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Review Article

Unusual locations for differentiated thyroid cancer nodal metastasis

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Abstract   Lymph node metastasis is common in differentiated thyroid cancer especially papillary thyroid cancer. Presence of lymph node metastasis does not have an impact on survival in younger patients. Therapeutic central and lateral neck dissection in the presence of clinically or radiologically evident lymph nodes has resulted in good overall survival. However, disease persistence in the lymph node/early recurrences may be seen in patients owing to lymph nodes that may be missed during the initial neck dissection. These observed locations are retropharyngeal and parapharyngeal nodal location, retro carotid location, sublingual, axillary, and intraparotid locations, supraclavicular and superficial to the sternothyroid muscle. We aim to highlight these locations with the goal to minimize persistence or early recurrence of disease at these locations.
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Introduction

Differentiated thyroid cancer (DTC), especially papillary thyroid cancer (PTC), has increased in incidence and is the third most common malignancy in woman as of 2019.[1-3] Although lymph node metastasis is extremely common for PTC, mortality is extremely low. With surgery being the first line therapy for most thyroid cancer, there has been great debate with regards to the impact of nodal metastasis on recurrence and overall survival. This is reflected in the 2015 ATA guidelines, endorsing therapeutic lymph node dissection over prophylactic surgery.

The extent of surgery to address clinically proven nodal metastasis in the central and lateral neck is well-defined. A neck dissection addressing these compartments aims to clear both clinically evident and occult disease. However, there are lymph nodes in unusual locations in the neck that are not typically incorporated during nodal dissection. If these areas are left undissected, they may manifest as persistent disease or a delayed recurrence following initial surgery. The aim of this paper is to bring these unusual locations to the fore, thus ensuring a thorough surgical removal of nodes that may harbor malignancy.

Common lymph node levels of DTC metastasis

DTC commonly follows a standard pattern and sequence of spread to the lymph nodes in the neck. The central compartment nodes (Level 6 and 7) are usually the first echelon of lymph nodes to be involved, followed by levels 3, 4 and 5 in DTC. Cancers located in the upper pole of the thyroid may skip level 6 and spread to the lateral neck nodes.[4]

Radiologically evident lymph node metastasis is present in up to 35% of patients[5-8] with PTC who do not have any suspicious nodes on a routine physical examination. Microscopic nodal metastasis in thyroid cancer is seen in up to 80% of patients with PTC. If not noted during preoperative sonography, intraoperative evaluation is limited.[9,10]

A high-resolution ultrasound serves as a good clinical adjunct in the detection of neck metastasis and has the potential to alter the surgical plan in at least 20% of patients undergoing surgery for cancer. The sensitivity to detect suspicious lymph nodes in the lateral neck is over 90%, though it is lower in the central neck due to the presence of the thyroid gland.[11] A thorough sonographic survey of lymph nodes levels in the bilateral central and lateral compartments helps to determine the extent of surgery. If the sonographic appearance of the lymph node is suspicious, and it meets the size criteria (lymph node is larger than 1 cm in the lateral neck and larger than 8 mm in the central neck), it would generally warrant a fine needle aspiration biopsy.[12,13] The use of thyroglobulin or calcitonin in the needle washout is extremely sensitive, even if cytopathology is indeterminate or benign.

Impact of PTC lymph node metastasis on recurrence and survival

Nodal metastasis is seen as a poor prognostic feature in most cancers. The AJCC/TNM cancer staging system helps predict survival based on the staging, while the ATA risk stratification system serves to estimate the risk of recurrence. The effect of nodal metastasis on overall survival appears to be limited, while the risk of recurrence is clearly increased.

Impact of lymph node metastasis on survival

The impact of lymph node metastasis has been debated widely in PTC. Sugitani et al,[14] Ito et al[15] and Zaydfudim et al[16] proposed that metastatic lymph nodes >3 cm is adversely affects survival in patients over 55 yrs of age especially when in the lateral compartment. Three other studies have highlighted that the presence of extranodal extension than the mere presence of lymph node metastasis is predictive of poorer survival in patients of all age groups owing to a higher incidence of distant metastasis.[15,17,18] One of the major takeaways from these studies is that distant metastasis more than locoregional disease is the cause of mortality.[19] In addition, the presence of a BRAF mutation along with ENE, worsens the DSS due to increased tumor aggressiveness and RAI resistance.[20] However, a more recent population level study which combines the SEER as well as the NCDB is the only study along with findings reported by Tran et al.[21] which found that presence of nodal metastasis (>6) has a negative influence on survival even in patients younger than 45 years.[21,22] However, the 8th edition of the AJCC has revised the age criteria and has down-staged the patients with DTC with lymph node metastasis as a stage 2 disease rather than stage 3 disease in patients over 55 years of age. This was due to low clinical impact on survival in patients <55 years (though statistically significant) while recognizing that in patients over 55 years of age, lateral neck disease negatively affects the 10 year DSS.[23]

Impact of lymph node metastasis on recurrence

The 2015 ATA guidelines stratifies the risk of recurrence in DTC based on various clinicopathological factors of thyroid cancer following surgery with or without RAI. The ATA low risk category estimates recurrence risk to be <5% when there are <5 lymph nodes with micrometastasis. Intermediate risk category was defined as the presence of clinically evident lymph nodes (cN1), and greater than 5 lymph nodes all less than 3 cm in size which increases the risk of recurrence to >20%. High risk category is currently defined as any lymph node that is more than 3 cm in the largest dimension.[20,24]

Extranodal extension is a significant factor that increases the risk of recurrence. The risk of recurrence is almost 32% when there are greater than 3 nodes with extra nodal extension (ENE).[25] The presence of a BRAF mutation along with ENE portends a worse prognosis. Urken et al[26] reviewed the data on the impact of extranodal extension on survival and recurrence and has argued for considering age along with the presence of ENE in risk stratification more than any one factor alone.

Impact of location of lymph node metastasis

De Meer et al[27] demonstrated the only factor that influenced recurrence rate and disease-free survival in multivariate analysis was the presence of positive lymph nodes in the lateral compartment. Thirty percent of the patients with positive central lymph nodes developed recurrent or persistent disease compared with 60% of the patients with positive lateral lymph nodes. In another multivariate analysis, Nixon et al[19] demonstrated that 5 year DSS was poorer in patients with lateral neck disease than central neck disease (91% vs. 100%, $P < 0.001$). The distant recurrence free survival was again poorer in patients with lateral neck disease compared to patients with just central neck disease (84% vs. 99%, $P < 0.001$).[15]

Unusual sites of PTC nodal metastasis and clinical significance

Outside of the central and lateral neck compartments for nodal metastasis, papillary thyroid carcinoma has been found to metastasize to ectopic locations.[17] The prevalence of this is relatively uncommon but non-negligible and has been documented predominantly in a case report fashion. The clinical significance of this has not been clearly identified, but most ectopic sites of metastasis are associated with patients harboring recurrent/persistent disease.[17,18] Ectopic locations that have been documented include retropharyngeal, parapharyngeal, retrocarotid, sublingual, axillary and intraparotid locations. Other locations include the superficial supraclavicular area, the central neck area superficial to the strap musculature, and the level of the central neck medial to the external carotid in the thyrohyoid space (Table 1). Such areas have not been well described in the literature to date. We will illustrate nodal metastasis in these areas with a few case examples.

Retropharyngeal and parapharyngeal nodal location

Retropharyngeal and parapharyngeal lymph node metastasis are uncommon for papillary thyroid carcinoma. There have been 39 cases published, 14 of which were metastasis to the retropharyngeal space, and 25 to the parapharyngeal nodes.[28,29] Kainuma et al[28] reported that the average size of parapharyngeal nodes was larger than retropharyngeal nodes, although it was noted that the parapharyngeal space and retropharyngeal space are anatomically adjacent. As the flow of lymph between these sites is seamless, it has been

Table 1 Unusual locations for lymph node metastasis in DTC.

Retropharyngeal/Parapharyngeal
Retrocarotid
Sublingual
Axillary
Intraparotid locations
Supraclavicular
Superficial to strap musculature

reported that retropharyngeal metastasis spreads easily to the parapharyngeal space. For patients with occult disease, differentiation of these spaces is difficult.[28] In the majority of case reports, patients with retropharyngeal and parapharyngeal nodal metastasis had prior ipsilateral or bilateral modified neck dissections rather than occult disease.[30]

Otsuki et al[29] hypothesized that neck dissection and/or metastatic cervical lymph nodes themselves might alter the direction of lymphatic drainage to the retrograde fashion, resulting in the unusual metastasis to the retropharyngeal lymph nodes. Desuter et al[31] reported that only 0.43% (3/696) of thyroid papillary carcinomas had parapharyngeal node metastasis.

Among the reported cases with retropharyngeal lymph node metastases from papillary thyroid carcinoma, 10 cases represented an isolated metastasis of occult thyroid papillary carcinoma to the retropharyngeal space supporting the concept that this direct lymphatic pathway might also play a part in the metastatic route of thyroid cancer to retropharyngeal nodes.[30]

Lateral retropharyngeal nodes can be typically found medial to the internal carotid artery and the sympathetic chain, and may be seen at the level of C1. The parapharyngeal space is a potential space shaped like an inverted pyramid. The temporal bone comprises the base of the pyramid. The parapharyngeal space extends inferiorly tapering to an apex at the greater cornu of the hyoid bone. Lymph node metastasis from nasopharyngeal, oropharyngeal and hypopharyngeal tumors are common in the retropharyngeal nodal basin. Tumors from the parotid gland and the oropharynx commonly drain to the parapharyngeal space. For patients with papillary thyroid carcinoma, especially those with a history of neck dissection and an unexplained increase in serum thyroglobulin levels, it is important for periodic CT or MRI to be completed for surveillance rather than routine ultrasound, to detect the presence of nodes in these lymph node basins.

Retrocarotid location

The retrocarotid lymph node location is a unique location deep to the common carotid artery which may be missed at the time of a central neck dissection. The surgical approach to this area may be laterally or medially and therefore the location of the retrocarotid lymph node basin has been a subject of discussion. Radiologic identification of this area on CT or MRI may be part of the central or lateral neck compartments. Cunnane et al[32] described the discrepancy involved in the placement of retrocarotid nodes. In their study of thirty-three patients who underwent lymph node dissection, a review of the preoperative CT in three patients showed a discrepancy of retrocarotid nodes into either central or lateral neck. Through discussions between radiologists and surgeon, these nodes were categorized as lateral neck nodes.[32] A proposed nodal classification system defined the lateral compartment as inferior to the digastric muscle, posterior to submandibular gland, deep to the sternocleidomastoid muscle. This includes nodes that are located either anterior or posterior to the common carotid artery. Nodes posterior to the common carotid artery are part of the retrocarotid basin.

Sublingual, axillary, and intraparotid locations

Drainage to these ectopic locations has been found in a small cohort of patients with recurrent disease, and while rare these areas have been marked as ectopic areas of drainage for differentiated thyroid carcinoma. Goyal et al[30] published data that showed macroscopic nodes primarily reside in the central neck at initial surgery, with no ectopic nodes at initial presentation. In the recurrent setting, lateral neck nodes predominate and there is a 9% rate of ectopic nodal metastasis. The authors demonstrated drainage to the sublingual, axillary and intraparotid locations, with an overall 10 out of 416 cases that had ectopic nodal drainage. While there was no direct correlation between ectopic node location to prognosis, they did determine that patients with evidence of nodal metastasis to the lateral neck had decreased survival. In addition to nodal location, extracapsular nodal extension ENE is another nodal characteristic associated with worse prognosis. The literature supports an association between ENE and an increased risk of recurrence, and possibly a worse disease-specific survival. ENE is more frequently seen in patients with ectopic metastasis.[30]

Mediastinal location (supraclavicular)

The supraclavicular lymph nodes that exist above the sternal notch, just along the clavicle near the clavicular head, are not well described. At our institution, we have described this location distinct from level IV, superficial to the clavicular head. In patients undergoing lateral neck dissections, we have sent a specimen from this area separate from the lateral neck contents (Fig. 1). We have found that, in at least four cases, there was evidence of papillary thyroid carcinoma in at least one of the lymph nodes at this location (Table 2). The range of size for involved lymph nodes ranged from 0.1 to 2.5 cm. All of these patients underwent extensive central and lateral neck dissections with more than one compartment positive for disease. Given the existence of disease in this area, it may be important to clarify the dissection of this compartment, and study this as
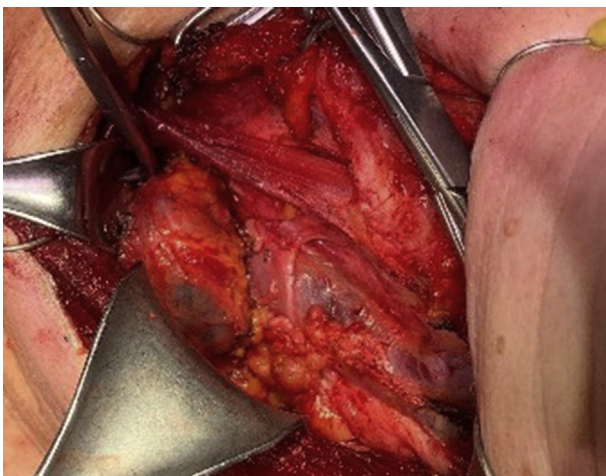

Fig. 1   Supraclavicular lymph nodes in PTC.

Table 2   Cases of mediastinal (supraclavicular) lymph node metastasis.

Patient	Diagnosis	# Lymph node in the supraclavicular area	Largest dimension of lymph node
Patient 1	Metastatic papillary thyroid cancer in central and lateral lymph nodes	1/2 lymph node in the supraclavicular area	2 mm
Patient 2	Metastatic papillary thyroid cancer in central and lateral lymph nodes	1/7 lymph node in the supraclavicular area	2 mm
Patient 3	Metastatic papillary thyroid cancer in central and lateral lymph nodes	1/3 lymph node in the supraclavicular area	1 mm

a separate compartment to determine the true incidence of involvement in this area.

Superficial to strap musculature

Lymph node metastasis to the area immediately superficial to the sternothyroid musculature has not been described. Evidence of lymph node disease in this superficial plane has been identified anecdotally and may signify extension from the central compartment perithyroidal or pre-tracheal lymph nodes.

Level VI at the thyrohyoid membrane

The central neck compartment is the bounded laterally by each common carotid artery, and the effective superior border is at the level of the cricothyroid membrane rather than the traditional superior border of the hyoid.[33,34] This is the area targeted for a comprehensive central neck dissection. However, the territory above the Delphian lymph node and below the hyoid is not well clarified for thyroid cancer. The area identified just lateral to the thyrohyoid membrane may harbor a lymph node at risk for involvement and is best accessed through a lateral neck dissection approach. Nodal metastasis to this area lies in the plane of, and remains medial to, the external carotid artery. At our institution we have identified three cases of nodal metastasis to this area and all had presence of gross lateral neck disease.

Conclusions

Lymph node metastasis from DTC may occur outside the confines of typically dissected areas for central and lateral neck dissection. It is important to recognize these possible unusual locations for thyroid cancer metastasis in the neck

during the work up for surgery as well as intraoperatively to prevent disease persistence.

Declaration of Competing Interest

Ralph P Tufano — Paid Consultant for Hemostatix, Medtronic.
None of the other authors have anything to disclose.

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