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Sentinel Lymph Node Biopsy in Differentiated Thyroid Cancer: A Review of its Evolving Role in Guiding Lateral Neck Dissection

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ABSTRACT

Thyroid carcinoma patients frequently have lymph node involvement, which is associated with the biology of the tumor (differentiated thyroid carcinoma/medullary thyroid carcinoma). For neck nodal dissection, it is crucial to understand surgical anatomy, classifications, and operative technique. For both central and lateral neck dissection, there are still some questions about the optimal surgical approach, extension, and criteria for lymph node dissection. The role of prophylactic central neck dissection in patients with clinically node-negative tumors is still up for debate, however in cases with differentiated thyroid carcinomas where there is macroscopic central neck nodal involvement, central neck dissection is required. Even if there is no overt involvement, central neck dissection is required during initial surgery for individuals with medullary thyroid cancer. According to guidelines, all patients with differentiated thyroid cancer or medullary thyroid carcinoma and lateral neck nodal metastases should have their lateral neck dissection done with therapeutic aim. Prophylactic lateral neck dissection indications for medullary thyroid cancer are still up for debate. The majority of endocrine surgeons do selective lateral neck dissection, including levels IIa–III–IV–Vb, while the extent of this procedure is still up for debate. In order to achieve a sufficient oncological surgical resection while lowering the risk of complications and sequelae from radical neck dissection, facial functional neck dissection has been recommended. The surgical procedure is explained, along with any potential complications.

KEYWORDS: Sentinel lymph node · Thyroid cancer – Neck dissection – differentiated thyroid cancer.

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INTRODUCTION

At the base of the throat, in front of the trachea, is the thyroid, a crucial endocrine gland. It is made up of two wing-shaped lobes and an isthmus that joins them; these are typically not palpable through the skin during a physical examination.[1]

The gland is lateral to the sternocleidomastoid muscle and carotid arteries, and posterior to the trachea, esophagus, laryngeal-recurrent nerve, and others. Any compression action that can be performed (dysphonia) depends on its relationship to the nerve. Two upper thyroid arteries, which are branches of the internal carotid, vascularize it. Approximately 300 microns in diameter and shaped like a cube, the "follicle" is the basic unit from an anatomical-microscopic perspective. It delineates the follicular cavity and is filled with colloid substance, including thyroglobulin, which contains iodinated tyrosine residues and is the form of thyroid hormone deposition.[2]

The thyroid hormones are composed of the hormones thyroxine (T4) and triodothyronine (T3). For 65%, they are iodine. The thyroid is actually iodine avaricious, capturing all of the circulating iodine due to an energy-dependent active transport pump mechanism. The brain produces a hormone called thyroid stimulating hormone, or TSH, which controls iodine intake. The oxidation process that converts the I. captate into the thyrosine radicals of thyroglobulin is then catalyzed by a peroxidase system. [3]

The frequency of thyroid cancer cases has dramatically increased during the last three decades. Over the past ten years, over 500,000 people have been living with thyroid cancer, according to the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (NCI). According to NCI statistics, the death rate from thyroid cancer increased by 0.8% annually over the previous ten years, while the incidence increased by an average of 5.5% annually.[4]

According to contemporary estimates, there are 12.9 new cases of thyroid cancer for every 100,000 men and women each year, and there are 0.5 fatalities from the disease for every 100,000 men and women. However, the 5-year survival rate has increased to 97.8%, and the lifetime risk for thyroid cancer is still at 1.1% because nearly 70% of cases are now identified early, when the cancer is localized at the gland.[4]

CLASSIFICATION AND PATHOLOGICAL FEATURES OF THYROID CANCERS:

Papillary carcinoma

PTC is a large differentiated adenocarcinoma that accounts for 90% of thyroid tumors and exhibits abnormal papillary proliferation. Although the majority of PTC cases have an exceptional prognosis, 10% of individuals experience recurrences, including lung metastases and lymph node recurrence. In addition to treating radioiodine-refractory PTC, the most significant problem is choosing such high-risk individuals. Age over 45, high tumor size, extra thyroidal invasion, distant metastases, vascular invasion, and poorly differentiated histology are all known to be negative prognostic markers in clinicopathology. [5]

Moreover, PTC typically exhibits a gray-white tint and a range of physical appearances, including lesional calcification, encapsulated tumors, and tumors with infiltrative borders and a central scar. Multifocal lesions and regional lymph node metastases are present in over half of PTCs. Long-term survival is unaffected by these traits.[6]

The majority of PTCs exhibit a papillary growth pattern, but nuclear features—which are present in practically every case—are a more significant diagnostic signature. PTC has clear, ground-glass, or orphan-Annie-eyed nuclear looks. The solid version When solid growth accounts for more than 50% of the tumor, PTC is diagnosed. Following the Chernobyl nuclear explosion, this variation is frequently linked to secondary PTC patients and is frequently observed in children. This variety is often characterized by both venous and lymphatic invasion. According to some research, the solid variation is linked to a poor prognosis, while other studies deemed this variant's prognosis to be nearly as favorable as typical PTC.[7]

Follicular carcinoma

FTC, which has follicular differentiation but no papillary nuclear feature, accounts for 5–15% of thyroid cancer cases. FTC is a single, gray-tan-pink, encapsulated tumor that typically has localized bleeding. Follicle cell invasion of the tumor capsule and/or blood vessels is a sign of FTC. The prognosis is poorer with vascular invasion than with capsular infiltration alone. [8]

The majority of FTCs only have a minor tumor capsular penetration, making them minimally invasive. These minimally invasive FTCs resemble follicular adenomas in appearance and infrequently spread to other locations. As a consequence, a minimally invasive FTC can only be identified during thyroidectomy and is challenging to differentiate from a follicular adenoma in cytology or frozen section. Although widely invasive FTC is far less prevalent, over 80% of these tumors disseminate to distant locations, which results in a high mortality rate of 20%. Distant metastases, age greater than 45, high tumor size, substantial vascular invasion, extra thyroidal expansion, and broadly invasive tumors are the unfavorable prognostic variables. [9]

Anaplastic carcinoma

With nearly 100% disease-specific mortality, ATC is an exceedingly aggressive undifferentiated tumor that contributes to 40% of thyroid cancer fatalities, yet only 70% of patients are female. Approximately half of patients with ATC have either contemporaneous or previous DTC. It implies that the dedifferentiation of DTC leads to the emergence of ATC. ATC typically does not absorb iodine like DTC does, which makes it resistant to radioiodine therapy. [10]

Intrathyroidal ATCs can be surgically removed, and this drastic excision provides better results than clinically evident ATCs, which are typically incurable. ATC displays a big, solid tumor that is very invasive, necrotic, and bleeding. One of the characteristics of ATC cells is their large, pleomorphic giant cells that resemble osteoclasts. [10]

D. Medullary carcinoma

MTC comprises less than 5% of thyroid carcinomas, which are neuroendocrine tumors that secrete calcitonin and are derived from C cells in the neural crest's ultimobranchial body. Forty to eighty percent of MTCs are sporadic, while twenty to thirty percent are familial. Familial medullary thyroid cancer (FMTC), multiple endocrine neoplasia 2A (MEN2A), and multiple endocrine neoplasia 2B (MEN2B) are the three types of familial MTCs that are all autosomal dominant inheritance of germ line RET mutations. [11]

Peak age of familial MTC is younger (approximately 35 years) that of sporadic MTC (40-60 years). The overall 5-year survival of patients with MTC is 86%. Poor prognostic factors include older age, advanced stage, the presence of lymph node metastasis at diagnosis, and somatic RET mutation. Sporadic MTC is usually solitary whereas most of familial MTC exhibit bilateral, multicentric foci. [11]

Additionally, MTCs usually feature firm, solid tumors that are gray-tan in color and lack a well-formed capsule. C cells are highly concentrated in tumors. MTC cells can be spindle, polyhedral, or round to oval in shape. Nodules and tumors are separated by wide fibrovascular bands. Nuclear chromatin is salt-and-pepper, and the nuclei are spherical to oval. Stroma often contains calcitonin-induced amyloid plaques. While sporadic MTCs may not exhibit a background of C cell hyperplasia, familial MTCs do. [12]

Levels of cervical lymph nodes

For the purpose of staging head and neck cancer and planning therapy, the neck's lymph nodes have historically been physically separated into at least six levels. There are variations in definitions among specializations. A summary of radiologically useful boundaries for each level is provided below: [1-4]

Level I: submental and submandibular

Superiorly: mylohyoid muscle and mandible
Inferiorly: inferior border of the hyoid bone
Anteriorly: platysma muscle
Posteriorly: posterior border of the submandibular gland

There are two sublevels:
Level Ia (submental nodes): anteromedial between the anterior bellies of both digastric muscles
Level Ib (submandibular nodes): posterolateral to the anterior belly of the digastric muscles
Level II: upper internal jugular (deep cervical) chainSuperiorly: base of the skull at the jugular fossa
Inferiorly: inferior border of the hyoid bone
Anteriorly: posterior border of the submandibular gland
Posterolaterally: posterior border of the sternocleidomastoid muscle
Medially: medial border of the internal carotid artery

There are two sublevels:
level IIa: inseparable from or anterior to the posterior edge of the internal jugular vein; includes jugulodigastric nodal group
level IIb: posterior to and separable by a fat plane from the internal jugular vein

Level III: middle internal jugular (deep cervical) chain
Superiorly: inferior border of the hyoid bone
Inferiorly: inferior border of the cricoid cartilage
Anteriorly: anterior border of the sternocleidomastoid muscle
Posterolaterally: posterior border of the sternocleidomastoid muscle
Medially: medial border of the common carotid artery

Level IV: lower internal jugular (deep cervical) chain
Superiorly: inferior border of the cricoid cartilage
Inferiorly: level of the clavicle
Anteriorly: anterior border of the sternocleidomastoid muscle
Posterolaterally: oblique line drawn through the posterolateral edge of the sternocleidomastoid muscle and the lateral edge of the anterior scalene muscle
Medially: medial border of the common carotid artery
includes medial supraclavicular nodes including Virchow node

Level V: posterior triangle
Superiorly: skull base at the apex of the convergence of sternocleidomastoid and trapezius muscles
Inferiorly: level of the clavicle
Anteromedially: posterior border of the sternocleidomastoid muscle
Posterolaterally: anterior border of the trapezius muscle

There are two sublevels:
Level Va: superior half, superior to inferior border of the cricoid cartilage (posterior to levels II and III); includes spinal accessory nerve
Level Vb: inferior half, inferior to inferior border of the cricoid cartilage (posterior to level IV); includes lateral supraclavicular nodes

Level VI: central (anterior) compartment
Superiorly: inferior border of hyoid bone
Inferiorly: superior border of manubrium (suprasternal notch)
Anteriorly: platysma muscle
Posteriorly: trachea (medially) and prevertebral space (laterally)
Laterally: medial borders of both common carotid arteries (medial to levels III and IV), includes anterior jugular, pretracheal, paratracheal, prelaryngeal/ precricoid (Delphian), and perithyroidal nodes

Neck Dissection Techniques and the Concept of Functional Neck Dissection

Thyroid cancer treatment relies heavily on cervical lymphadenectomy. Removing cervical lymph nodes, whether detected by radiographic imaging or clinical examination (therapeutic lymphadenectomy) or not (prophylactic lymphadenectomy), may improve disease-specific survival and reduce recurrence rates in several types of thyroid cancer.[13]

Neck dissection was first proposed by **George Crile** more than a century ago as a necessary component of upper-aerodigestive tract malignancy treatment. The anatomical region sampled is utilized for the most used classification for cervical lymphadenectomy. Historically, neck dissection was frequently performed with a comprehensive approach. Radical and modified radical neck dissections are the most well-documented nodal-harvesting methods for thyroid cancer among these categories.[13]

In order to preserve function while delivering appropriate oncological lymph node dissection for laryngeal cancer, **Suarez et al.**

established the idea of functional neck dissection. Although the terms "functional neck dissection" and "modified radical neck dissection" are frequently used interchangeably, the former refers to a concept rather than a specific kind of neck dissection. This idea entails cutting along the fascial planes to remove lymph nodes and maintain non-lymphatic tissues irrespective of anatomical borders, whereas modified radical neck dissection suggests cutting lymphatic tissue while minimizing non-lymphatic tissue. [14]

CENTRAL NECK DISSECTION

The central region includes just the level VI neck compartment and is bounded by the carotid arteries laterally, the clavicles and sternum inferiorly, and the hyoid bone superiorly. The lymph nodes of the prelarynx, pretrachea, and right and left paratrachea are located in the central region. In cases of thyroid cancer, central neck dissection can be done for both preventative and therapeutic purposes. When clinical or radiological examination reveals metastatic lymph nodes in the central region, therapeutic dissection is carried out; when no discernible metastatic lymph nodes are found, prophylactic dissection is carried out. [15]

Because the risk of metastasis is lower for T1 and T2 tumors, central neck dissection is not recommended. However, the risk of metastasis to the central lymph nodes is higher for tumors that are larger (T3, T4), multicentric, aggressive subtypes, young patients, or those with BRAF mutations. The pretracheal lymph nodes are removed inferior to the innominate artery, the paratracheal lymph nodes are removed inferior to the cricoid cartilage, and the prelaryngeal lymph nodes are excised superiorly during central dissection. [16]

During central neck dissection, it is essential to preserve the parathyroid glands and the ipsilateral recurrent laryngeal nerve. The inferior thyroid artery supplies blood to the parathyroid glands. To prevent the devascularization of the parathyroid gland, the branch of the inferior thyroid artery entering the parathyroid gland must be preserved by ligating it near its branch entering the thyroid capsule. Autologous transplantation can be used when the parathyroid gland stops receiving blood, however in order to prevent the implantation of metastatic lymph nodes, a biopsy is typically necessary. [15]

LATERAL NECK DISSECTION

When there is a metastatic lymph node in the lateral neck compartments, the lymph nodes in these compartments are dissected as part of the treatment for thyroid cancer. A physical examination may reveal metastases, or a neck ultrasound may reveal them. Additionally, ultrasonography is useful for guiding the extent of the lymphadenectomy in addition to detecting nonpalpable lymph nodes. [17]

The anterior side of level V, level III, level IV, and level II, if positive lymph nodes are suspected, are the main neck regions dissected during lateral dissection. However, as papillary thyroid cancer seldom spreads to level I and V dissection, there is disagreement on their efficacy. [18]

Moreover, Neiderman et al. also found that there was no significant difference between patients who underwent level V node dissection compared to those who did not. As a result, it might not be necessary to perform lymph node dissection on level I and V in all cases.[19]

Whether a thyroidectomy is done during the same procedure determines how much of an incision is made. The Kocher incision can be extended laterally to encompass the affected side of the neck if a thyroidectomy is also performed; otherwise, a transverse incision can be made from the anterior border of the trapezius muscle to the lower edge of the cricoid cartilage. [20]

Subplatysmal flaps are created and extended superiorly up to the carotid artery and internal jugular vein, and medially up to the thyroid cartilage. The sternocleidomastoid muscle's anterior border is dissected, and the dissection plane between it and the strap muscles is created. When the omohyoid muscle is encountered, it can be transected and ligated. The carotid artery may be dissected at this point in the procedure or later on. Lymph nodes are located in front of the internal jugular vein. [20]

The lateral border of the internal jugular vein is dissected once the carotid sheath is opened. Retraction of the internal jugular vein medially exposes the soft tissue that contains lateral lymph nodes. If required, the phrenic nerve can be sacrificed during dissection. It is situated on the anterior scalene muscles at the inferior edge of this lymphatic tissue, which is posterior to the transverse cervical artery. [21]

The carotid artery and vagus nerve are identified and preserved as the dissection continues inferiorly along the internal jugular vein's lateral margin. If the dissection is done on the left side, the horacic duct may be seen looping behind the internal jugular vein. Soft tissue is separated from the anterior scalene muscles and elevated anteriorly, including the lymph node package. The cervical plexus inferiorly and spinal accessory nerve superiorly are conserved during the specimen's dissection, which involves retracting the specimen anteromedially. The specimen includes the lymph nodes inferior and medial to the spinal accessory nerve, but excludes the contents superior and medial. [22]

In order to prevent potential lymphatic leakage and to use negative pressure to promote faster flap adhesion, a suction drain is frequently inserted. An absorbable monofilament suture is used to seal the skin, while an interrupted-polyfilament absorbable suture is used to close the platysma. The drain is removed once the drainage flow has decreased enough. In particular, when lateral lymph node dissection occurs, the drain is typically left in the thyroid lodge for three days on average.[22]

Sentinel lymph node biopsy in thyroid cancer

A prominent surgical method for locating subclinical lymph node metastases in node basins that appear to be untouched by a range of original cancers is sentinel node mapping (SNM). The idea of a sentinel node, which is believed to be the first lymphatic station to drain from a main tumor, has been around since the latter part of the 20th century. Thyroid cancers are among the solid tumors to which this idea has since been used. Its usage is justified by the desire to detect clinically occult metastases without the need for a prophylactic lymph node dissection, which is linked to greater expenses and non-neglectable rates of consequences.[23]

Three more options are available for thyroid cancers without clinical evidence of node metastases (cN0), as the goal of thyroid cancer surgery is to remove the thyroid and any impacted lymph nodes: (a) execute a preventive neck dissection based on particular risk factors, with the risk of surgical overtreatment and associated increase in morbidity; (b) forego dissecting nodes in favor of observation, with a certain risk of disease persistence or recurrence in case of occult metastases; (c) If the SN has metastases, SNM with SN biopsy and therapeutic compartmental lymphadenectomy.[24]

The methods of SNM in thyroid cancer

The methods commonly used for harvesting the sentinel nodes in thyroid cancer can be schematized as follows: [25]

A. Visual tracers (e.g., blue dye, carbon nanoparticles and indocyanine green);
B. Radioactive tracers (e.g., 99mTc saline solution, 99mTc-phytate and 99mTc-nanocolloid albumin);
C. Hybrid tracers (e.g., nanocolloid albumin and methylene blue, indocyanine green and nanocolloid albumin); and
D. Magnetic tracers, such superparamagnetic iron oxide (SPIO) nanoparticles

Methods of sentinel lymph node biopsy in PTC

Although the trajectory of the PTC's propagation is not always predicted, it primarily affects the local drainage LN. Actually, the lymphatic fluid is drained by the intra-thyroid capillaries to the lymphatic channels connected to the capsule, possibly interacting with the opposite lobe and the isthmus. About 90% of patients have involvement in the central neck compartment, and the frequency of micro-metastases (less than 2 mm) can reach 80%.[26]

The second most affected region is the lateral caudal compartment LN. On the other hand, lateral levels were found to have a higher incidence of LN metastases. The next site of involvement is the supraclavicular nodes (10–52%). Less frequently, mediastinal LN involvement occurs (2–15%). Up to 20% of individuals have been found to have lateral skip metastases, while 25% of patients had contralateral LN involvement. Vital dye, lymphoscintigraphy, or a combination of vital dye and 99mTc-nanocolloid particles can be used to perform the SNB in PTC. Lastly, the use of SPECT/CT to assist with the lymphoscintigraphy approach is becoming more and more common. [27]

Vital blue dye technique

The site, injection timing, injection volume, and tracer type distinguish the many blue dye procedure variations. The dye enters the lymphatic channels after injection and travels to the SLN. Once discovered, the LNs are removed and sent for histological analysis.[28]

The disadvantages include:

The possibility of lymphatic disruption, the inability to follow the lymphatics through the collar incision for thyroidectomy because they drain outside the central compartment, the removal of the parathyroid gland as a sentinel node due to its uptake, the skin flare response, anaphylaxis (isosulphan dye), and a steep learning curve.[28]

Lymphoscintigraphy and intraoperative gamma-probe technique

The preoperative injection of radioisotope eliminates risk of lymphatic disruption during operation, allows identification of SLN located outside the central compartment without parathyroid glands uptake. The lymphatic drainage after US guided thyroid injection (2–24 h before thyroidectomy) of 99mTc-nanocolloid particles is studied and monitored from the thyroid gland by dynamic (1 frame per 15 s; 64 × 64 matrix; antero-posterior projection for up to 10 min) and static (5-minute; anterior, lateral, oblique views; 256 × 256 matrix) images until the radiotracer accumulates in the SLN.[29]

Furthermore, SPECT/CT is becoming more and more popular since it enables the anatomical localization of SLNs through the acquisition of a low-dose CT scan. The cutaneous projection of the radiotracer storage site, which is tagged with a water-resistant dye, is identified using a cobalt-57 sheet source following the detection of a sentinel LN. [29]

Because the "shine-through" effect of the radioactive thyroid makes it more difficult to detect the LNs that are close to the thyroid, the thyroid should be removed before the SLN is sought. The central and lateral compartments are then scanned for radioactive LNs using a handheld collimated gamma probe through the collar incision. The probe tracks the lymphatic bed to show a decrease in radioactivity counts to background levels following total surgical SLN extirpation. The SLN is then sent for a histologic analysis.[30]

LYMPHOSCINTIGRAPHY WITH INTRAOPERATIVE GAMMA-PROBE TECHNIQUE

Two hours before surgery, 99mTc-nanocolloid particles are injected intra-tumorally. After that, a dynamic scintigraphy is carried out, and then static acquisitions are made till the SLN is visible. To maintain the lymphatic outflow during surgery, the dye is injected straight into the thyroid nodule prior to the surgical incision. The dye's flow and accumulation, which corresponded to the radio-isotopic accumulation site, were then used to identify SLN.[31]

Additionally, novel tracers and methods, such (68) Ga-tilmanocept PET/CT, are presently being developed and assessed. The tracer used, the tools required to locate the sentinel nodes, and the logistics involving the tracer injection and the surgical procedure vary across these approaches. Tracer dosage and injection locations, timing from injection to optimal node spotting, and other factors can vary even among studies that utilize a comparable methodology. Consequently, it is important to proceed with caution when comparing the findings of the different research because minor variations in specifics may account for disparate findings. [32]

However, there have been some attempts to compare the different methods. Vital-dye (VD) alone, Tc-nanocolloid planar lymphoscintigraphy with intraoperative hand-held gamma probes (LS), Tc-nanocolloid planar lymphoscintigraphy with intraoperative gamma probe and VD (LS + VD), Tc-nanocolloid planar lymphoscintigraphy with preoperative SPECT/CT, and intraoperative gamma probe (LS-SPECT/CT) were the four types of procedures compared in a meta-analysis by **Garau et al. (2019)** that comprised 45 studies. The inclusion of SPECT/CT enhanced the detection of metastatic SLNs outside the central neck, and Tc nanocolloid outperformed methylene blue. [29]

Gelmini et al., (2018) conducted a prospective, non-randomized study comparing blue dye SNM (40 patients), lymphoscintigraphy (5 patients) and the combined technique (40 patients) with apparently better results with the single tracer techniques. [30]

Since blue dye is more affordable and doesn't require a nuclear medicine facility, some surgeons have switched to using nano colloidal albumin in place of patent blue dye in recent years. However, blue dye is more challenging to work with intraoperatively because it can easily stain the operative field, gloves, swabs, and parathyroid glands, and it can also conceal the recurrent laryngeal nerve from view. In contrast, radioisotope SNM is recommended when it is available since it better localizes SN in the lateral compartments, does not fix in the parathyroid glands, and does not obscure the view of the operational field.

Moreover, a new technical adjunct to limit the false negative rate of SNM on frozen sections is one-step nucleic acid amplification (OSNA), which allows real-time (intraoperative) detection of mRNA encoding for cytokeratin 19; OSNA has been tested for papillary thyroid carcinoma, with satisfying results.

SENTINEL LYMPH NODE BIOPSY IN MEDULLARY THYROID CANCER

A minority of the working group favored prophylactic LND when LN metastases were seen in the adjacent paratracheal central compartment because of the high likelihood of microscopic lateral nodal involvement.

However, this is controversial due to a potential risk of surgical complications and related morbidity from unnecessary LND. Because complete removal of the cancer is critical, and debates on LND are continuing in treating MTC, it is important to detect and treat occult LN metastases in the lateral neck. Previous groups have initiated studies of sentinel lymph node biopsy (SLNB) in MTC, but few studies have focused on lateral LNs.

While, the basic procedural steps are similar in both PTC and MTC, several important differences exist:

Feature	PTC	MTC
Common use	More established and studied	Experimental\ limited use
Clinical stage	Often cN0	Frequently cN1 or micro-metastatic early
Tracer accuracy	Higher predictability of drainage	More unpredictable and variable drainage
Use of SLNB	To avoid lateral neck dissection	To detect occult lateral metastases
Pattern of spread	Stepwise (central → lateral	Skip metastasis common (lateral without central)

In MTC, SLNB often more technically challenging due to the tumor's frequent skip metastasis, where lateral lymph nodes may be involved even if central nodes appear negative. In contrast, PTC tends to spread more predictably in a stepwise fashion, making it more reliable.

There are several studies reporting the accuracy of SLNB in thyroid cancer, but few studies have performed frozen analysis. One study performed both frozen and permanent analyses for SLN in central neck compartment using the blue dye technique. Frozen analysis had 68.8% sensitivity, 100% specificity, 100% PPV, and 94.4% NPV, while histopathologic analysis showed values of 89.6%, 100%, 100%, and 98.1%, respectively.[33]

Using the radiotracer technique, **Kim *et al.*** showed similar results of frozen analyses with lower sensitivity and NPV compared to permanent analyses. Possible reasons for these differences are the limitations of frozen analyses, technical error, and misinterpretation.[33]

Moreover, **Machens *et al.*** demonstrated a positive correlation between numbers of central and lateral LN metastases through quantitative comparative analyses of 195 patients with MTC. Based on **Kim *et al.*** results, lateral SLNB is feasible in patients with MTC with extensive central LN metastases, even without preoperative evidence of lateral metastasis. This procedure also

can be useful in identifying unexpected lateral LN metastasis in those with no central metastasis (skip metastasis).[33, 34]

RATIONALE FOR SLNB IN THE LATERAL NECK

The primary rationale is selective staging. The goal is not to replace therapeutic LND for known disease, but to accurately identify those cN0 patients who harbor occult metastases and would therefore benefit from dissection. This approach aims to:

Reduce recurrence rates by identifying and treating occult disease at the initial operation.
Reduce morbidity by avoiding comprehensive LND in patients with a negative SLN.
Provide precise pathological staging, which may influence decisions regarding adjuvant Radioactive Iodine (RAI) therapy, as the presence of N1b disease often upstages patients to ATA Intermediate-Risk or higher[29].

TECHNICAL ASPECTS OF SLNB FOR DTC

The technique for SLNB in the lateral neck has evolved, with two main methods employed:

Vital Dye Technique: Methylene blue or patent blue is injected around the tumor or the peritumoral capsule intraoperatively. The dye is taken up by lymphatic vessels and accumulates in the SLN, which is identified by its blue discoloration within 5-15 minutes. This method is cost-effective but has a steeper learning curve and can cause temporary skin staining. Deeper nodes can be challenging to visualize.

Radiotracer Technique (99mTc-nanocolloid): A radiotracer is injected pre- or intra-operatively. Pre-operative lymphoscintigraphy provides a "roadmap" of the lymphatic drainage pathways. Intraoperatively, a handheld gamma probe is used to identify the radioactive "hot" nodes. This method is highly sensitive and allows for the detection of nodes not visible to the naked eye. The combination of radiotracer and blue dye (dual-agent technique) is considered the gold standard by many, maximizing detection rates.

Injection Site: Debate exists regarding the optimal injection site: peritumoral, intratumoral, or subtumoral (in the thyroid parenchyma around the nodule). The peritumoral/subtumoral injection is most common to avoid injecting directly into the tumor core, which may have compromised lymphatic drainage. [33]

EVIDENCE AND DIAGNOSTIC PERFORMANCE

Numerous single-institution studies and meta-analyses have demonstrated the feasibility and accuracy of SLNB in DTC.

Detection Rate: The success rate of identifying at least one SLN is consistently high, typically >95% for the radiotracer technique and slightly lower for blue dye alone.

Sensitivity and Negative Predictive Value (NPV): This is the most critical metric. Meta-analyses report pooled sensitivity rates of 88-95% and NPV of 94-98% for the central compartment. Data specific to the lateral neck shows similar high performance, with studies reporting sensitivity often exceeding 90%. This means that if the SLN is negative, there is a very high probability (>94%) that the remaining nodal basin is also disease-free.

Lateral Neck-Specific Findings: Studies focusing on the lateral compartment show that SLNB successfully identifies occult metastases that would have been missed by pre-operative US. The SLN is found in the lateral compartments (Levels III, IV, and II most commonly) in a significant portion of patients, even when the central compartment is the primary drainage site. This "skip metastasis" phenomenon, where lateral nodes are involved without central node involvement, is well-captured by SLNB. [33, 34]

SLNB AS A GUIDE FOR LATERAL NECK DISSECTION

The surgical algorithm based on SLNB results is straightforward:
1. SLNB is performed at the beginning of the thyroidectomy.
2. Intraoperative frozen section analysis of the SLN is crucial for real-time decision-making. The accuracy of frozen section for detecting DTC metastases is generally high.
3. If the SLN is negative: A lateral neck dissection is omitted. The patient proceeds with total thyroidectomy ± central neck dissection.
4. If the SLN is positive: A comprehensive compartment-oriented lateral neck dissection (Levels II-V, preserving critical nerves and vessels) is performed during the same operative session.

This selective approach prevents approximately 80-90% of patients (those with a true-negative SLN) from undergoing an unnecessary LND. [32]

LIMITATIONS AND CHALLENGES

Despite its promise, SLNB for lateral neck DTC is not yet a standard-of-care due to several challenges:

Lack of Standardization: Injection techniques, tracer types, and protocols vary significantly between institutions.

Learning Curve: The procedure, especially the blue dye technique, requires experience to avoid missing nodes or causing collateral staining.

False Negatives: While the NPV is high, false negatives do occur. Reasons include obstruction of lymphatic flow by tumor, technical failure to identify the true SLN, or pathological missed diagnosis on frozen section.

Long-Term Outcome Data: There is a scarcity of large, prospective, randomized controlled trials (RCTs) proving that an SLNB-guided strategy improves disease-specific survival or recurrence-free survival compared to observation in cN0 patients. Most evidence is from retrospective cohorts. [26]

CONCLUSION AND FUTURE DIRECTIONS

Sentinel lymph node biopsy represents a highly accurate and minimally invasive staging procedure for detecting occult lateral lymph node metastases in clinically node-negative differentiated thyroid cancer. When combined with intraoperative frozen section, it provides a rational and evidence-based guide for the selective application of lateral neck dissection.

Its adoption has the potential to personalize surgical treatment, minimizing morbidity for the majority while ensuring adequate oncologic resection for those with occult disease. For SLNB to transition from a promising tool to a standard practice, future efforts must focus on:

1. Standardizing the technique through multi-institutional consensus.
2. Conducting large, prospective RCTs to validate its impact on long-term oncologic outcomes and quality of life.
3. Refining molecular analysis of the SLN (e.g., using RT-PCR for thyroglobulin) to further enhance sensitivity.

Until then, SLNB for lateral neck staging remains a valuable option in high-volume centers with dedicated surgical and pathological expertise, particularly for patients with higher-risk primary tumors where the risk of occult lateral disease is significant. [26]

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