

Is Prophylactic Central Compartment Lymph Node Dissection Necessary for Papillary Thyroid Carcinoma?

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ABSTRACT

The need for prophylactic central compartment lymph node dissection in patients with papillary thyroid carcinoma continues to be a subject of ongoing debate. Regional lymph node metastases are a common finding with papillary thyroid carcinoma, with an incidence as high as 50% or more. With the widespread use of high resolution ultrasound and sensitive thyroglobulin assays, lymph node metastases, not appreciated at the time of surgery, are showing up in the follow-up period, creating significant angst amongst patients, endocrinologists, and their surgeons. It was previously thought that lymph node metastases in papillary thyroid carcinoma had little bearing on survival, but this has more recently been challenged. Opponents of prophylactic central compartment node dissection cite high perioperative morbidity as a word of caution in performing prophylactic central neck dissections. The following review will look at the most up-to-date literature and best evidence for arriving at logical and sensible recommendations. This review will also look at specific definitions of what is a central compartment lymph node dissection. In the hands of experienced thyroid surgeons, prophylactic central compartment lymph node dissection, performed in a meticulous manner, can limit persistent or recurrent disease in the central compartment, and can diminish the need for routine administration of radioactive iodine, with acceptable perioperative morbidity.

KEYWORDS: Central lymph node dissection, papillary carcinoma, thyroid, prophylactic, cancer.

INTRODUCTION

The need for prophylactic central compartment lymph node dissection (CLND) in patients with papillary thyroid cancer (PTC) is the subject of ongoing debate. Approximately 37,000 new cases of thyroid carcinoma are diagnosed each year in the United States, with 80 to 85% of these being papillary carcinomas.¹ Regional lymph node metastases are a common finding with PTC, with an incidence as high as 50%.² In addition, micrometastases are common, being present in up to 90% of examined nodes in one series.³ Furthermore, many patients having clinically negative nodes on preoperative evaluation are found to have CLN metastases upon postoperative review.⁴⁻⁶ It has been shown that 10 to 15% of patients treated with total thyroidectomy develop palpable regional recurrence in cervical lymph nodes over the ensuing decade.^{7,8} Historically, it has been widely accepted that the presence of disease in CLN is associated with increased subsequent locoregional

recurrences.⁹ However, this has traditionally been thought to have little effect on survival.¹⁰⁻¹⁴ Currently, this view has been reevaluated. A study of 9,904 patients with well-differentiated thyroid cancer showed that important predictors of poor outcome include the presence of lymph node metastases. Multivariate analysis demonstrates that 14 years all cause survival was 82% for patients without lymph node metastases compared to 79% for those with lymph node involvement ($p < 0.05$).¹⁵ Furthermore, results of a large population-based study demonstrate increased mortality in patients with regional LN metastases.¹⁶ Kloos and Mazzaferri state that “although mortality rates for DTC are low, tumor recurrence rates are high and may portend death from thyroid cancer.”¹⁷ Based on the above data, much attention has been focused on determining the role of CLND in the treatment of PTC with clinically negative lymph nodes, also known as *prophylactic* central compartment lymphadenectomy. Many clinicians advocate this approach.

However, prophylactic CLND is not without risk, including hypoparathyroidism and injury to the recurrent laryngeal nerves (RLN). Prophylactic lymphadenectomy differs from *therapeutic* lymphadenectomy, which entails a *therapeutic en bloc* dissection of clinically suspicious or biopsy proven lymph nodes contained within level VI. Individual removal of grossly involved lymph nodes at the time of thyroidectomy, also known as “berry-picking,” is to be avoided.^{18,19}

RATIONAL FOR AND PROCEDURE OF PROPHYLACTIC COMPARTMENT VI LYMPHADENECTOMY

The rational behind prophylactic dissection of the central compartment revolves around the lymphatic anatomic pattern of spread of PTC. The lymph node compartments of the neck and upper mediastinum are divided into levels I-VII (Fig. 1). The thyroid contains abundant intraglandular lymphatic drainage, which communicate across the isthmus. The lymphatics drain along with the named thyroid vessels; cephalad with the superior thyroid vessels, caudad with the inferior thyroid veins and lateral with the middle thyroid vein. In the setting of PTC, tumor cells typically spread through the lymphatic system in a somewhat predictable sequence. Initial lymphatic spread of PTC is typically from the thyroid gland to the ipsilateral and then contralateral

central compartment (VI). Subsequent lymphatic spread progresses to the lateral cervical lymph node compartments on the ipsilateral side followed by spread to the contralateral compartment and the mediastinum.^{7,20,21} Although spread tends to be predictable and sequential, skip lesions to the lateral compartment or mediastinum do occur.²² Submental and submandibular nodal spread rarely occurs.²³ As can be inferred from the above data, the central compartment lymph nodes (VI) are at greatest risk for harboring metastatic disease and therefore may be an acceptable target for prophylactic dissection in patients with clinically negative CLNs.

Prophylactic CLND is done in a systematic manner with removal of all nodal tissue from the larynx superiorly to the innominate artery inferiorly. The lateral borders of level VI are defined by the carotid arteries. After or during removal of the thyroid gland, an *en bloc* dissection is performed that includes the Delphian lymph nodes, pretracheal nodes, and nodes along both paratracheal regions (Figs 2 to 4). Paratracheal dissection generally begins on the side ipsilateral to the cancer. The medial side of the common carotid artery is exposed inferiorly down to the innominate artery. The RLN is identified and all fibroadipose tissue above and below the plane of the nerve is removed. Care is taken to preserve the blood supply to the inferior parathyroid gland but this frequently is not possible. If the parathyroid gland must be sacrificed, it should be autotransplanted after

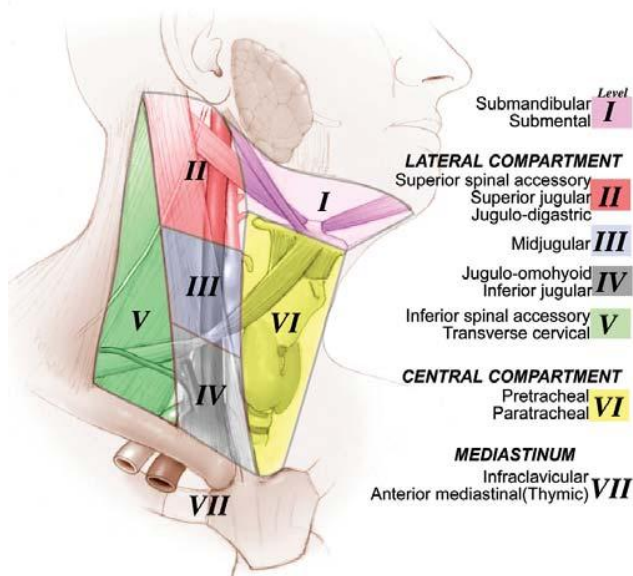


Fig. 1: Compartmental division (I-VII) of cervical lymph nodes. Compartment VI is bounded by the carotid arteries bilaterally, the hyoid bone superiorly, and the innominate vessels inferiorly

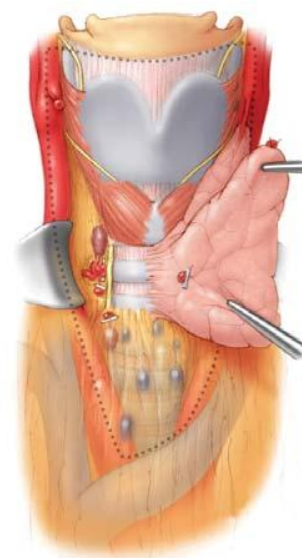


Fig. 2: Malignant appearing lymph nodes in the central compartment. Dotted line outlines central compartment (Level 6)

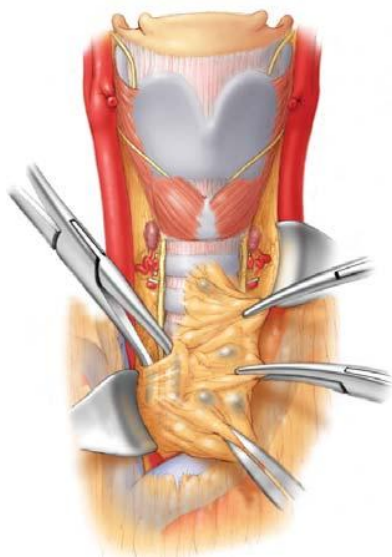


Fig. 3: Dissection of the central compartment (VI) lymph nodes

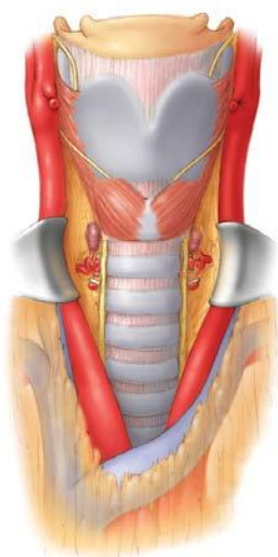


Fig. 4: Central compartment (VI) after systematic lymphadenectomy

biopsy and frozen section confirmation. The superior parathyroid gland is identified and blood supply preserved. The common carotid is retracted laterally and the cervical esophagus and trachea are skeletonized, removing all fibroadipose and lymphatic tissue along the tracheoesophageal groove. Hemostasis is obtained with bipolar cautery and hemoclips. A similar procedure is performed on the contralateral side for complete systematic dissection of compartment VI. This procedure has been best defined by a recent review by Carty et al.²⁴

CURRENT ROLE OF LYMPH NODE DISSECTION AND DEBATE REGARDING PROPHYLACTIC CLND

Surgical resection is the primary therapy for patients with differentiated thyroid carcinoma. The American Thyroid Association (ATA) guidelines define the goal of initial surgical therapy as the removal of primary tumor, disease that has extended beyond the thyroid capsule, and involved CLNs.¹⁸ Other stated goals are to minimize treatment related morbidity, to permit accurate staging, to facilitate post-operative treatment with radioactive iodine when appropriate, to permit accurate long-term surveillance for recurrence, and to minimize risk of recurrence and metastatic spread. Central to these goals are the evaluation and removal of involved nodal disease. In order to determine the presence of suspicious appearing lymph nodes in patients with PTC, preoperative neck ultrasound is strongly advocated, an approach supported by the ATA guidelines.^{18,22,25} Preoperative ultrasound has been shown to identify suspicious cervical adenopathy in 20 to 31% of cases, thereby altering the surgical approach in over 40% of cases.^{26,27} It is particularly valuable in the lateral neck and reoperative central neck. Features that are concerning for involved lymph nodes include microcalcifications, cystic changes, hyperechogenicity, increased vascularity, and loss of the fatty hilum and normal oval shape (Fig. 5). For cervical nodes found to be clinically suspicious or those confirmed to be nodal metastases by FNA, systematic, therapeutic lymphadenectomy is performed. However, the precise role of CLND performed prophylactically in patients without suspicious CLN's preoperatively is less clear.



Fig. 5: Ultrasonographic image of a suspicious appearing lymph node in the central compartment. Suspicious features include microcalcifications, rounded architecture, loss of central fatty hilum

The ongoing debate regarding the role of prophylactic CLND in patients with PTC revolves around four key questions, as outlined by White et al.²⁸ These issues will be explored in some detail here. First, does prophylactic CLND decrease locoregional recurrence or disease-specific mortality in patients with PTC? Second, does prophylactic CLND substantially increase the risk of permanent hypoparathyroidism and RLN injury? Third, does the potential added morbidity of prophylactic CLND compare with the morbidity of CLND done as a second operation for locoregional recurrence (persistence)? Finally, does prophylactic CLND have implications on the use of post-operative radioiodine ablative therapy?

While it is generally accepted that systematic neck dissection should be performed on grossly involved LNs in patients with PTC, prophylactic neck dissection remains controversial, as there are no prospective randomized data to definitively show that prophylactic CLND will provide survival benefit that would justify subjecting patients to the potentially increased morbidity associated with CLND. However, there is a single prospective study²⁹ and multiple retrospective cohort studies,³⁰⁻³³ that attempt to shed light on the subject. A single study from Goteborg, Sweden prospectively examines a group of 195 patients with PTC and compares their outcomes with other contemporary PTC patients in Scandinavia.²⁹ The patients in the Goteborg cohort underwent a total thyroidectomy and CLND with only 4% of patients receiving postoperative radioiodine. Disease-related death in the Goteborg cohort with resectable disease at the time of diagnosis was 1.6% with a median follow-up of 13 years. The Goteborg cohort contrasted with other similar disease and stage type PTC patients in Scandinavia who did not routinely undergo CLND for clinically negative lymph nodes. Disease related death in this comparison cohort was 8.4 to 11.1% with a median follow-up of 10 to 11.5 years. The difference in survival between these two groups suggests a survival benefit when CLND is performed in the setting of clinically negative lymph nodes.

The systematic review by White et al²⁸ found no prospective randomized data to describe the outcome of prophylactic CLND on mortality in patients with differentiated thyroid carcinoma. Upon review of the evidence, the authors concluded that systematic compartment-oriented CLND decreases recurrence of PTC and likely improves disease-specific survival in select patients (grade C recommendation—Expert Opinion).

The second issue central to the debate regarding performance of prophylactic CLND revolves around the

morbidity associated with this procedure. No randomized data exist which directly addresses this issue. Studies have shown that total thyroidectomy without lymph node dissection carries a 1 to 2% risk of permanent hypoparathyroidism and a 1 to 2% risk of permanent RLN injury when performed by surgeons experienced in the management of thyroid carcinoma.³⁴⁻³⁶ Two prospective cohort studies address this issue. The first study³⁷ examines 100 patients, equally divided between total thyroidectomy alone and total thyroidectomy with prophylactic bilateral CLND. The data demonstrates that 4% of patients in the prophylactic CLND group developed permanent hypoparathyroidism, while no one in the control group developed permanent hypoparathyroidism. There were no injuries to the RLN in either group. The authors of this study conclude that it is difficult to advocate the routine use of prophylactic CLND given the high rate of permanent hypoparathyroidism. The second prospective study³⁸ looked at 159 patients with PTC. Groups were those with therapeutic (n = 42), prophylactic (n = 29), and no CLND (n = 88). Of patients who underwent prophylactic CLND, there were no cases of permanent hypoparathyroidism or nerve injury. This was likewise true of the group without CLND. Of the group who underwent therapeutic CLND, 2.4% developed permanent hypoparathyroidism while 7.1% incurred injury to the RLN.

In contrast to the above data, a recent retrospective review from Mayo Clinic, Rochester by Grant et al³⁹ reviewed 420 patients with PTC who underwent total or near-total thyroidectomy with routine CLND from the years 1999 to 2006. 51% of patients had positive nodes. There was a 1.2% incidence of hypoparathyroidism and 0.4% incidence of injury to the RLN. The authors concluded that when performed by experienced endocrine surgeons, routine CLND can be performed safely without a significant risk of increased morbidity. Furthermore another retrospective study reviewed 447 patients who underwent either a total thyroidectomy (n = 391) or total thyroidectomy with ipsilateral CLND (n = 56). The study did not demonstrate a significant difference between groups with regard to permanent hypoparathyroidism or RLN injury.⁴⁰ While there is conflicting data as to whether morbidity increases with prophylactic CLND, these studies suggest that it can be performed safely during the primary operation.

This then raises the question as to whether the morbidity of prophylactic CLND done at the time of the primary operation is comparable to the morbidity of CLND performed as a secondary procedure for recurrent or persistent disease in the central compartment. Non-

randomized data suggests that the risk of permanent hypoparathyroidism or RLN injury may be higher when CLND is performed as a second operation for recurrent/persistent PTC. A retrospective study analyzed data from 503 patients with PTC, specifically determining the rate of hypoparathyroidism and RLN injury between primary operation and secondary operation for recurrence.⁴¹ At primary operation, 5.0% of patients developed permanent hypoparathyroidism and 5.8% of patients experienced permanent nerve injury. For those undergoing secondary procedures for recurrence, 8.3% incurred permanent hypoparathyroidism, while 25% suffered permanent nerve injury. Conflicting data exists from the University of Sydney⁴² in which the authors retrospectively reviewed a total of 193 patients who underwent CLND along with thyroidectomy for PTC. 170 of these patients underwent CLND at the time of the primary procedure, while 23 underwent CLND as a secondary procedure. Patients at this institution included those having CLND for recurrence as well as those having prophylactic CLND as a secondary operation. The authors found that there was no additional morbidity when CLND was performed as a secondary procedure for patients with PTC. They concluded that secondary CLND can be performed safely in patients with proven central compartment metastatic disease after previous thyroidectomy. Likewise, they conclude that prophylactic CLND can be safely offered to high-risk patients when CLND has not been performed at the time of primary operation.

In the systematic literature review, White et al²⁸ conclude that there may be a higher rate of permanent hypoparathyroidism and unintentional RLN injury when CLND is performed in addition to total thyroidectomy *vs* total thyroidectomy alone (grade C recommendation).

Radioiodine therapy is given postoperatively with the intent to eliminate small amounts of residual normal thyroid tissue (remnant ablation) in addition to eradicating occult residual disease that may be harbored in lymph nodes. Furthermore, elimination of residual thyroid aids in postoperative surveillance with stimulated serum thyroglobulin (Tg) measurements. Most recently, an updated systematic review regarding the effectiveness of remnant ablation showed a 2% reduced risk of distant metastatic disease recurrence with remnant ablation.⁴³ ATA management guidelines¹⁸ suggest the use of radioiodine ablation for select patients harboring cervical lymph node metastases. However, remnant ablation is not without risks including radiation injury to salivary glands, lacrimal ducts, bone

marrow, and other organs, which may, in time, increase the risk of secondary malignancies.⁴⁴ Furthermore, it has been shown that the risk of secondary malignancy increases with the amount of radioactive iodine administered.⁴⁵ A recent retrospective study of 115 patients who underwent total thyroidectomy and prophylactic dissection of both central (VI) and ipsilateral lateral (III and IV) compartments demonstrated that the performance of prophylactic dissection altered the indication for radioiodine ablation in 30% of patients who initially had clinically negative lymph nodes (preoperative T1N0 tumors).⁴⁶ The authors of this study conclude that prophylactic dissection can be performed safely and that this may alter the postoperative use of remnant ablation. Furthermore, they demonstrate that 97% of patients had undetectable stimulated Tg levels at 1-year follow-up, thereby further enhancing postoperative surveillance

SUMMARY

In patients with PTC, central compartment lymph nodes are at significant risk of harboring metastatic disease. While it has been historically accepted that the presence of central compartment lymph node metastases increases the risk of recurrence, without altering survival, this view has been brought into question. Therefore, many groups now advocate the use of prophylactic CLND. Although there is no randomized, prophylactic data available, grade III evidence suggests that prophylactic CLND likely decreases recurrence and may thereby improve long-term survival in select cases. Although the addition of prophylactic CLND may slightly increase the risk of permanent hypoparathyroidism and RLN injury when compared to thyroidectomy alone, prophylactic CLND may be justified given improved survival and the increased morbidity associated with secondary procedure. The 2009 ATA guidelines for the management of differentiated thyroid cancer suggest, "Prophylactic central-compartment (level VI) neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4)"¹⁸ (Grade C recommendation).

Prophylactic CLND provides specific information regarding tumor stage by directly evaluating the presence of lymph node metastases at the time of the primary (hopefully definitive) operation for PTC. This may result in more specifically directed use of radioiodine therapy,

while foregoing the use and therefore the risk of radioiodine for others. The ATA recommends every 6 to 12 months Tg assessment for postoperative surveillance. Postoperative surveillance may be enhanced due to greater numbers of patients achieving athyroglobulinemia after prophylactic CLND.

When performed by experienced endocrine surgeons, PCLND seems justified for all but clinically node-negative incidentally discovered papillary thyroid microcarcinomas.

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