

## Advanced Thyroid Cancer Controversy and Consensus

The overall incidence of differentiated thyroid cancers displaying aggressive behavior, by local invasion, distant metastasis, treatment resistance, and increased mortality ranges between 10% and 15%.<sup>[1-4]</sup> Due to this relatively low incidence and unstandardized definition for locally advanced thyroid cancers (LATC), there is a great amount of discrepancy regarding the definition and management of LATC. There is also a lack of good quality prospective studies to guide the correct approach and management of this group of patients. Majority of existing papers have a distinct heterogeneity in the subject population and disease characteristics. All existing guidelines are derived from retrospective observational studies with possible bias and incomplete data.

In this review, we would like to highlight the main controversies and possible consensus in the management of LATCs.

### Controversies in Locally Advanced Thyroid Cancers

#### Definition of locally advanced thyroid cancers

There is a lack of consensus in defining locally advanced thyroid cancers. The most commonly accepted definition of LATC is: any thyroid cancer, with tumor or nodal disease involving the recurrent laryngeal nerves (RLN), aerodigestive tract, great vessels (internal jugular vein and internal carotid artery), extensive soft-tissue involvement with or without multiple bulky bilateral nodal metastasis to the central or lateral compartment.

#### Preoperative evaluation

A sound clinical acumen is indispensable for the preoperative recognition of LATC. There are specific signs and symptoms associated with the disease invading into the surrounding structures, which must be recognized to raise suspicion of it being a LATC. Furthermore, it is important to note that the majority of LATCs maybe asymptomatic. Hence, in many cases, clinical examination and symptomatology maybe the only guide to investigate further for LATC and to plan the necessary treatment strategies.

The common symptoms which will guide the clinician to suspect LATC include change of voice, voice weakness, vocal fatigue or hoarseness, suggesting RLN or laryngeal involvement; dyspnoea, stridor, hemoptysis, suggesting laryngotracheal framework involvement; and odynophagia and/or dysphagia, suggesting pharyngeal or esophageal involvement. Neck pain, neck stiffness, and inability to extend the neck suggest involvement of the prevertebral muscle or fascia. The presence of large cervical metastatic

nodes and/or inability to feel the lower border of the thyroid swelling may suggest mediastinal extension.

Routine ultrasonography alone may not be sufficient to map the extent of the disease in LATC, and cross-sectional imaging is required for the complete evaluation of a thyroid nodule with clinical signs and symptoms of extrathyroid extension. Contrast-enhanced computed tomography (CECT) is the diagnostic imaging of choice in most patients where one suspects advanced disease.<sup>[5]</sup> The sensitivity and specificity of predicting RLN involvement by CECT were found to be 78.2% and 89.8%, respectively. Tracheal infiltration can be assessed by the degree of tumor contact with the trachea [Figure 1], a contact  $>90^\circ$  of tracheal circumference on a computed tomography (CT) scan is sensitive in 68.1% and specific in 76.6% for the prediction of tracheal involvement.<sup>[6]</sup> Shin *et al.*<sup>[7]</sup> described the pathological staging of papillary thyroid carcinoma with airway invasion. In their article, a system of five stages of tracheal invasion based on the resected specimens was described. There is, however, no published data on the validation of CECT for Shin's pathological staging of tracheal invasion, but radiologists should be encouraged to report tracheal involvement by thyroid cancers as per Shin's classification. With regard to esophageal involvement, CT scan may not have a good low sensitivity to detect invasion into the layers of the esophageal wall, especially the outer layer.<sup>[6]</sup>

Magnetic resonance imaging (MRI) may add to CECT for the prediction of invasion into the RLN, laryngotracheal complex, and esophagus. Although MRI has a slight edge over CECT to predict the invasion into the esophagus and

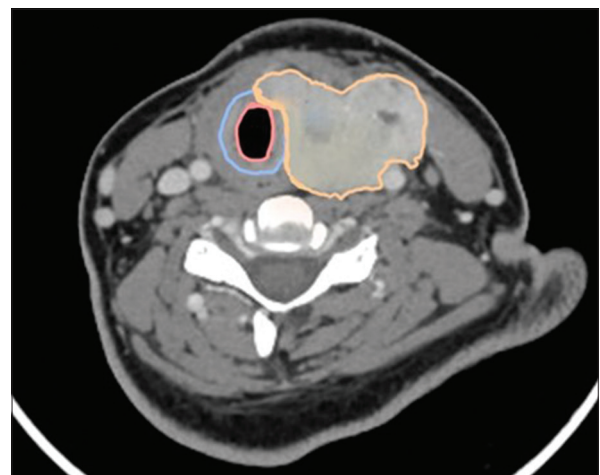


Figure 1: Contrast enhanced computed tomography scan of locally advanced thyroid cancer with disease infiltrating into the trachea without mucosal breach (Shin III). (Orange – tumour outline, Blue – Tracheal cartilage and Pink – Tracheal mucosa)

RLN, it lacks the ability to predict the depth of tracheal invasion in comparison with CECT.<sup>[6,8,9]</sup> Esophageal involvement is a rare occurrence even in LATCs, and MRI is generally reserved as a problem-solving tool.

Tracheo-bronchoscopy and esophagoscopy may provide additional information about the invasiveness of the disease and help in surgical planning. Endoscopic ultrasonography (EUS) has a better accuracy than the conventional esophagoscopy and MRI to detect in the esophageal infiltration.<sup>[10,11]</sup> The EUS was able to better detect the depth of infiltration into the esophagus leading to accurate surgical plan.<sup>[10]</sup> EUS has its drawbacks because (a) the upper portions of the thyroid gland cannot be imaged by EUS, primarily due to the lack of all five esophageal layers at this site, as the lower pharyngeal constrictor muscle transforms to the esophageal muscularis propria and the gag reflex and (b) EUS also cannot determine minor muscular propria invasion.<sup>[10,11]</sup>

### Surgical Issues

An attempt to perform a complete resection (R0) is vital and offers the patient the best possible chance of cure.<sup>[12]</sup> As per the Memorial Sloan Kettering LATC case series, elderly patients, tumors more than 4 cm in size, gross residual disease, and distant metastases were the predictors of poor survival.<sup>[12]</sup> The spectrum of surgeries performed in patients with LATC range from a total thyroidectomy with bilateral central and lateral neck dissections to multiorgan resections, sometimes requiring sternotomies and vascular resections. The aim of performing such extensive surgeries is to achieve R0/R1 resections, thus optimizing the outcomes. A balance between the morbidity of such surgeries, the poor prognostic factors, and the possible outcomes should be maintained before decision-making. Radical surgeries must not be performed in poor surgical candidates and in patients with poor prognosis.

### Intraoperative neuromonitoring use versus no use

Intraoperative neuromonitoring (IONM) can help the surgeon identify the RLN in a distorted anatomy, it can estimate the residual nerve function following surgery, it can provide pointers to decision-making when both the RLN are at risk due to bilateral disease and the postoperative residual nerve potential might provide clues to possible postoperative complications. The exact role of IONM has not been clearly defined and whether IONM can decrease the incidence of temporary or permanent RLN palsy, especially in these cancers, is a matter of contention.

In a meta-analysis by Bai and Chen consisting of 34 studies, they found a significant decrease in total injury, transient injury, and permanent injury with IONM. A subgroup analysis reported that IONM had a prevented the complete, permanent, and transient RLN paralysis in total thyroidectomies. It also reduced the rate of complete and transient RLN injury in thyroidectomies for

malignancies.<sup>[13]</sup> However, a Cochrane systematic review by Roberto Cirocchi in 2019 showed that there was no distinct advantage of IONM versus visual identification in the permanent and transient RLN palsies.

It is also found that IONM is cost-effective when the prevalence of transient nerve injury is >38% and in high-volume centers with >5 IONM procedures per week.<sup>[14,15]</sup>

IONM may not be mandatory for every thyroidectomy, but, surgeons should use IONM, if they feel more comfortable using the device during thyroidectomy, especially for LATCs where there is a chance of distorted anatomy. In LATC, where bilateral RLNs are engulfed and/or involved, IONM may guide the surgeon to assess the functional integrity of the RLNs following a complete dissection, in addition to its anatomical integrity. Vagal stimulation before and after dissection helps to confirm the critical point of injury and may guide us in identifying the correct segment in case of a segmental injury. The advances in continuous IONM technology may minimize the limitations of intermittent IONM monitoring.<sup>[16]</sup> However, IONM should not replace anatomical identification of the nerve and following of correct techniques of surgery

### Recurrent laryngeal nerve (save vs. sacrifice)

Management of recurrent laryngeal nerve during surgery for LATCs is critical, Falk and McCaffrey and Nishida *et al.* studied the effect of RLN preservation versus resection in functionally intact nerves in LATC cases. They found that there were no differences in survival when the RLN was preserved, if patients received adjuvant RAI therapy with TSH suppression and there was no gross residual following resection.<sup>[4,17]</sup> The basic principle of management of the RLN during surgery for LATCs is to make all attempts to dissect the nerve out of the tumor/nodal mass and preserve the continuity, without leaving back gross residual disease.

A nonfunctioning RLN involved by tumor may be resected *en bloc* with the thyroid resection. However, if there is no evidence of tumor infiltrating the RLN, then even in a nonfunctional nerve, it must be meticulously dissected and preserved to allow for recovery.<sup>[17,18]</sup> The use of IONM here may help in determining the amplitude of EMG, suggesting the possible recovery pattern in the postoperative setting.

If the RLN is resected for oncological purposes, every attempt should be made to reconstruct the nerve using the ansa cervicalis or other nerve grafts. This would only be possible if the proximal and distal nerve ends are available for anastomosis. Typically, this is not feasible when the disease is infiltrating the nerve at the entry point, near the Berry's ligament. This kind of resection and anastomosis is generally possible when a nodal mass, rather than a primary thyroid tumor, involves the nerve.

Table 1 summarizes the factors determining the RLN sacrifice v/s safety as per the International neuromonitoring study group guidelines 2018.<sup>[19]</sup>

**Table 1: Factors determining the recurrent laryngeal nerves sacrifice and safety**

Favouring nerve sacrifice	Favouring nerve sparing
Aggressive histology and genetic variants	Young patients, generally radioiodine avid patients, papillary thyroid carcinoma
Iodine refractory, previous EBRT, recurrence following adjuvant therapy	Good efficacy to RAI and EBRT
Nerve invasion at point of entry to the larynx	Elderly (increased risk of aspiration)
Normal contralateral vocal cord function	Reduced pulmonary capacity
No distant metastasis	Voice professionals
	Contralateral RLN paralysis
	Distant metastasis

RLN – Recurrent laryngeal nerves; EBRT – External-beam radiotherapy; RAI – Radioactive iodine

### Management of laryngotracheal and esophageal invasion (How much to resect?)

#### Laryngeal invasion

Less than 12% of patients are known to have laryngeal infiltration. Laryngeal involvement is generally restricted to the involvement of the outer framework of the larynx in most cases, without mucosal involvement. Every attempt should be made to preserve the larynx by performing conservative procedures rather than a total laryngectomy. Total laryngectomy may benefit patients with varying degree of airway obstruction, intraluminal bleed, intraluminal invasion, or loss of laryngeal function and in patients who are unsuitable for conservative laryngeal surgery. The commonly performed operative procedures, in patients with laryngeal invasion are peeling or shaving the tumor off the laryngeal framework, window resections of the thyroid cartilage, partial laryngectomy and total laryngectomy. A simple shave excision can be considered if the tumor is just abutting the outer perichondrium without gross involvement. Mucosal laryngeal invasion may be amenable to vertical laryngectomy if the disease is lateralized and the patient had a functioning larynx.

#### Tracheal invasion

Conflicting data on the management of tracheal invasion is due to nonstandardized definitions of invasion and performing complete versus conservative procedures, tracheal invasion is most often classified by the Shin's staging [Figure 2]:

Stage I: invasion of the capsule of the thyroid with the disease abutting the outer perichondrium of the trachea without eroding the cartilage. Stage II: Outer tracheal cartilage invasion, either in between the tracheal rings or destroying the cartilage. Stage III: tracheal cartilage invasion or extension between the rings into the underlying tracheal lamina propria without mucosal invasion. Stage

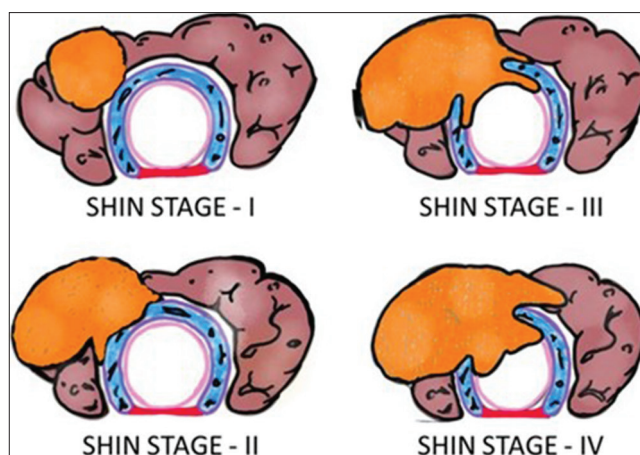


Figure 2: Shin staging: Thyroid cancers invading the trachea: (top left) Stage I, (bottom left) Stage II, (top right) Stage III, and (bottom right) Stage IV (diagram conceptualized from Shin *et al.*<sup>[7]</sup>)

IV: a complete tracheal cartilage invasion with intraluminal disease, seen as ulceration.<sup>[7]</sup>

Intraoperatively, tracheal shaving of the tumor can be done for Shin I tumors, a window/sleeve resection can be advocated in Shin II tumors, with lateral or anterior invasion of trachea. Circumferential resection is generally performed in patients with Shin III and IV tumors.<sup>[20]</sup> All attempts should be made to avoid leaving back gross residual disease on the trachea as this is associated with poorer outcomes.<sup>[21-23]</sup>

#### Esophageal involvement

This invasion typically occurs along with tracheal invasion but can also occur when paratracheal or paraesophageal lymph nodes have extranodal extension. It is usually considered a poor prognostic factor and correlates with significant reduction in overall survival.<sup>[17,20]</sup> All attempts should be made to perform a simple cuff excision of the muscularis layer of the esophagus, and in most cases, this is adequate. Segmental resection should be performed if the tumor is extensively involving all three layers. Appropriate reconstruction will be required if full-thickness excisions are needed and a preoperative suspicion of esophageal involvement will help plan this better.

#### Adjuvant therapy

The evidence for use of adjuvant external-beam radiation therapy (EBRT) in advanced thyroid cancers is derived from retrospective studies, and it has been found to offer a small benefit in improving the locoregional control and in R1 resections with gross Educational Testing Service and multiple nodes with perinodal extension.<sup>[24]</sup> In a systematic review by Fussey *et al.*, it was found that the use of EBRT in patients with thyroid cancer, improved the locoregional control in the high risk cases and those aged over 45 years.<sup>[25]</sup> A case series from the Memorial Sloan-Kettering institute showed that EBRT was effective in advanced and recurrent thyroid cancers with acceptable

acute toxicities.<sup>[26]</sup> Intensity-modulated radiotherapy has shown to have limited toxicity in these patients and should be the radiation technique if choice. However, there have been two large retrospective studies which did not show improvement in the outcomes with the use of EBRT.<sup>[27,28]</sup>

Therefore, there is no consensus on the routine use of EBRT in patients with LATC with R0/R1 resection and RAI therapy may suffice in them. In the absence of any prospective data on this issue, decisions for adjuvant RT should be made after a multidisciplinary discussion along with the radiation oncologist, endocrinologist, pathologist, and nuclear medicine physicians. It is important to balance the risks with benefits before decision of use of EBRT in patients with complete resections and well-differentiated thyroid cancers.

## Conclusion

Management of locally advanced thyroid cancer remains a contentious subject. Much of the disagreements are centred around workup, extent of thyroidectomy, neuromonitoring, and adjuvant therapy. Precise patient assessment, comprehensive clinical and radiological evaluation is vital for therapeutic planning. A cross-sectional imaging in the form of CECT or MRI will aid in the assessment of extent of the disease and status of surrounding visceral and neural structures. Aggressive surgical *en bloc* resection of all gross disease with and possibly preservation of critical structures, when oncologically safe, along with adjuvant therapy (RAI with or without EBRT) provides the best outcomes.

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