

# Elective Central Compartment Neck Dissection for Papillary Thyroid Cancer-Hot Topics

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## Introduction

The American Thyroid Association (ATA) guidelines for differentiated thyroid cancer, published in 2006 and revised in 2009 [1] brought up some hot questions surrounding the emerging elective selective central compartment neck dissection procedure for Papillary Thyroid Cancer (PTC). Controversy exists regarding the indication of an elective surgical treatment for central compartment lymph nodes. The incidence of central compartment lymph node micro metastatic disease varies from 20% to 90% [2-5]. Some factors are associated with a higher risk of lymph node metastatic spread in PTC, including multifocal tumor [2], follicular variant of PTC, extra capsular extension, thyroiditis [6], male gender, tumor size, aggressive histologic type [7], MACIS score, lymph vascular invasion [8], over expression of D1 cyclin and galectin [9] and BRAF mutation [10]. The influence of lymph node metastasis on outcome in patients with PTC is widely known in the literature and determines a higher incidence of recurrence and decreases disease-free interval [11-13]. Otherwise the influence of micro metastatic disease on survival of patients harboring PTC is not well defined and maybe doesn't carry any risk. Beasley et al. [5], analyzing 522 patients with well differentiated thyroid cancer who presented neck node metastasis outside the central compartment, observed a 6-fold risk of developing recurrences, mostly in the neck, and disease-free and overall survival rates were significantly lower in these patients. Lundgren et al. [14] conducted a nested-case control study within the cohort of 5,123 patients diagnosed with Differentiated Thyroid Cancer (DTC) in Sweden between 1958-1987 and observed that approximately 36% of PTC patients were found to have loco-regional spread. These cases with lymph node metastasis experienced a higher mortality rate (O.R. 2.5; 95% C.I. 1.6-4.1). Zaydfudim et al. observed that for patients over 45 years-old, lymph node involvement was associated with a 46% increased risk of death [15]. The impact on disease free-interval and overall survival of micro metastatic lymph node disease comparing with macro metastatic disease seems to be different. The controversy is that a macro metastatic clinically evidenced disease starts as a micro metastatic lymph node implant. Continuously, almost 87% of thyroid cancers diagnosed in U.S. between 1988 and 2002 measured 2 cm or less [16]. This circumstance, lead us to suppose that for small tumors we probably will find small metastatic disease. The gene expression profile of a DTC tumor can be associated with an increased risk for Lymph Node (LN) metastasis [17] and the biological aggressiveness of some mutations can be found in small PTC as well. Rodolico et al. described that the presence of a BRAF mutation and p27 expression in PTC  $\leq$  1 cm is significantly associated with LN metastasis. In paired cases with the primary tumor and LN metastasis harboring the same mutation, they found a wider diameter of the largest metastatic area, a higher number of involved LNs and a higher percentage of metastatic lesions with extra capsular extension of LN [18]. This suggests that the potential aggressiveness of the tumor should be based on the tumor's biological profile, and not only on the primary tumor size.

The ATA 2009 revised guidelines [1] at the recommendation 27 states:“(b) Prophylactic central-compartment 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). Recommendation rating: C. (c) Near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTCs and most follicular cancer. Recommendation rating: C”.

The rationale for these statements is based on the surgical expertise available and the decision to recommend a prophylactic Central Compartment Neck Dissection (CCND) has to consider the surgical team's experience. On experienced hands the elective (prophylactic) CCND carries almost the same rate of complications, except for temporary hypocalcaemia, where for every 7.7 CCNDs performed with thyroidectomy, there was one extra case of temporary hypocalcaemia when compared to thyroidectomy alone [19]. In literature, despite of the ATA recommendation for a selective indication for an elective CCND, we are observing an emerging number of studies, from different countries, showing good results with the use of an elective CCND for small and large PTCs [7,20-23]. When indicated, the use of an ipsilateral CCND, described according to the ATA consensus statement on the anatomy and terminology of central neck dissection [24], showed a high therapeutic efficacy with a low incidence of complications, when compared with the bilateral procedure [25].

Some authors advocate the indication of an elective CCND based on the issues that lymph node metastasis have a negative effect on patient outcome, cannot be reliably identified at operation, CCND can be performed safely at the first operation, allows a better staging of the disease, and reoperation for central neck recurrences has greater morbidity[26,27]. Others argue against these rationale based on the facts that this elective procedure can potentially increase the risk of operative complications mainly hyperparathyroidism and recurrent laryngeal nerve injury with resultant vocal cord palsy, for a non-aggressive disease; the majority of thyroidectomies are performed by low-volume surgeons; and the central compartment reoperation is a safe procedure when performed among experienced surgeons [28]. The emerging question is that in literature we have few studies showing the results of the central compartment reoperation surgery. The majority of them come from high-volume hospitals showing good results with their procedures [29-31]. Central compartment

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and thyroid bed reoperations are stressful, challenging and can cause unexpected complications sometimes life-threatening like pharyngeal or esophageal lesions. The other conflicting data is that when we analyze the clinical predictors associated with these reoperative cases, we can find a high number of primary tumors measuring less than 4 cm. Al-Saif et al. described their results with LN reoperation for persistent PTC where 93.8% of the patients had their primary tumors measuring less than 4 cm and 58.3% were submitted to CCND [32]. Clayman et al. analyzing 63 cases of CCND in patients with recurrent PTC observed 37% of patients with primary tumors measuring less than 4 cm [29].

For those who argue against elective CCND for small PTC (T1 and T2), one point is extremely debatable, based on the ATA recommendation 27 (c): "...central neck dissection may be appropriate for small (T1 or T2), noninvasive, clinically node-negative..." According to literature, the incidence of extra-thyroidal extension in PTC varies from 9% to 49% [12,33-35]. Analyzing the opposite point of view, the presence of an invasive extra-thyroidal extension determines the indication of a prophylactic approach to the central compartment nodes in 9% to 49% of the cases. Extra-thyroidal extension can be divided in two categories: minimal or massive extension. Ito and Miyauchi observed an incidence of massive extra-thyroidal extension in 13% among 5,931 cases [13]. Kouvaraki et al. described the presence of extra-thyroidal extension as responsible for 33% of the reoperations in preventable reoperations for persistent and recurrent PTC, including completion thyroidectomy and lymph-node dissection [36]. Then, a preoperative or intra-operative finding of minimal or massive extra-thyroidal extension precludes the indication for a prophylactic CCND. Extra-thyroidal extension is associated with a higher incidence of central compartment subclinical lymph node metastasis in a frequency ranging from 21% to 43% [20,21,37].

The concerning question about the presence of occult central compartment node metastasis in patients having a clinically evidenced lateral compartment node metastasis is emerging also. Roh et al. studied 22 cases of patients submitted to neck dissection for lateral nodal recurrence of PTC and were submitted to prophylactic CCND, observed an incidence of occult node metastasis in central compartment in 79% [38]. Machens et al. found skip metastases (negative central and positive lateral or mediastinal compartments) in only 13 (20%) of 66 cases of PTC. Fifty-three (80%) cases had a lateral compartment or mediastinal positive lymph node metastasis in conjunction with a central compartment node involvement [39]. Lee et al. described an incidence of occult lymph node metastasis in central compartment in 88% of their patients who had lateral LN metastasis [37].

Some other clinical and pathologic features are attributed to elevate the risk of central compartment node metastasis. Male gender, multifocality of the primary tumor, size over 0.5 cm and more aggressive histologic type (tall cell variant) are the most important factors [3,7,21,37]. These features are not enough to characterize a high risk profile for PTC [33], probably with a low impact in overall survival. By selecting a group of patients with high risk for central compartment node metastasis, we can define a more personalized treatment. This personalized approach will avoid over treatments for node metastasis low risk patients and will provide an adequate treatment for patients with an elevated incidence of central compartment node disease. It is common sense to carefully weigh the risks and benefits of an elective CCND before spreading this procedure widely. The benefit of this procedure in experienced hands supplants the low risk of definitive complications that is similar to a total thyroidectomy alone. Popadic et al. in a multicenter study observed that the group of patients submitted to an elective CCND, the stimulated thyroglobulin (Tg) values

were lower before initial radioiodine ablation and there was a trend toward a lower Tg at the final follow-up in this group as well The rate of reoperation in the central compartment was lower in the elective CCND group [40].

In conclusion, since the revised version of the ATA guidelines in 2009, literature has been helping to find the risk group of patients for central compartment node metastasis. Patients with central compartment node metastasis have a high disease associated morbidity which provides a persistent elevated thyroglobulin, elevated risk for local and regional recurrences, risk for reoperations and these patients are frequently submitted to sequential doses of radioiodine ablation by clinicians. The diagnosis of a pre-operative or intra-operative extra-thyroidal extension and a lateral neck compartment lymph node metastasis constitutes strong risk for occult lymph node metastasis, and adding an elective CCND seems reasonable. For male patients, over 45 years-old and with multifocal tumors diagnosed pre-operatively, the indication of an elective CCND can be based on the presence of two or more of these factors together For patients with primary tumor under 0.5 cm the risk of micro metastatic disease is very low and elective CCND is probably not justified in this scenario[7,37].

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