

# Regional Lymph Node Metastasis in Papillary Thyroid Cancer

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Papillary thyroid cancer is a common endocrine cancer and commonly presents with lymph node metastases. It has been generally accepted that lymphatic drainage occurs from the thyroid primarily to the central lymphatic compartment and secondarily to the lateral compartment nodes. Recently, improvements in the resolution of imaging studies and the availability of highly sensitive thyroglobulin assays have highlighted the importance of identifying disease in the pre-operative assessment and dealing effectively with metastatic regional disease in order to prevent recurrence. However, there are limitations to diagnosing central lymph node metastases. With unreliable imaging modalities, prophylactic central lymph node dissection should be performed on all patients with papillary thyroid cancer. In comparison with the central compartment, prophylactic lateral node dissection has little or no effect on improving the prognosis of patients with papillary thyroid cancer. Therefore, lateral node dissection is recommended only as a part of the therapeutic procedure. The extension of lateral neck dissection is recommended a comprehensive selective neck dissection of levels IIa, III, IV, and Vb. The rich lymphatic supply of the thyroid gland coupled with the propensity for nodal metastases in papillary thyroid cancer require the modern thyroid surgeon to be familiar with the indications for and techniques of regional lymph node dissection.

**Key Words:** Papillary thyroid cancer, Lymph node, Metastasis, Central compartment, Lateral neck

## Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy, with an increasing incidence of, now, approximately 8.7 cases/100,000 per year.<sup>1)</sup> Overall, the 10-year disease-specific survival rate for PTC is 90%.<sup>2)</sup> Despite this excellent prognosis, cervical lymph node metastases are found in 40–90% of cases, and up to 20% of patients encounter recurrence of PTC after their primary operation.<sup>3–5)</sup> Almost four-fifths of all PTC recurrences occur in the neck alone, and, of these, three-fourths are associated with lymph node metastases.<sup>6,7)</sup> Because of its high incidence, regional lymph node metastasis has long been a critical issue with

PTC. However, the true impact of local lymph node metastasis on survival in PTC remains controversial. Nonetheless, there are ample data in the literature associating lymph node metastasis with decreased disease-specific survival and increased risk of local recurrence. Outcome data from large institutional cohorts from the United States, Canada, and Germany have shown a significant and independent negative impact on survival with lymph node metastasis.<sup>8–10)</sup> Analysis of large cancer registry databases from the United States and Sweden has similarly shown poorer outcomes and increased mortality rate in patients with locoregional lymph node metastases.<sup>11,12)</sup> Additionally, the presence of local lymph node metastasis has been associated with an increased risk of future local

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recurrence.<sup>13)</sup>

Recently, improvements in the resolution of imaging studies and the availability of highly sensitive thyroglobulin assays have highlighted the importance of identifying disease in the pre-operative assessment and dealing effectively with metastatic regional disease in order to prevent recurrence. The aim of this review is to describe the contemporary approach to assessment and management of regional lymph node metastasis in PTC.

## Lymphatic Drainage of the Thyroid

Accurate characterization and prediction of lymphatic drainage of the thyroid gland is technically challenging because it is extensive and flows in many directions. Some authors have reported that each lobe of the thyroid gland has its own internal lymphatic system, and there is no communication with contralateral regional lymph nodes<sup>14,15)</sup> (although PTC can spread to regional lymph nodes bilaterally<sup>16–18)</sup>) It has been generally accepted that lymphatic drainage occurs from the thyroid primarily to the central lymphatic compartment and secondarily to the lateral compartment nodes.<sup>19,20)</sup> As a result, locoregional spread of thyroid cancer predominantly involves the ipsilateral, and sometimes also the contralateral central and lateral neck nodes.<sup>21–24)</sup>

Dralle and Machens<sup>25)</sup> suggested that lymphatic tumor cell dissemination is modulated by the anatomical location of the primary thyroid tumor. PTCs lodging in the upper thyroid pole often spread first to the upper parts of the ipsilateral lateral compartment, whereas primary tumors arising from the mid- and lower portions of the thyroid gland favor the central compartment.<sup>26,27)</sup> The different drainage of the superior and inferior thyroid pole is a natural consequence of the peculiar anatomy of the thyroid gland's lymphatic system, which is organized in parallel to the gland's venous drainage system: lymph vessels draining the upper thyroid pole accompany the superior venous vessels to the ipsilateral lateral neck nodes; lymph vessels draining the middle portion of the thyroid gland follow the middle venous vessels to the

middle internal jugular nodes; and lymph vessels draining the inferior thyroid pole course together with the inferior pole veins to the central and lower ipsilateral lateral (supraclavicular) nodes.<sup>28,29)</sup>

## Presentation of Nodal Metastases

In the past, the identification of cervical lymph node metastases was based primarily on palpation. However, enlarged cervical lymph nodes may not be easily palpable, especially when they are small, located behind the sternocleidomastoid muscles, or located behind a carotid artery or jugular vein and in level VI. The introduction of diagnostic imaging modalities such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) has increased detection of non-palpable cervical lymph node metastases.

US allows for accurate fine needle aspiration of suspicious nodes which will further aid the clinician in surgical planning. Fine needle aspiration samples may be evaluated with cytology and thyroglobulin assay on the aspirate sample. For these reasons it has become the gold standard for assessment of regional metastases. Also, Kim et al.<sup>30)</sup> attempted to create a new staging system by building a risk model associated with the disease-free survival rate using, with the factors that can be clinically ascertained with the operation, preoperative US as the basis and they verified its usefulness by comparing this new staging system with 13 prior staging systems.

Despite the advantages of US, there are limitations to diagnosing central lymph node metastases. The sensitivity (27.3–55%) and specificity (69–90.0%) of preoperative US within the central compartment are lower than those (sensitivity 65–90.3%, specificity 82–94.8%) of the lateral compartment.<sup>31–34)</sup>

Recently several investigators have reported that preoperative US with CT had superior diagnostic performances to US alone, although the routine preoperative usage of CT is not recommended by the American Thyroid Association (ATA) guidelines under revision.<sup>33,35,36)</sup> However, US and CT together were still not sufficiently sensitive to detect small lymph node

metastases in the central neck.

### Central Neck Dissection

Lymph nodes in the central compartment are from the thyroid notch to the innominate artery cephalocaudal, and from one carotid artery to the other. Central neck dissection refers to the systematic excision of the prelaryngeal, pretracheal, and paratracheal lymph nodes that reside in the level VI compartment of the neck, and can be unilateral or bilateral.<sup>37)</sup>

In the published clinical guidelines of organizations such as the Korean Thyroid Association (KTA), the ATA, the National Comprehensive Cancer Network (NCCN), and the British Thyroid Association (BTA), in cases of lymphadenopathy, the general recommendation is to perform lymph node dissection of the affected compartments.<sup>38–41)</sup> However, there is virtually no consensus on the indications for prophylactic lymph node dissection. The NCCN guideline indicates prophylactic central neck dissection for patients aged <15 or >45 years, with tumors >4 cm in diameter or with extrathyroidal extension.<sup>40)</sup> In the BTA guidelines, the above-mentioned indications for prophylactic central neck dissection are limited to male patients only.<sup>41)</sup> In the KTA and ATA guidelines, prophylactic central-compartment neck dissection (ipsilateral or bilateral) are recommended in patients with PTC with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4).<sup>38,39)</sup> Even among the major guidelines, there is no clear consensus regarding the appropriate neck compartments to be dissected; therefore, many thyroid surgeons do not routinely perform systematic cervical lymph node dissection due to elevated postoperative morbidities.<sup>42)</sup> This inconsistency between published guidelines for prophylactic lymph node dissection could be attributable to the lack of unbiased information on the patterns of lymph node metastases.

Proponents of routine prophylactic central neck dissection argue that lymph node metastases occur in 21–82% of cases<sup>43)</sup> and that removing involved nodes reduces disease persistence. An argument against

routine prophylactic central neck dissection is the absence of evidence for improvement of long-term outcomes. Furthermore, clinically apparent metastatic lymphadenopathy (i.e., larger size, greater number, and extranodal extension) has a much worse prognosis than microscopic lymph node metastases,<sup>44–46)</sup> thus the long-term benefit of resection of occult microscopic nodal metastases is unclear. Other important concerns include increased risks of temporary hypocalcaemia after central neck dissection (compared with no neck dissection).<sup>47,48)</sup>

Some medical evidence suggests that prophylactic central neck dissection leads to decreased overall or disease-associated mortality in low-risk PTC. Two meta-analyses<sup>48,49)</sup> including mostly retrospective data have shown an absence of a clinically significant reduction in disease recurrence from prophylactic central neck dissection. One single-center study has reported that routine central neck dissection might significantly reduce disease persistence or recurrence.<sup>50)</sup> In a multicenter observational study by Popadich and colleagues,<sup>51)</sup> fewer individuals treated with central neck dissection had central neck reoperations (1.5%), than did those not treated with central neck dissection (6.1%;  $p=0.004$ ), although overall re-operation rates were no different. Permanent hypocalcaemia and vocal cord paralysis are not statistically significantly different in some studies<sup>47,48)</sup> although temporary hypocalcaemia is higher in patients with a history of a thyroidectomy who are being treated with prophylactic central neck dissection compared with those without central neck dissection.<sup>47,48,52)</sup>

While it is clearly understood that mortality rates attributable to PTC are low, the problem of locoregional recurrence can represent a major challenge to treating physicians and surgeons and is an issue that consumes considerable medical resources in the follow-up period. A serious problem caused by disease relapse in the central compartment might occlude the airway or esophagus, or paralyze the recurrent laryngeal nerve,<sup>53)</sup> and recurrent nerve injury frequently occurs during additional surgery for the dissection of recurrent nodes in the central compartment in comparison to the initial surgery.<sup>54,55)</sup>

Accurate preoperative prediction of central lymph node metastases may be helpful in the management of patients with PTC, and may help to more carefully select patients for central neck dissection. But more sensitive and accurate methods are required to improve the detection of small lymph node metastasis in the central neck. With unreliable imaging modalities, prophylactic central lymph node dissection should be performed on all patients with PTC.

## Lateral Neck Dissection

Metastatic PTC to the lateral compartment is clinically significant as it is thought to be a predisposing condition to distant metastasis. Due to the increasing incidence of thyroid cancer over the past four decades, there may also be a rise in the number of patients presenting with lateral neck disease and requiring neck dissection.<sup>1,56)</sup>

Historically, the management of lateral lymph node metastasis varies from “berry-picking” to modified radical neck dissection,<sup>57)</sup> and there is still no clear consensus regarding the appropriate neck level to which nodes must be removed.

The ATA in their 2009 thyroid nodule management guidelines advocated that a “therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy.”<sup>35)</sup> The Triological Society followed in 2010, advocating a comprehensive selective neck dissection.<sup>58)</sup> Due to the variability in extent and definition of neck dissections, the ATA has recently published a consensus review on the anatomy, terminology, and rationale for lateral neck dissection in this population.<sup>59)</sup> The anatomic neck regions described include the upper jugular (II), the midjugular (III), the lower jugular (IV), and the posterior triangle (V). Level II can be divided into level IIa nodes, which surround the internal jugular vein, and level IIb nodes, which lie posterior to the spinal accessory. Level V can also be divided into level Va nodes, which lie between the skull base and the level of the lower margin of the cricoid cartilage arch behind the posterior edge of the sternocleidomastoid muscle, and

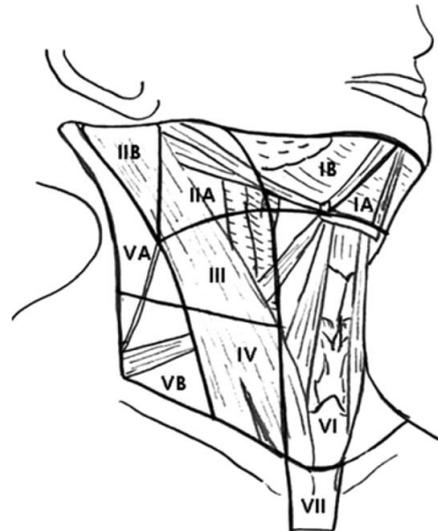


Fig. 1. Nodal levels with corresponding anatomic landmarks.

level Vb nodes, which lie between the level of the lower margin of the cricoid cartilage and the level of the clavicle (Fig. 1).<sup>59)</sup>

In the absence of significant lymphadenopathy at levels IIa, III, IV and Vb, disease above the spinal accessory nerve (IIb or Va) or in level I is uncommon. Sparing these lymph node basins will minimize risk of injury to the marginal mandibular and accessory nerves, whilst also preserving the submandibular salivary gland. Therefore, the ATA recommended a comprehensive selective neck dissection of levels IIa, III, IV, and Vb.<sup>59)</sup>

In comparison with the central compartment, the lateral neck harbors lower rates (23%)<sup>60)</sup> of occult metastasis and elective surgery results in higher postoperative complication rates. Despite this, some experts continue to advocate selective prophylactic lateral neck dissection. Such groups report rates of occult disease greater than 20%, low rates of complication in their hands and more accurate staging of initial disease.<sup>60)</sup> However, even expert groups report complication rates as high as 50% following total thyroidectomy and lateral neck dissection, including hypocalcemia (30%), chronic neck pain (30%), chyle leak (3%) and recurrent laryngeal nerve palsy (10%).<sup>61)</sup>

There have been many studies suggesting that prophylactic lateral node dissection has little or no effect on improving the prognosis of patients with PTC.

A similarly good prognosis can be achieved by a salvage operation after lymph node recurrence in the lateral compartment, in comparison to prophylactic node dissection. Therefore, lateral node dissection is recommended only as a part of the therapeutic procedure.

### Conclusion

The rich lymphatic supply of the thyroid gland coupled with the propensity for nodal metastases in PTC require the modern thyroid surgeon to be familiar with the indications for and techniques of regional lymph node dissection. Overt nodal metastasis is related with poor outcome in PTC, and they should be resected with the minimum of morbidity in order to reduce rates of regional recurrence and prolong survival. Accurate preoperative prediction of regional lymph node metastases by the variables obtained through the patient's preoperative clinical information, imaging studies and intraoperative findings may be helpful in the management of patients with PTC, and may help to more carefully select patients for neck node dissection.

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