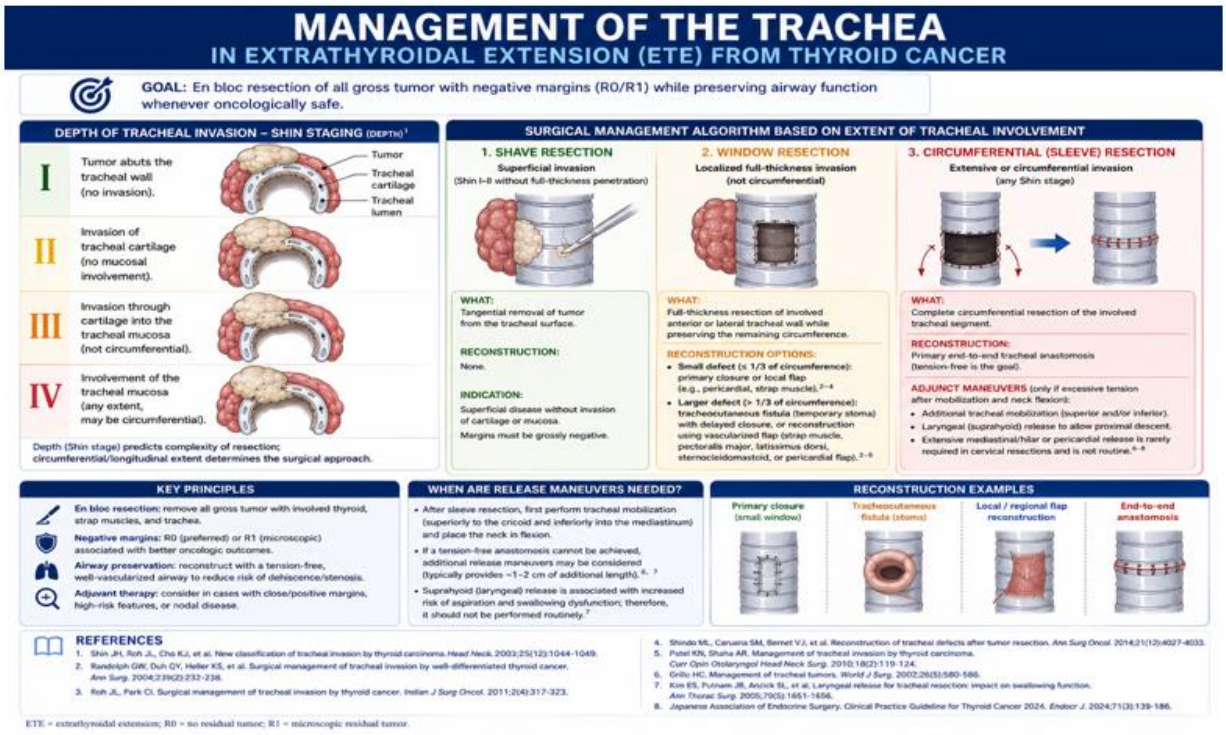



**Figure 17:** Management of the Trachea in Advanced Thyroid Cancer.

The AHNS consensus similarly endorses shave excision for a short segment with minimal cartilage invasion, and circumferential sleeve resection for intraluminal or significant cartilage invasion [16]. The evidence base, however, remains predominantly retrospective; no randomized or high-quality prospective trial has established the superiority of one full-thickness technique over another for comparable disease, and a 247-patient analysis of cT4a PTC found that neither the type of tracheal surgery nor the reconstruction method independently affected progression-free survival across Shin groups [92].

*Shave Resection*

Tangential or shave resection is appropriate when involvement is superficial and complete macroscopic clearance can be obtained without entering the airway. The tumor is sharply dissected from the perichondrium or superficial cartilage while preserving the tracheal lumen. This approach minimizes morbidity and avoids airway reconstruction, and in carefully selected superficial disease local control rates of approximately 95% or greater have been reported [16].

The principal limitation of shaving is uncertainty regarding microscopic residual disease within cartilage or intercartilaginous tissue, where the peritracheal fascia is continuous with dense interring fibrous tissue and tumor can track along intercartilaginous lymphatics. In circumferential resection specimens, disease extended beyond the tracheal adventitia in the large majority of cases, and reported local-recurrence rates after shaving for deeper disease range widely, from 17% up to 63% in individual series where microscopic disease was knowingly left [16,82]. Stage

2 disease therefore represents a clinically important gray zone: limited cartilage involvement may be managed with shaving when gross clearance is confidently achieved, whereas more extensive or deep cartilage invasion should lower the threshold for full-thickness resection. Shaving should not be used simply to avoid airway reconstruction when doing so knowingly leaves gross disease, because salvage surgery after recurrence is more morbid and less successful than appropriately planned primary resection [16].

*Window Resection*

A window resection removes the involved anterior or anterolateral tracheal wall through its full thickness while preserving the uninvolved circumference (Figure 18). It is particularly useful for localized full-thickness disease in which an adequate margin can be obtained without circumferential resection. Window resection should not be equated with sleeve resection, because tracheal continuity is maintained, end-to-end anastomosis is not the reconstruction after a window resection [89].

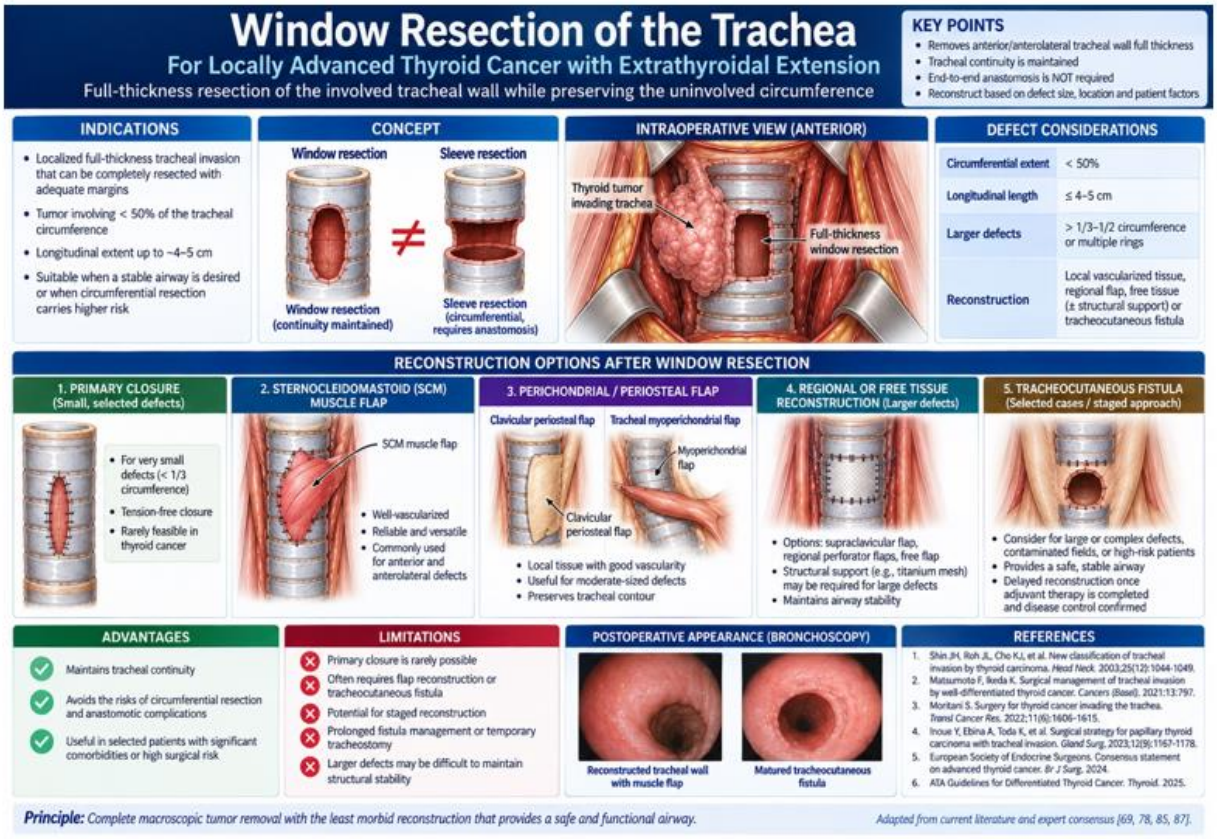



Figure 18: Window Resection of the Trachea for Locally Advanced Thyroid Cancer with ETE.

Feasibility is governed by defect size and location. Full-thickness defects are generally considered amenable to window resection when the tumor involves less than roughly 50% of the circumference over a segment up to about 4 to 5 cm; primary closure is rarely possible, so the defect is reconstructed with local vascularized tissue (sternocleidomastoid muscle or myoperichondrial flap, clavicular periosteal flap, supraclavicular or regional perforator flaps, or free tissue with titanium mesh support), or matured as a controlled tracheocutaneous fistula for

delayed / staged repair [16,87]. Larger defects, those greater than one-third to one-half of the circumference or spanning several rings, risk airway collapse and require structural support. Window resection is attractive when a stable airway is desirable or when the physiologic and technical risks of circumferential resection are substantial; its disadvantages include potential staged reconstruction, prolonged fistula management, temporary tracheostomy, and, for larger defects, difficulty maintaining structural stability [16,80].

Contemporary comparative evidence does not establish a universal oncologic advantage of sleeve over window resection. In a 2023 series of 51 patients with PTC requiring full-thickness resection, Inoue and colleagues compared sleeve resection with end-to-end anastomosis against window resection with tracheocutaneous fistula; sleeve resection was associated with shorter hospitalization and less permanent tracheostoma dependence, whereas local recurrence-free and cause-specific survival did not differ significantly, although window resection was preferentially used in more advanced disease, limiting direct comparison [93]. A meta-analysis of 96 studies and 1,179 patients likewise reported broadly overlapping outcomes, with circumferential resection yielding major complications in ~ 14% of cases, locoregional recurrence ~ 15% of cases, and 5-year overall survival ~ 75%, versus ~ 20% major complications, ~ 26% locoregional recurrence, and ~ 77% overall survival after window resection, figures constrained by heterogeneity and selection [94].

Where a full-thickness defect is intermediate, involving less than ~ 60% of the circumference but with a unilateral longitudinal defect approaching 5 to 7 cm, both standard window flap repair (risking collapse) and sleeve anastomosis (risking excess tension) are suboptimal. In this niche, spiral tracheoplasty and adjacent tracheal-flap ("modified spiral") techniques have been described, achieving high decannulation rates without anastomotic dehiscence or significant stenosis in small cohorts [80,87].

Following window resection, a vascularized SCM–clavicular periosteal flap can provide single-stage reconstruction of selected noncircumferential tracheal defects. A periosteal segment slightly larger than the airway defect is elevated from the medial clavicle while maintaining its attachment to the SCM, which serves as the vascular pedicle (Figure 19). The SCM is mobilized only sufficiently to permit tension-free medial transposition, avoiding unnecessary dissection that could compromise its vascular supply. The myoperiosteal flap is then rotated into the tracheal defect and secured to the residual tracheal wall, providing vascularized coverage and structural support. Temporary intraluminal stenting with a T-tube may be used for larger reconstructions. Because the periosteum is initially less rigid than native tracheal cartilage, careful patient and defect selection is essential to minimize postoperative deformation and airway stenosis [95].

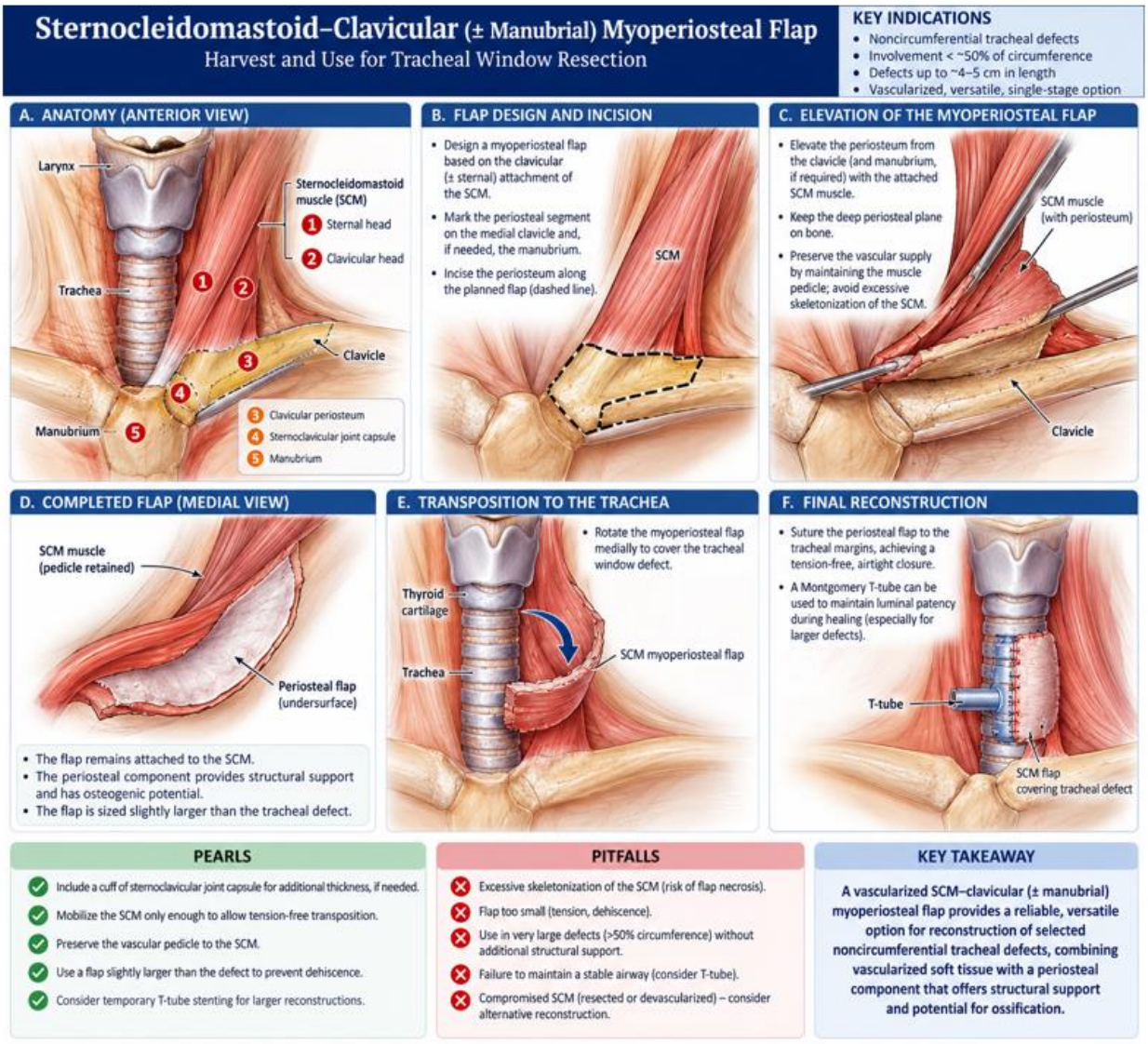



**Figure 19:** Sternocleidomastoid-Clavicular Myoperiosteal Flap.

*Circumferential (Sleeve) Tracheal Resection and Primary Anastomosis*

Circumferential or sleeve resection is most appropriate when deep invasion is extensive, involves a substantial portion of the circumference (generally > 50%), or cannot be oncologically encompassed by a limited window resection. The involved segment is removed circumferentially and continuity restored with a primary end-to-end anastomosis. When feasible, this permits complete full-thickness pathologic assessment, provides a normal mucosa-lined airway, avoids a permanent tracheal defect, and completes reconstruction in a single stage [89].

Sleeve resection is generally considered feasible for a resection length under about 5 cm, corresponding to up to roughly nine tracheal rings after adequate mobilization [80]. The principal limitation is the risk of anastomotic complications, dehiscence, ischemia, stenosis, and airway compromise. A systematic review of 37 studies comprising 656 patients undergoing crico-tracheal resection and anastomosis for locally advanced thyroid carcinoma reported

pooled perioperative mortality of ~ 2%, overall surgical complications in ~ 27% (unilateral or bilateral RLN palsy being most common), and permanent tracheostomy in ~ 4%, with 5-year overall survival of 61% to 100% and 5-year DSS of 75.8% to 90% [96]. These outcomes were mirrored in a 2026 single-institution cohort of 120 patients undergoing segmental tracheal resection for thyroid cancer (68% PTC; median 4 rings resected), perioperative mortality 3%, 30-day return to the operating room 22%, anastomotic air leak 6%, permanent tracheostomy dependence 9%, and new vocal-fold paralysis 33% (predominantly from planned RLN sacrifice), with 5-year locoregional control and overall survival of 79% and 77%, respectively [81]. Extension of the resection onto the cricoid plate and poorly differentiated histology are adverse prognostic factors [38]. Collectively these data support feasibility in appropriately selected patients while underscoring why complex airway resection should be concentrated in experienced multidisciplinary centers.

*Mobilization and Preservation of Tracheal Blood Supply*

A successful primary anastomosis depends as much on vascularity and absence of tension as on the suture line itself. The trachea receives a segmental blood supply entering predominantly through lateral vascular pedicles that form longitudinal intramural networks; extensive circumferential skeletonization of the residual proximal and distal trachea must therefore be avoided. Circumferential dissection should be confined to the segment requiring resection, and lateral dissection adjacent to the future anastomosis minimized [97,98]. This principle is reinforced in laryngotracheal thyroid resections, where simultaneous neck dissection, strap-muscle sacrifice, or resection of a patch of esophageal muscle can devascularize the tracheal wall and predispose to dehiscence, a rationale for buttressing the anastomosis with a sternocleidomastoid or other vascularized flap [90].

Before any formal release maneuver, additional length should be obtained through conservative anterior mobilization (Figure 20). The relatively avascular pretracheal plane is developed with gentle sharp and blunt dissection and extended inferiorly toward the superior mediastinum as required. The essential principle is to mobilize anteriorly rather than skeletonize laterally, preserving the lateral vascular pedicles of both anastomotic ends. Following resection, the ends are approximated and tension assessed. Neck flexion decreases the distance between the larynx and mediastinal trachea and is a fundamental component of tension reduction; anterior / pretracheal mobilization together with neck flexion and paratracheal dissection allows resection of up to approximately 4 cm without additional maneuvers [99,100].

The practical sequence is therefore: anterior / pretracheal mobilization → preservation of lateral vascular attachments → neck flexion → reassessment of comfortable approximation, with formal release added only when unacceptable tension remains

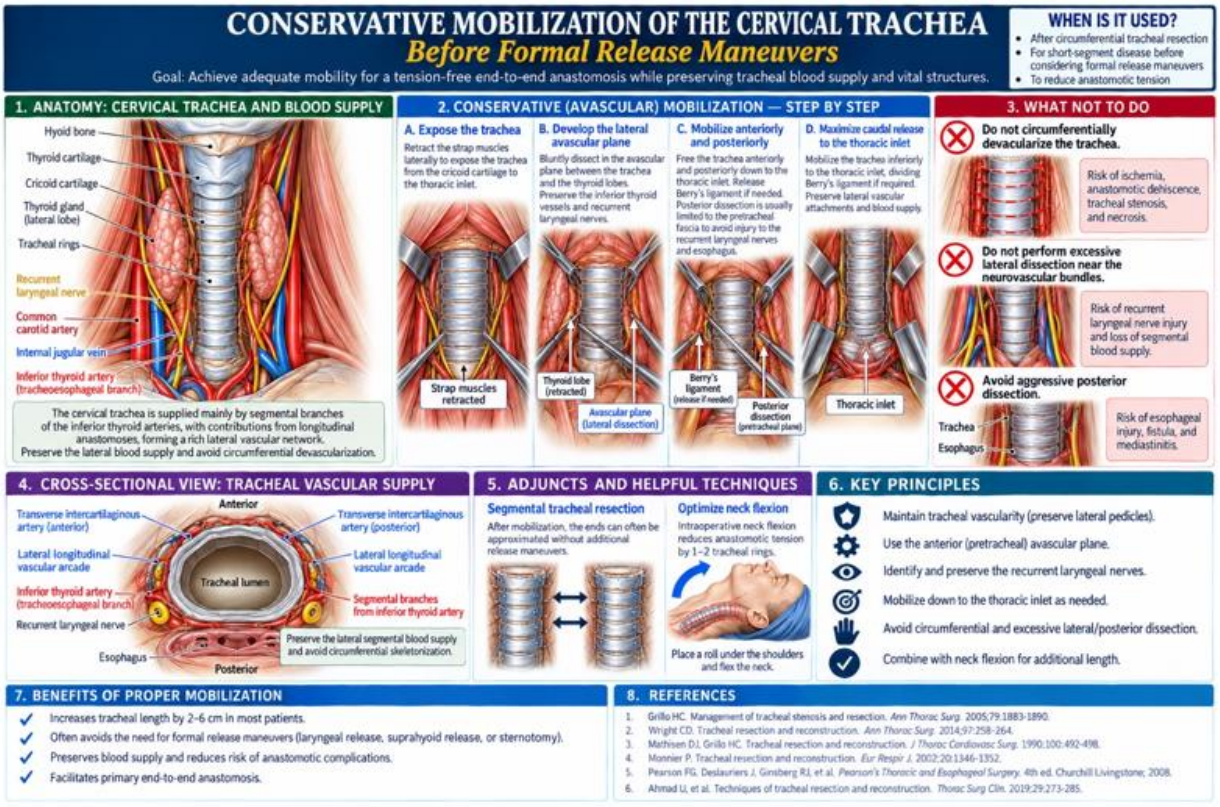



**Figure 20:** Mobilization of the Cervical Trachea Before Formal Release Maneuvers.

*Release Maneuvers*

For cervical tracheal resections, persistent anastomotic tension despite standard mobilization and neck flexion may be addressed with a suprahyoid laryngeal release (Montgomery maneuver), first described in 1974 (Figure 21). By dividing selected suprahyoid attachments while preserving critical lateral structures, the larynx descends caudally to provide approximately 1 to 2 cm of additional mobility, and full release can permit resection of substantially more of the tracheal length [99,101]. Because laryngeal release disrupts the suprahyoid and infrahyoid musculature and limits laryngeal elevation, it increases the risk of postoperative dysphagia and aspiration. Therefore, it should be employed selectively and tailored to the length of resection: limited release for short resections, and full release only for long ones [100,101].

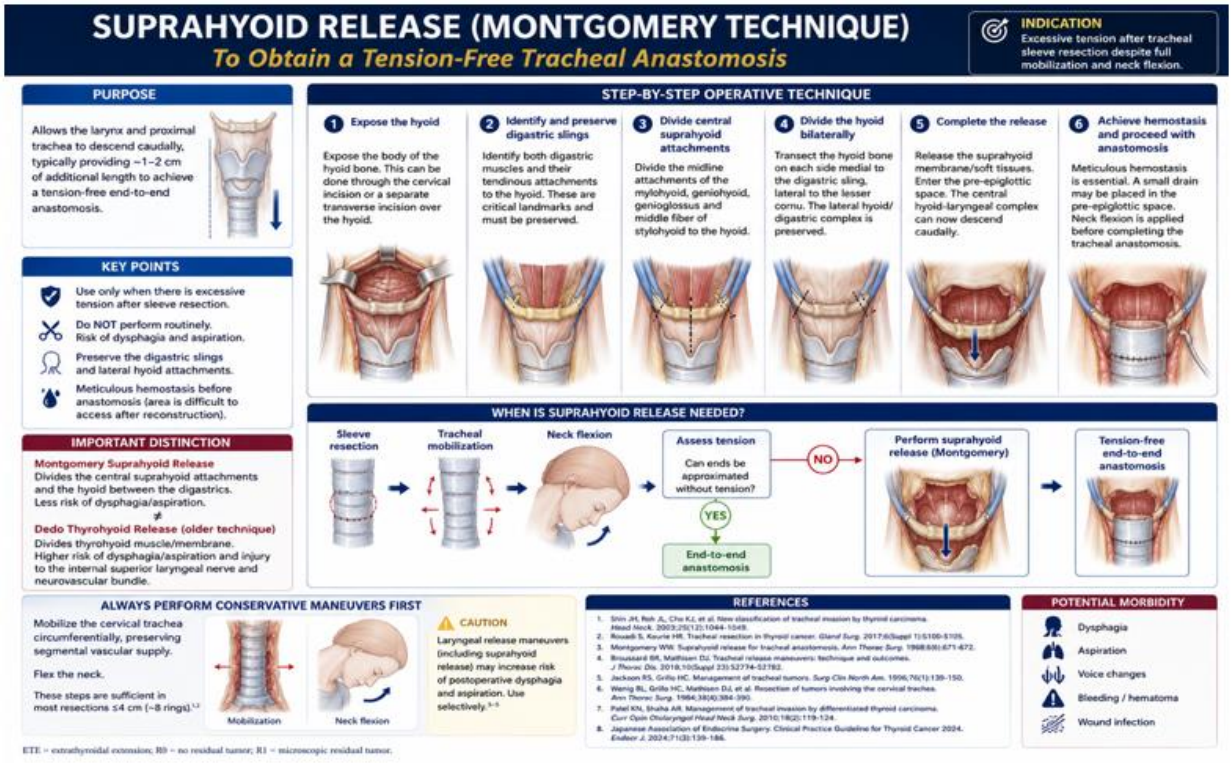



**Figure 21:** Suprahyoid Release.

More extensive inferior mediastinal, pericardial, or hilar release maneuvers are established in thoracic tracheal surgery and can now be performed via minimally invasive (VATS) approaches but are rarely required for typical cervical thyroid-cancer resections [99]. In a large MGH series, release maneuvers were used in only ~ 11% of airway resections and were not themselves associated with anastomotic complications; because intraoperative assessment can underestimate tension, a lower threshold for release is prudent, particularly in diabetic patients and after resections ≥ 4 cm [102]. If a proposed resection would require extensive release simply to approximate the airway, the surgeon should reconsider whether primary anastomosis is appropriate or whether an alternative reconstruction would provide a safer airway.

*Technique of Primary Tracheal Anastomosis*

Following circumferential resection, both ends should be inspected for viability and oncologic adequacy; frozen-section assessment of proximal and distal airway margins may be useful when margin status is uncertain. The anastomosis should achieve accurate mucosa-to-mucosa approximation without deliberate eversion or excessive inversion. Preservation of blood supply and avoidance of suture tension matter more than the specific suture material [97,103].

Interrupted absorbable sutures are widely used. The classic Massachusetts General Hospital / Grillo technique employs 4-0 absorbable polyglactin; contemporary airway surgeons may also use 3-0 or 4-0 polydioxanone (PDS). Full-thickness bites are placed several millimeters from the cut edge, with the posterior membranous wall generally aligned first (often as a continuous "parachute" suture), followed by the lateral and anterior cartilaginous portions with

interrupted pericartilaginous sutures. Sutures are tightened to approximate — not strangulate — the tissue, and knots are positioned extraluminally to reduce intraluminal foreign-body exposure and granulation [98,103].

After completion, the anastomosis is inspected for symmetric approximation and tested for an air leak under saline with positive-pressure ventilation. The neck is maintained in sufficient flexion during early healing, secured with a guardian chin-to-chest ("sterno-mental") suture in some protocols. Where feasible, a tracheostomy at the time of resection should be avoided, as it may compromise the structural integrity of the anastomosis and introduce saliva and bacteria into the surgical bed; in the 2026 segmental-resection cohort, most patients who did require a perioperative tracheostomy were later decannulated [81]. Postoperative vigilance is required for subcutaneous emphysema, air leak, wound infection, stridor, respiratory deterioration, vocal-fold dysfunction, and signs of anastomotic ischemia or dehiscence; early bronchoscopy directly assesses mucosal viability when the integrity of the reconstruction is in question [103].

*Oncologic and Multidisciplinary Considerations*

The extent of airway surgery should not be dictated by the T category alone. T4a defines anatomic extent; it does not mandate a particular tracheal operation. The least morbid procedure capable of achieving complete macroscopic clearance should be selected according to depth, longitudinal and circumferential involvement, RLN and laryngeal function, involvement of the esophagus or larynx, distant disease burden, patient comorbidity and habitus, and the anticipated role of postoperative therapy [81,89]. The AHNS consensus emphasizes weighing the morbidity of resection against the need for negative margins and stresses multidisciplinary decision-making [16].

The literature should not be read as proving that sleeve resection is oncologically superior to window resection or to appropriately performed shaving in all patients. Most studies are retrospective, patient selection differs substantially between procedures, more aggressive operations are performed for anatomically more advanced tumors, and at least one large cT4a PTC analysis found no independent effect of tracheal technique on progression-free survival [92,94]. The central principle is procedure selection according to the actual pattern of invasion rather than maximal resection for its own sake.

When gross tracheal invasion is encountered unexpectedly and adequate resection and reconstruction cannot be performed safely by the operating team, knowingly leaving gross disease merely to complete the operation should be avoided when referral remains feasible. The AHNS consensus explicitly favors referral to a tertiary center over staging the airway resection after thyroidectomy when appropriate expertise is unavailable — a point reinforced by the fact that salvage tracheal resection after prior surgery, fibrosis, or recurrence is technically harder and more morbid than planned primary resection [16,101].

Finally, airway resection must be integrated into the overall oncologic strategy. RAI remains an important adjuvant, with survival benefit demonstrated even among T4a patients with tracheal invasion in some series [92]. The 2025 ATA guidelines permit selective consideration of postoperative EBRT in patients with high-risk features for locoregional progression — gETE, visceral or soft-tissue invasion, aggressive histology, or positive margins — especially when anticipated progression would not be amenable to surgical salvage; EBRT with or without concurrent chemotherapy may also be considered for gross residual or unresectable disease [4]. This is a conditional, low-certainty recommendation: retrospective and propensity-matched data (including improved 10-year locoregional

relapse-free survival and, in the pT4a subset, better local failure-free survival with EBRT plus RAI) suggest improved locoregional control, but a consistent overall-survival benefit has not been demonstrated, one SEER analysis associated EBRT with worse survival in T4 PTC, and clinically meaningful acute and late toxicity is expected [4,84,104,105]. The decision, timing, and sequencing with RAI are best made by a multidisciplinary team including a radiation oncologist [14].

*Practical Surgical Principle*

Management can be summarized as a depth- and extent-adapted approach:

- Superficial invasion amenable to complete gross removal → shave resection.
- Localized full-thickness anterior / anterolateral involvement (< ~ 50% circumference, ≤ ~ 4 to 5 cm) → window resection with defect-appropriate reconstruction (vascularized flap or matured tracheocutaneous fistula), reserving spiral / adjacent-flap tracheoplasty for intermediate long-segment unilateral defects.
- Extensive, deep, or circumferential involvement (> ~ 50% circumference, ≤ ~ 5 cm / ~ 9 rings) → circumferential sleeve resection with tension-free primary end-to-end anastomosis.
- Regardless of technique, durable reconstruction depends on preservation of segmental tracheal vascularity, minimal unnecessary lateral dissection, accurate mucosal approximation, and avoidance of anastomotic tension.

These principles reconcile oncologic clearance with the functional goal that should guide surgery for locally advanced thyroid carcinoma, complete macroscopic removal of disease while preserving a safe, stable, functional airway whenever oncologically appropriate.

*Esophageal Invasion in Locally Advanced DTC*

Esophageal invasion is an uncommon but clinically consequential manifestation of gETE in DTC. In the AJCC eighth edition staging system, gross invasion of the esophagus constitutes T4a disease irrespective of primary tumor size; in patients aged 55 years or older this corresponds to AJCC prognostic Stage III, distinguishing it from prevertebral fascia or major-vessel invasion (T4b, Stage IVA) [4,28]. The 2025 ATA guidelines recommend total thyroidectomy with gross removal of all primary tumor for cancers demonstrating gETE (cT3b or cT4), unless contraindications preclude this approach [4]. Involvement of the esophagus should not, however, automatically imply a need for full-thickness esophageal resection. The operative strategy is determined principally by the depth, circumference, and longitudinal extent of esophageal wall invasion, together with the feasibility of complete macroscopic tumor removal while maintaining acceptable swallowing and airway function [16,38,39,42].

Aerodigestive tract invasion is reported in approximately 10% of DTC series overall, with locally invasive disease identified in roughly 6% to 15% of patients at diagnosis; the esophagus is among the less commonly involved structures [106]. Reported rates rise substantially in selected tertiary cohorts: in the MSKCC experience with 153 highly selected patients undergoing surgery for gross locally advanced DTC, the esophagus was involved in 39.2%, emphasizing that figures from referral cohorts should not be extrapolated to unselected DTC populations [10]. Esophageal invasion frequently accompanies involvement of the trachea and RLN, which were involved in 46.4% and 51.0% of the MSKCC cohort, respectively, and may arise from direct posterior extension of the primary tumor or from extranodal extension of paratracheal or paraesophageal nodal metastases [9,10,16,106].

*Preoperative Evaluation and Surgical Planning*

When esophageal invasion is suspected, the objective of preoperative evaluation is not simply to establish whether the tumor contacts the esophagus, but to determine whether invasion is limited to the muscular wall or extends through the submucosa and mucosa. The 2025 ATA guidelines recommend contrast-enhanced CT or MRI of the neck and mediastinum, in addition to ultrasound and physical examination, when gETE or aerodigestive involvement is suspected [4]. Cross-sectional imaging is particularly valuable for defining the relationship of the tumor to the tracheoesophageal groove, RLN, esophagus, larynx, major vessels, and mediastinal structures.

MRI performs well for esophageal wall assessment, with reported predictive values of 82% and 100% for outer-layer and inner-layer invasion, respectively, whereas contrast CT is highly specific but relatively insensitive for esophageal invasion [16]. When intraluminal extension is suspected, preoperative esophagoscopy, with or without endoscopic ultrasonography, may provide additional information regarding mucosal involvement, although the yield is generally low because intraluminal extension is rare [4,16].

Radiographic abutment or loss of the fat plane between the tumor and esophagus should not, by itself, be interpreted as transmural invasion. The final assessment of depth frequently occurs intraoperatively. The esophageal mucosa and submucosa are relatively resistant to direct invasion, and thyroid carcinoma involving the esophagus most commonly affects the external muscular layer while sparing the mucosa and submucosa [16,106]. This distinction is critical because muscularis-only involvement can usually be managed without entering the esophageal lumen.

*Surgical Management According to the Pattern of Esophageal Invasion*

- Tumor Abutment Without Definitive Esophageal Wall Invasion

When the tumor abuts the esophagus, but a clear surgical plane can be developed without leaving gross disease, esophageal resection is unnecessary (Figure 22). The tumor should be separated using meticulous sharp dissection, avoiding unnecessary thermal injury to the esophageal wall. Apparent adherence should not automatically be interpreted as invasion, particularly in previously biopsied, inflamed, or reoperative fields.

The distinction between adherence and true invasion is ultimately an intraoperative judgment. If separation exposes a grossly uninvolved esophageal muscular wall and complete macroscopic tumor removal has been achieved, additional esophageal resection provides no established oncologic benefit. Conversely, attempting to peel gross tumor away from demonstrably invaded muscularis simply to preserve the muscle risks leaving macroscopic disease and should be avoided [9,16,38,106].

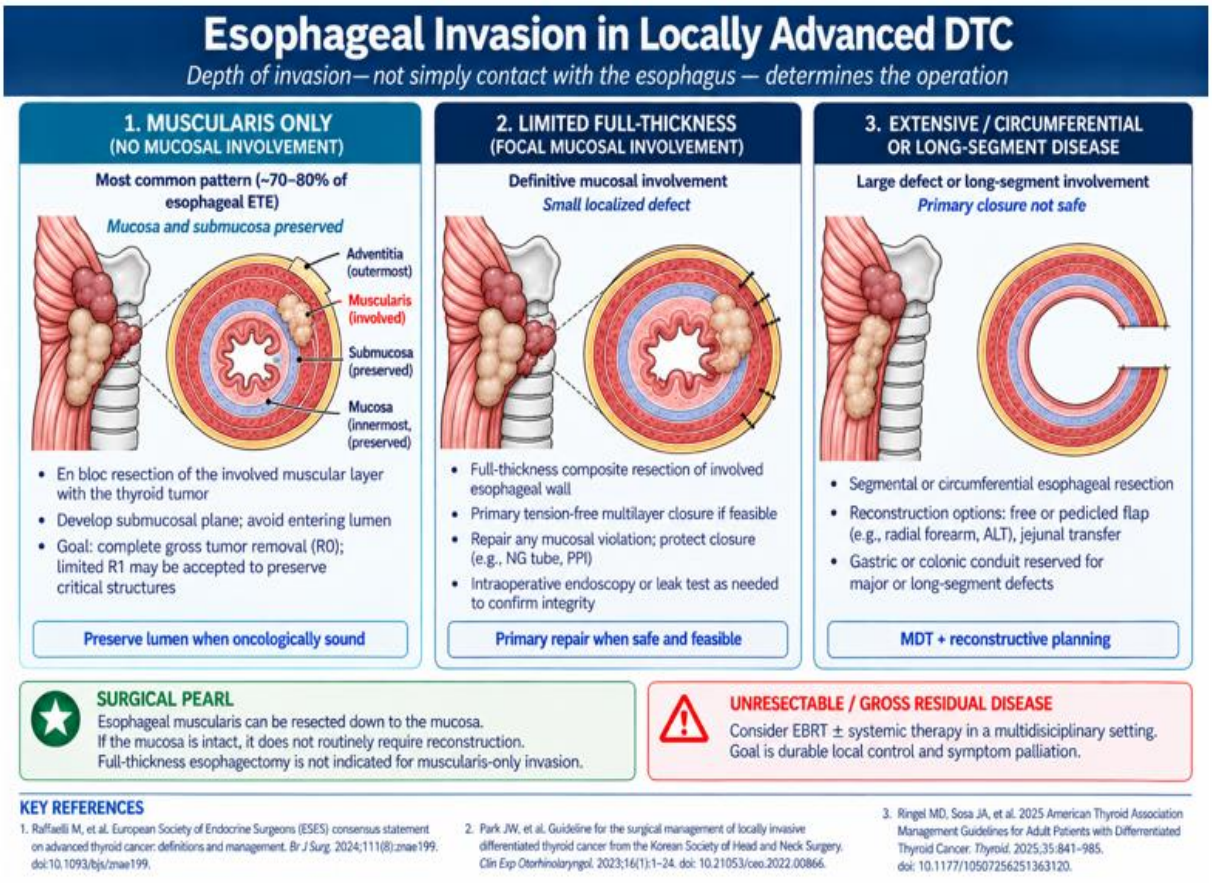



**Figure 22:** Management of Esophageal Invasion in Locally Advanced DTC.

- Invasion Limited to the Muscularis: Extramucosal Resection

The most characteristic pattern of esophageal invasion by DTC is involvement of the muscularis with preservation of the submucosa and mucosa [16]. In this setting, the preferred operation is en bloc resection of the involved muscular layer with the thyroid tumor while preserving the underlying submucosal / mucosal tube.

The AHNS consensus specifically states that thyroid tumors without intraluminal esophageal invasion can be managed by resection of the involved muscularis while avoiding esophageal entry [9,16]. Contemporary European guidance similarly supports removal of involved esophageal muscle down to the mucosa when the lumen is not involved [38]. Dissection is most safely performed by identifying an uninvolved plane proximal or lateral to the area of invasion and developing the plane between the muscularis and submucosa (Figure 23). The involved muscular tissue is then incorporated en bloc with the tumor rather than shaved away from it. A nasogastric / orogastric tube or esophageal bougie / dilator can be useful in selected cases to define the lumen and provide tactile guidance during posterior dissection [106].

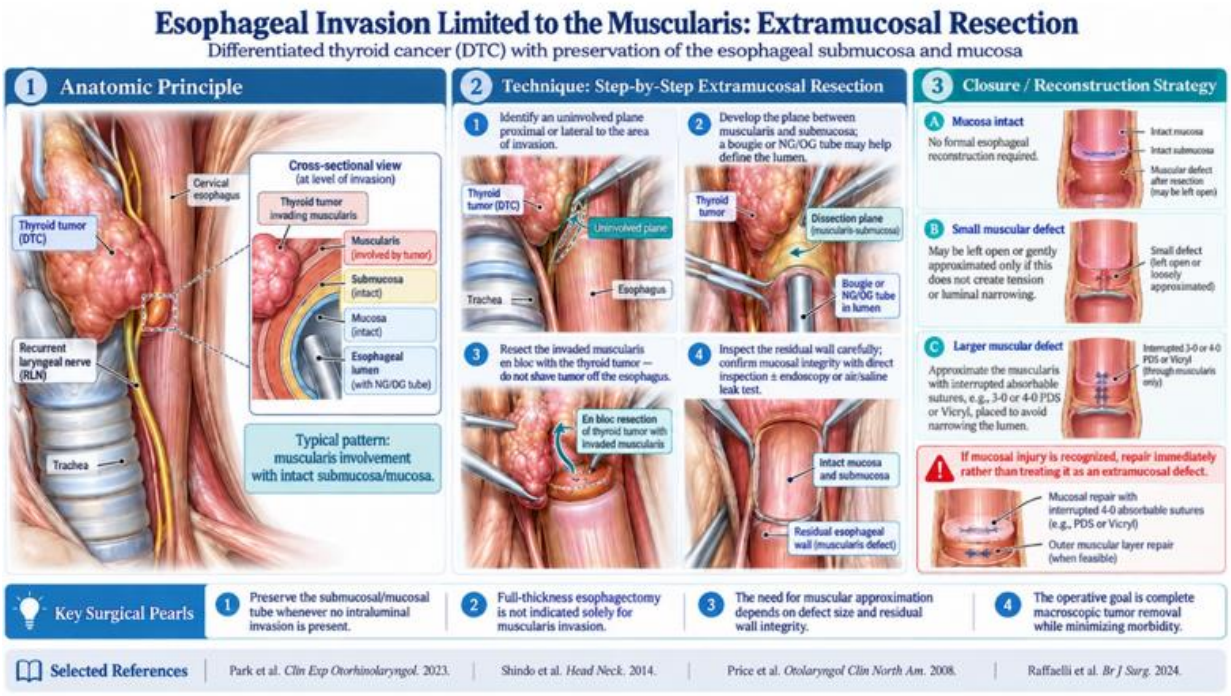



**Figure 23:** Extramucosal Resection of Locally Advanced Thyroid Cancer.

The residual mucosa should be carefully inspected. If the mucosa and submucosa remain intact, formal esophageal reconstruction is generally unnecessary. Small muscular defects may be left without reconstruction, whereas larger defects can be approximated when this can be achieved without tension or luminal narrowing. A mandatory "two-layer closure" should therefore not be stated as a requirement for muscularis-only resections; the need for muscular approximation is determined by defect size and residual wall integrity [16,38,106]. If mucosal integrity is uncertain, direct inspection, intraoperative endoscopy, and / or an air or saline leak test may be used selectively. An occult mucosal injury recognized intraoperatively should be repaired immediately rather than treated as an extramucosal defect.

Formal full thickness esophagectomy is not indicated solely for muscularis invasion. Escalating an otherwise complete extramucosal resection to full-thickness resection merely to obtain a wider radial margin may substantially increase morbidity without established oncologic benefit.

- Focal Full-Thickness or Mucosal Invasion

Once tumor penetrates the submucosa or mucosa, an extramucosal muscular resection is no longer oncologically appropriate. The AHNS consensus recommends composite full-thickness excision for tumors demonstrating full-thickness esophageal involvement [16].

For a small, localized area of transmural invasion, the involved esophageal wall should be removed en bloc with the tumor (Figure 24). The defect may be managed by primary tension-free multilayer closure when the remaining tissue is healthy and adequate luminal caliber can be maintained, an approach specifically supported by the AHNS consensus

for small full-thickness defects, with multilayered closure recommended to prevent salivary leak and a salivary bypass tube used selectively during healing [16].

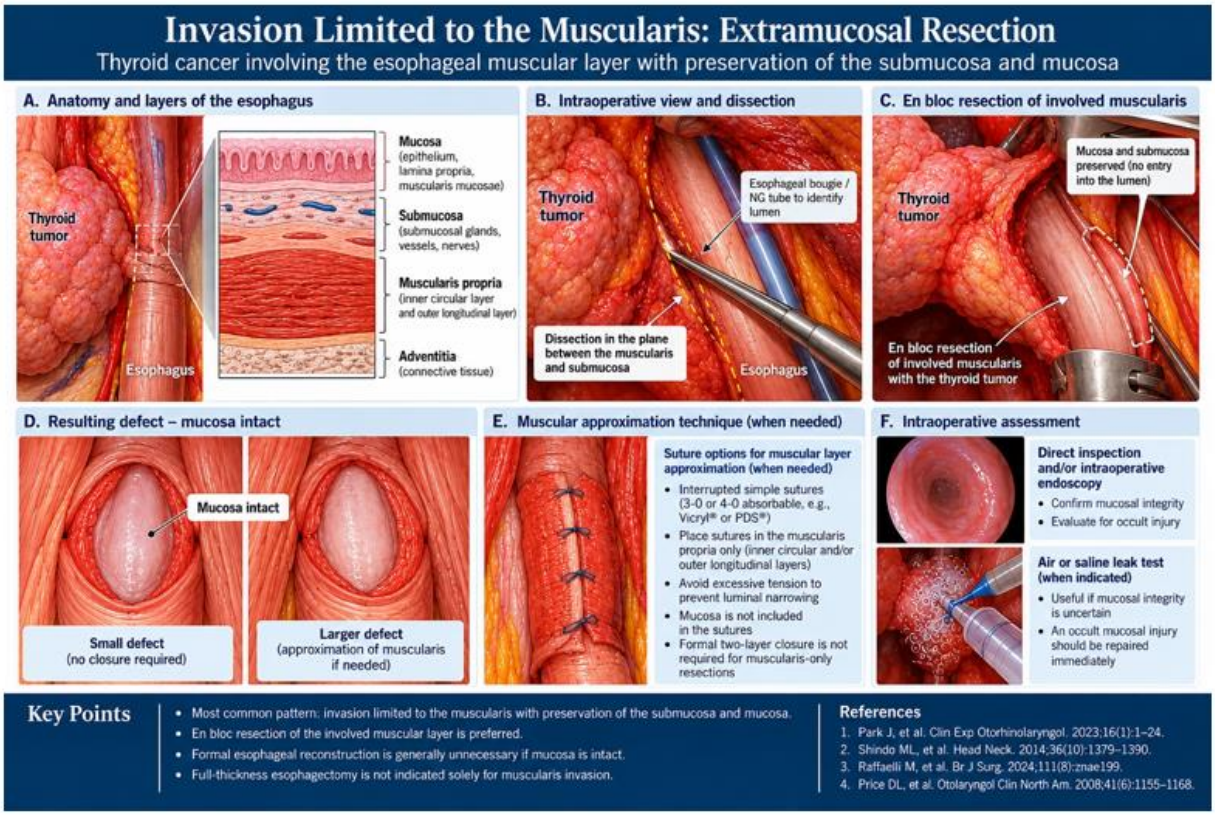



**Figure 24:** Management of Full Thickness Involvement.

Closure should be oriented to minimize stenosis, with particular attention to preserving vascularity of the residual esophageal wall. Adequacy of the repair can be assessed by direct inspection and selective endoscopic or leak testing. Vascularized tissue reinforcement should be considered when the closure is tenuous, when a simultaneous airway resection has been performed, or in previously irradiated or otherwise compromised tissue.

Focal mucosal invasion therefore does not automatically require segmental esophagectomy. A limited full-thickness composite resection with primary repair may achieve complete gross removal while preserving substantially greater swallowing function.

- Large Partial-Circumferential Defects

When full-thickness tumor involvement produces a defect too large for primary closure without excessive tension or clinically significant luminal narrowing, reconstruction with vascularized tissue becomes necessary. The operative strategy depends on the longitudinal length of the defect, percentage of circumference removed, proximity to the hypopharynx, associated tracheal or laryngeal resection, previous radiation, and the condition of the remaining esophagus.

Partial-circumferential defects can be reconstructed using pedicled myofascial or myocutaneous tissue (e.g., pectoralis major or sternocleidomastoid muscle) or free tissue transfer. Fasciocutaneous free flaps, particularly the radial forearm

and anterolateral thigh flaps, provide thin, pliable tissue suitable for patch reconstruction of selected cervical esophageal defects. The AHNS consensus recommends pedicled or free-flap reconstruction for extensive esophageal defects [16]. Reconstruction should restore a well-vascularized conduit of adequate caliber while separating the esophageal lumen from the carotid sheath, any tracheal reconstruction, and other exposed critical structures. When simultaneous tracheal or laryngotracheal reconstruction is required, interposition of vascularized tissue between suture lines is particularly valuable.

- Circumferential or Long-Segment Esophageal Invasion

Extensive circumferential or long-segment transmural involvement represents a fundamentally different reconstructive problem. If complete macroscopic resection remains appropriate from an oncologic and functional standpoint, segmental or circumferential esophagectomy may be required [16,106]. Reconstruction should be planned before tumor resection in conjunction with an experienced reconstructive team. Options include a tubed radial forearm free flap, anterolateral thigh free flap, free jejunal transfer, or other pedicled / free-tissue techniques. Free jejunum provides a mucosa-lined conduit and remains particularly useful for selected circumferential pharyngoesophageal defects. For exceptionally long defects extending into the thoracic esophagus, gastric transposition / pull-up or, less commonly, colonic interposition may be required [16,106].

These procedures carry substantially greater risks of fistula, stenosis, dysphagia, aspiration, nutritional dependence, and perioperative morbidity than extramucosal or limited full-thickness resections. Consequently, the decision to perform circumferential esophagectomy should incorporate more than technical feasibility, including tumor biology, distant disease burden, expected survival, available adjuvant / systemic therapy, baseline swallowing and pulmonary function, and anticipated postoperative quality of life.

- Combined Esophageal, Tracheal, and/or Laryngeal Invasion

Esophageal invasion frequently occurs as part of multivisceral central neck disease rather than as an isolated finding [10,106]. Combined involvement of the esophagus, trachea, larynx, and RLN substantially changes both the magnitude of resection and the functional consequences of surgery.

In these circumstances, the surgical plan should be developed around the entire aerodigestive defect rather than treating each involved structure independently. A limited esophageal muscular resection may remain reasonable even when an adjacent tracheal resection is required, whereas extensive circumferential esophageal involvement combined with major laryngotracheal disease may require complex pharyngolaryngoesophageal reconstruction. Preservation of one structure should not result in gross residual disease on another; conversely, multivisceral contact should not automatically trigger radical exenterative surgery when function-preserving complete gross resection is feasible.

Particular attention should be paid to avoiding juxtaposition of esophageal and airway suture lines. When simultaneous full-thickness repairs are required, interposition of well-vascularized tissue can help separate the reconstructions and may reduce the consequences of a leak or fistula.

Margin Status and the Extent of Resection

The operative objective in locally advanced DTC is complete macroscopic tumor removal, preferably with microscopically negative margins (R0). R0 and R1 resections should not be grouped together as "negative-margin

surgery": R0 indicates no microscopic residual tumor, R1 indicates microscopic residual tumor, and R2 indicates gross residual disease. This distinction is particularly relevant when deciding whether increasingly radical aerodigestive resection is justified solely to convert a potentially microscopic margin into a wider negative margin. In the MSKCC series of 153 patients with gross locally advanced DTC, 5-year DSS was 94.4% following R0 resection, 87.6% following R1 resection, and 67.9% following R2 resection, with no statistically significant difference between R0 and R1 [10]. Because these data are retrospective and subject to substantial selection bias, they should not be interpreted as demonstrating equivalence between R0 and R1 resection; they do, however, emphasize the adverse prognostic significance of leaving gross residual (R2) disease.

Accordingly, an R0 resection should be pursued when it can be achieved with acceptable morbidity. Radical esophageal sacrifice solely to obtain a wider microscopic margin should be weighed against the functional consequences when complete macroscopic tumor removal can otherwise be achieved. The principle is therefore oncologically complete but function-conscious surgery, rather than either indiscriminate organ preservation or indiscriminate radical resection. This is consistent with the 2025 ATA guidelines, which recommend total thyroidectomy with gross removal of all primary tumor for gETE while emphasizing multidisciplinary planning for advanced disease [4].

*Unresectable Disease and the Role of Multimodality Therapy*

Not all esophageal invasion should be approached surgically. The concept of resectability must incorporate both anatomical and oncologic considerations. Extensive esophageal involvement associated with unreconstructable vascular disease, prevertebral fixation, extensive mediastinal involvement, rapidly progressive distant metastases, or a requirement for an operation whose morbidity is disproportionate to the expected oncologic benefit may favor nonsurgical or multimodality management.

The 2025 ATA guidelines state that EBRT may be considered in select DTC patients with high-risk features for locoregional progression, including gETE, positive margins, and visceral or soft-tissue invasion, particularly when anticipated progression would not be amenable to salvage surgery. For patients with gross residual or locally advanced unresectable disease, EBRT with or without concurrent chemotherapy may be considered to improve locoregional control, although this evidence is of low certainty and toxicity must be carefully weighed [4].

Molecularly targeted systemic therapy may also alter the concept of resectability in selected patients with actionable alterations. For tumors in which the initial operation would require exceptionally morbid aerodigestive resection, multidisciplinary consideration of systemic therapy followed by reassessment of surgical options is reasonable in appropriately selected patients. At present, however, neoadjuvant targeted therapy should not routinely replace potentially curative surgery; the evidence remains disease- and genotype-specific and is derived predominantly from small retrospective series and institutional experience.

*Neoadjuvant Therapy for Locally Advanced DTC*

Locally advanced DTC invading the trachea, esophagus, larynx, RLN, or great vessels accounts for roughly 5% to 15% of DTC and is the principal driver of disease-specific mortality and surgical morbidity in an otherwise prognostically favorable disease [107,108]. In these patients, upfront complete resection may be impossible or achievable only at the cost of laryngopharyngectomy, tracheal or esophageal resection, RLN sacrifice, or vascular

reconstruction. Cytotoxic chemotherapy and radiotherapy alone offer negligible cytoreductive benefit in this setting [107]. Against this background, neoadjuvant targeted therapy, multikinase inhibitors (MKIs) and genotype-matched selective inhibitors, has emerged as a strategy to downsize tumors, retract them from vital structures, and convert unresectable or high-morbidity disease to a margin-negative (R0) or microscopically positive (R1) resection.

The efficacy of MKIs in radioactive iodine–refractory (RAIR) DTC provides the mechanistic basis for neoadjuvant use. In the phase III SELECT trial, lenvatinib produced an objective response rate of roughly 65% and improved median progression-free survival from 3.6 to 18.3 months versus placebo; sorafenib in DECISION trial yielded a roughly 12% response rate and improved median PFS from 5.8 to 10.8 months [109]. Lenvatinib's rapid and often substantial tumor shrinkage, mediated by potent VEGFR1-3, FGFR, RET, KIT, and PDGFR inhibition, creates a therapeutic window in which borderline-resectable or unresectable tumors can be reassessed for surgery [110]. In parallel, genotype-directed agents, RET inhibitors (selpercatinib, pralsetinib), NTRK inhibitors (larotrectinib, entrectinib, repotrectinib), and BRAF / MEK inhibitors (dabrafenib / trametinib), achieve deep, durable responses (e.g., selpercatinib and pralsetinib ORRs of ~ 79% and ~ 89% in RET fusion–positive DTC) with generally favorable tolerability, making them attractive for short-course preoperative cytoreduction in biomarker-selected patients [15, 111].

*Evidence for neoadjuvant therapy in DTC (Table 1)*

*Systematic review:*

- The most comprehensive synthesis to date pooled 119 patients across 23 observational studies plus two prospective phase II studies [112]. Lenvatinib was the most frequently used agent, followed by sorafenib and apatinib. Tumor volume reduction ranged from 25% to 87%, and partial response rates from 33.3% to 76.9%, with progressive disease in only seven cases. Of 114 patients with inoperable or high-morbidity resectable tumors, 95 (83.3%) proceeded to surgery, and R0 / R1 resection was achieved in 88.3% (83/95) of operated patients. A multicenter comparison found greater median volume reduction with lenvatinib than sorafenib (47% vs. 23%).

*Prospective trials:*

- In a single-arm phase II study, neoadjuvant surufatinib plus the anti–PD-1 antibody toripalimab in borderline-resectable / unresectable DTC produced an ORR of 60%; nine of ten patients underwent surgery with R0 / R1 resection in all operative cases [113].
- A single-arm phase II trial of neoadjuvant lenvatinib 24 mg daily (≥ 8 weeks) in locally advanced DTC reported an ORR of 33.3% and a disease control rate of 91.7%, with R0 / R1 resection in 8 of 9 operated patients (88.9%) [114].
- A separate neoadjuvant apatinib trial reported partial response in 53.8% with R0 / R1 resection in all operated patients [112].

Real-world and retrospective cohorts:

- A single-institution series of nine DTC patients treated with neoadjuvant TKIs (dabrafenib / trametinib, lenvatinib / pembrolizumab, or lenvatinib) for unresectable or high-morbidity disease achieved R0 resection in all who reached surgery, without major complications or aerodigestive resection, with visible response within weeks and most receiving therapy for less than six months [115].
- In a real-world cohort of advanced / unresectable DTC, median tumor-burden reduction was 23%; no patient progressed on therapy, all nine proceeded to surgery, and neoadjuvant treatment enabled R0 resection in two previously inoperable patients (prevertebral and carotid involvement), tracheal preservation in four, and avoidance of pharyngoesophagectomy in two, underscoring that even modest volumetric response can yield organ preservation [107].
- A CT-based patient-selection cohort of 23 patients treated with neoadjuvant lenvatinib used anatomical complexity scores to triage candidates and reported conversion to complete resection or surgical de-escalation in a substantial proportion [110].
- A scoping review of 122 patients found R0 in 62, R1 in 38, and R2 in 10, with 51% achieving R0 resection overall across mixed histologies [116].

Genotype-matched neoadjuvant therapy:

- Case reports demonstrate R0 resection after neoadjuvant selective inhibitors in biomarker-defined DTC: selpercatinib and pralsetinib each enabled R0 resection in RET fusion–positive PTC after approximately four months of therapy without major complications [117, 118]. These data support early molecular profiling to match therapy to driver alterations (BRAF V600E, RET, NTRK, ALK) before committing to a neoadjuvant regimen [115].

**Table 1:** Representative neoadjuvant studies in DTC

**Representative neoadjuvant studies in differentiated thyroid carcinoma (DTC)**

| Study (year) | Design / N | Agent(s) | Key efficacy | Surgical / margin outcome |
|---|---|---|---|---|
| **Primary studies** | | | | |
| Chen et al. (2023) | Phase II N = 10 | Surufatinib + toripalimab | ORR 60% | 9/10 underwent surgery; R0/R1 100% of operated |
| Yu & Wu (2023) | Phase II N = 12 | Lenvatinib 24 mg daily | ORR 33.3%; DCR 91.7% | 9/9 underwent surgery; R0/R1 88.9% of operated |
| Apatinib trial (per Bauzon 2025) | Phase II N = 13 | Apatinib | PR 53.8% | All operated patients underwent surgery; R0/R1 100% of operated |
| Dickerson et al. (2025) | Retrospective N = 9 | Lenvatinib ± pembrolizumab; dabrafenib + trametinib | Mean primary tumor reduction 61% | All operated patients underwent R0 resection; R0 100%; Aerodigestive structures preserved |
| Dorman et al. (2026) | Retrospective N = 9 | TKIs (lenvatinib; dabrafenib + trametinib) | Median tumor-burden reduction 23%; No progression | 9/9 underwent surgery; Organ-preserving resections achieved |
| **Evidence syntheses** | | | | |
| Bauzon et al. (2025) | Systematic review N = 119 | Lenvatinib > sorafenib > apatinib | Tumor-volume reduction 25–87%; PR 33.3–76.9% | 83.3% underwent surgery; R0/R1 88.3% of operated |
| Herzog et al. (2026) | Scoping review N = 122 (mixed) | Multiple regimens | PR 64%; CR 10% | R0 resection 51%; R0 / R1 / R2 62% / 38% / 10% |

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; R0, margin-negative resection; R1, microscopic residual disease; R2, macroscopic residual disease; TKI, tyrosine kinase inhibitor.

*Practical considerations*

Patient selection:

- Candidates are those with cT3b to cT4 or recurrent locoregional DTC that is unresectable or resectable only with unacceptable morbidity; selection is best made at a multidisciplinary tumor board with cross-sectional imaging and validated anatomical complexity / surgical morbidity scores (e.g., MMM score, Invasive Thyroid Class) [110,111]. Not all patients benefit, across several series only 55% to 66% ultimately proceeded to curative surgery, highlighting the need for reliable predictive markers [107].

Agent choice and dosing:

- Lenvatinib, typically started at 24 mg daily with dose modification for toxicity, is the most-used MKI and the preferred agent in RAIR DTC per NCCN and ATA; genotype-matched selective inhibitors are favored when an actionable driver is present [4, 110]. Dabrafenib / trametinib may be chosen in BRAF V600E tumors when VEGF-mediated fistula risk is a concern given tumor location, though response rates appear lower than lenvatinib [107].

Duration and timing of surgery:

- Reported treatment durations range from two to 18 months, most commonly under 6 months, with radiologic / clinical response often evident within 1 to 2 weeks and first formal reassessment at 12 to 16 weeks [110, 112]. A preoperative MKI washout of 2 to 4 weeks is typical to mitigate wound-healing and bleeding risk; the interval should generally not exceed three months because of the risk of regrowth or anaplastic transformation [112].

Safety:

- Adverse events are predominantly grade 1 to 2 (hypertension, diarrhea, fatigue, hand-foot skin reaction), but VEGF-pathway inhibition carries a risk of aerodigestive fistula, hemorrhage, and impaired wound healing, particularly relevant when tumors abut the trachea or esophagus [107, 113]. Careful perioperative management and dose holds are essential.

For locoregionally invasive, rapidly progressive, symptomatic, or RAIR DTC, lenvatinib is the category 1 preferred systemic agent, with genotype-matched selective inhibitors preferred for RET fusion–positive (pralsetinib, selpercatinib) and NTRK fusion–positive (entrectinib, larotrectinib, repotrectinib) tumors; sorafenib and cabozantinib are alternatives [14]. NCCN formally designates a neoadjuvant systemic-therapy pathway for borderline-resectable anaplastic carcinoma but does not yet define an analogous dedicated neoadjuvant algorithm for DTC, so neoadjuvant use in DTC remains an extrapolation from the advanced-disease systemic therapy principles and should be individualized through multidisciplinary review [14].

The 2025 ATA guidelines recommend first-line lenvatinib (starting 24 mg/day in most patients) and second-line cabozantinib for RAIR DTC without actionable alterations, with genotype-matched therapy (NTRK, RET, ALK first-line; BRAF V600E typically second-line) when drivers are present [119]. The guidelines explicitly acknowledge that for large, locally invasive DTC in whom R0 / R1 resection is unlikely without high morbidity, neoadjuvant systemic multikinase or targeted therapy with or without immunotherapy has been reported, with variable results depending on agent and toxicity, stopping short of a formal recommendation [4].

The 2026 ASCO guideline addresses systemic therapy for recurrent / metastatic RAIR DTC rather than neoadjuvant conversion specifically; it recommends first-line lenvatinib or sorafenib (lenvatinib preferred) and, for tumors harboring NTRK or RET fusions, genomically targeted therapy before MKIs [15].

Prospective evaluation is underway. Registered neoadjuvant DTC trials include lenvatinib with an R0 / R1 resection rate endpoint (NCT04321954), lenvatinib plus an immunotherapy agent with major pathologic response and R0 / R1 endpoints (NCT06848920), selpercatinib in RET-altered T3/T4 thyroid cancer (NCT05852223), donafenib plus sintilimab (NCT06787911), surufatinib (NCT05989425), and zanzalintinib (NCT06959511) [112].

Across prospective trials, retrospective cohorts, and a systematic review, neoadjuvant MKI and genotype-matched targeted therapy convert the majority of initially unresectable or high-morbidity locally advanced DTCs to resectable disease, with R0 / R1 resection achieved in roughly 85% to 90% of operated patients and meaningful rates of aerodigestive and neurovascular preservation. The evidence remains dominated by small, heterogeneous series without long-term oncologic outcomes, and a substantial minority of patients fail to reach surgery because of progression or inadequate response.

Early molecular profiling, multidisciplinary selection using anatomical complexity scoring, attention to VEGF-related perioperative risk, and defined washout and surgical timing are the current pillars of practice. Adequately powered prospective trials with standardized selection criteria, response assessment, and survival endpoints are needed to establish neoadjuvant targeted therapy as a standard conversion strategy in locally advanced DTC.

## CONCLUSION

Locally advanced thyroid cancer remains one of the most complex challenges in thyroid oncology, demanding a careful balance between oncologic control and the preservation of function. Optimal management hinges on accurate assessment of the extent and depth of invasion, meticulous surgical planning, and delivery of care within an experienced multidisciplinary team. Surgery remains the cornerstone of treatment for resectable disease, with the goal of complete macroscopic tumor removal while sparing the recurrent laryngeal nerve, airway, larynx, and esophagus whenever this is oncologically appropriate.

Advances in imaging, reconstructive techniques, molecular characterization, and targeted systemic therapy are increasingly enabling treatment to be individualized according to both anatomy and tumor biology. Neoadjuvant strategies may further expand surgical options for selected patients with disease that is initially unresectable or amenable only to highly morbid resection.

The central principle is that locally advanced thyroid cancer does not invariably require maximally radical surgery; rather, it requires the least morbid operation capable of achieving durable oncologic control. The extent of resection should be dictated by the structure involved, the depth of invasion, the underlying tumor biology, and the feasibility of complete gross resection. In experienced multidisciplinary centers, the thoughtful integration of precise surgery, reconstruction, and multimodality therapy offers the best opportunity to achieve the ultimate goal: long-term disease control without the unnecessary sacrifice of voice, swallowing, airway function, or quality of life.

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