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REVIEW

Central neck compartment dissection in papillary thyroid carcinoma: An update

César P Ramírez-Plaza

César P Ramírez-Plaza, Department of General and Digestive Surgery, Hospital Quirón Málaga, 29004 Málaga, Spain

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Correspondence to: Dr. César P Ramírez-Plaza, MD, Chief of General and Digestive Surgery Department, Hospital Quirón Málaga, Avenida Imperio Argentina, 1, 29004 Málaga, Spain. cprptot@gmail.com
Telephone: +34-61-7476927
Fax: +34-95-2000968

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Abstract

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for approximatley 90% of thyroid malignancies in areas of the world without deficit of Iodine. It's universally accepted that total thyroidectomy is the minimal surgical treatment for patients with PTC higher than 1 cm. When a quality surgery is performed, the prognosis for PTC is excellent with 10 and 20-year overall survival rates around 90% and 85%, respectively. Lymph node metastases are very frequent in PTC, occurring in 50%-80% of PTC patients, the most of them being located in the central compartment of the neck (CCN) and with a high rate of occult or clinically undetectable disease. A lot of controversy exists regarding how to treat the central nodal compartment disease of PTC. The first problem is the lack of standardization of the terminology and concepts related to the CCN, which are clearly established and defined in this paper according to the most recent consensus documents of endocrine societies. This uniformity will provide a more consistent and clear communicaction between all the specialist involved in the treatment of PTC. CCN can be performed to treat patients with clinically detectable, radiologically suspected of intraoperative visualized nodal disease (this is defined as therapeutic) or when these findings are absent (also called prophylactic). Indicactions, advantages and disadvantages of both therapeutic and prophylactic CCN dissection are widely discussed and clear recommendations provided.

Key words: Thyroid; Cancer; Papillary; Central; Node; Compartment; Dissection; Prophylactic; Therapeutic

Core tip: When papillary thyroid cancer is discussed anywhere, there are two main matters of controversial which centralize the debates. The first one is the need of having an uniform standardization of the concepts related to the dissection of the central compartment: limits and terminology. The second point is about the concept of prophylactic dissection of the central compartment if patients with neither clinical nor radiological nodal disease related to papillary thryroid carcinoma. Both of the points are clearly defined in this paper and the readers will have clear ideas about what to when facing a papillary thyroid carcinoma.

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INTRODUCTION

During the period from 1973 to 2002, the incidence of thyroid cancer (TC) increased from 3.6 to 8.7 per 10^5[1]. This is almost entirely related to an increase in papillary thyroid cancer (PTC) likely influenced by detection of smaller cancers, accounting for 80% of TC and ranking as the sixth most common cancer in females[2,3]. Nowadays the most part of PTC are nonpalpable lesions incidentally diagnosed because of the proliferation and widespread of multiple different radiographic evaluations, specially neck ultrasound (US) and its increasing sensitivity in screening of small thyroid nodules. Papillary thyroid microcarcinoma, which is defined as a PTC measuring equal or less than 10 mm in diameter according to the World Health Organization classification, accounts for 38.5% of PTC in the United States, 35.7% in Shangai and 48.8% in France[4,5]. The therapeutic mainstay for PTC is resection consisting of total thyroidectomy (TT) with or without lymphadenectomy.

PTC tends to exhibit intra- and extraglandular lymphatic spread, being lymph nodes (LN) involvement and dissemination common; unlike other malignancies, and this is a very important detail, presence of LN metastases generally does not adversely influence prognosis, especially in patients under the age of 45 years. Up to 40% of patients with PTC have clinically detectable macroscopic LN metastases at initial diagnosis and up to 85% have occult or microscopic LN metastases, being clinically apparent LN more common at the extremes of age[6]. The yield of metastatic LN in every compartment of the neck is significantly related to the number of LN retrieved in the neck dissection and to the extent of pathologic examination[7,8]. At this point, it is important to know that all LN metastases are not the same in terms of their implications for locoregional recurrence and mortality, which are the main endopoints to be evaluated in the surgery of PTC. Clinical LN metastases, specially if macroscopic at the time of surgery, are associated with higher recurrence rates and poorer prognosis than are similar cases in which LN metastases are preoperatively undetectable[9-13]. In addition, an increased mortality rate has also been observed in patients with LN metastases who are 45 years or older[13,14]. By contrast, microscopic LN metastases are associated with much lower rates of recurrence and do not affect patient survival, suggesting that they remain dormant and rarely become clinically significant[15,16].

The purpose of this paper is to review and update the concepts and surgical options related to the central neck compartment (CNC) dissection in PTC, the most common well-differentiated thyroid carcinoma, according to the best evidence recently published. At this point, it is important to emphasize that no level of evidence 1 information is available in the literature with the highest reported being level 4 (http://www.cebm.net/?O=125). Papillary thyroid cancers are poorly suited for prospective studies as they tend to be clinically indolent and highly responsive to radioactive iodine (RAI) therapy, with extremely high percentage of long-term survival.

CNC: THE ANATOMICAL CONCEPT

The CNC includes LN levels Ⅵ and Ⅶ. It is bounded superiorly by the hyoid bone, laterally by the sheath of the carotid arteries, anteriorly by the superficial layer of the deep cervical fascia (undersurface of the sternothyroid muscles) and posteriorly by the deep layer of the deep cervical fascia (prevertebral fascia). Initially, the CNC was considered only as LN level Ⅵ and inferiorly bounded by the sternal notch. As the thyroid gland is located low in the neck, its lymphatic drainage is contiguous with the anterior superior mediastinum that can be accessed by a cervical approach. Then, LN level Ⅶ was added to the concept of CNC and its inferior border is actually defined approximately at the level of the innominate artery crossing the trachea on the right and the corresponding axial plane on the left (Figure 1). Anyway, this inferior boundary is more theoretical than practical and somehow arbitrary because the innominate arterial trunk does not exist in the left side and its relation with the sternal notch is variable with the artery rising above the notch in 25% of cadaveric dissections[17].

The CNC contains critical anatomical structures as the trachea, esophagus, parathyroid glands and recurrent laryngeal nerves (RLNs) (Figure 2). Other structures are the larynx, the hipopharynx, cervical thymus, superior laryngeal nerves and vessels (superior and inferior thyroid arteries and superior, middle and inferior thyroid veins).

LN IN CNC: SURGICAL ANATOMY AND TERMINOLOGY

The most commonly involved LN in the CNC in thyroid carcinoma are the prelaryngeal (also known as Delphian), pretracheal and both right and left paratracheal. Paratracheal LN have been also described as *"the nodes of the recurrent laryngeal nodes"* and typically start cranially at the lower margin of the cricoid cartilage and extend caudally to the level of the innominate artery crossing the trachea. The right sided paratracheal LN may be found posterior to the common carotid artery because of its more ventral and medial location compared with the left (Figure 3). LN related to superior pole PTC may sometimes be located in the paralaryngopharyngeal space along the course of the superior thyroid vasculature. Other nodal basins included in the CNC are retroesophageal, retropharyngeal and superior mediastinal

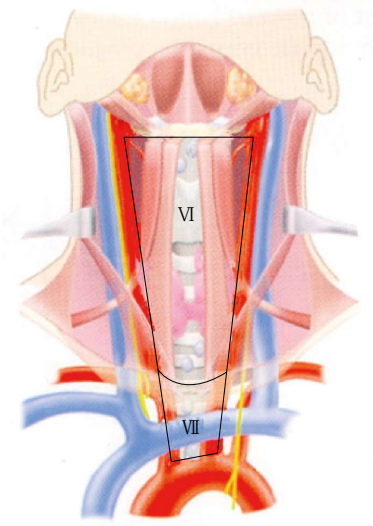

Figure 1 Lymph nodes groups of central neck compartment and their anatomic boundaries.

(inferior to the innominate artery). The mean number of LN in the paratracheal region has found to be an average of 2 to 15 in each side. Weber *et al*[18] reported a mean number of 3.9 paratracheal LN removed (range, 1 to 30) in the analysis the medical records of 645 patients who underwent total laryngectomy for squamous cell carcinoma of the larynx, hypoparynx and cervical esophagus. Pereira *et al*[19] published a mean of 8.4 ± 6.6 nodes resected in the series of 43 patients who had a TT and CNC dissection (CNCD) for PTC.

Generally, cervical LN metastases tend to spread in a stepwise fashion from the thyroid to the ipsi-lateral central LN, then to lateral compartment and/or contra-lateral central compartment. Therefore, the CNC is considered to be the first echelon of LN metastasis in PTC and its removal may theoretically alter the prognosis of this neoplasm. The surgical literature has classically lacked of standardization to define a consistent terminology relevant to the CNCD and this lacking is the main responsible of the great variability and bias in the published series. In 2009, the American Thyroid Association (ATA) published a consensus manuscript with the purpose of establishing the standard definitions to be used in future publications in order to obtain a more effective and safe CNC surgery for TC. This document was supported by the American Association of Endocrine Surgeons, American Academy of Otolaryngology - Head and Neck Surgery and the American Head and Neck Society[20]. The following definitons were suggested (and are still actually accepted) regarding a CNC.

A therapeutic CNCD (*tCNCD*) implies resection of LN metastases that are clinically apparent (cN1) in an attempt to decrease recurrence and theoretically improve survival. Clinical appearance means that there is macroscopic nodal disease grossly apparent preoperatively by physical exam (5%-10%), imaging studies (up to 30% of patients with PTC, biopsy-proven or not) or intraoperatively by visual inspection (LN larger than 1 cm and dark blue or dark appearance).

The most frequently imaging study performed is US of the neck. Preoperative US is recommended for all patients undergoing thyroidectomy for malignancy and may reduce rates of recurrent/persistent disease by allowing an adequate initial surgical treatment[21]. Some sonographic features raising suspicion for LN metastasis have been described: a diameter > 1 cm; loss of the normal fatty hilum; an irregular rounded contour with a long-access to short-access ratio < 1.5; heterogeneous echogenicity; microcalcifications; hypervascularity; and cystic changes. Anyway, US is much more sensitive for detection of metastatic LN in the lateral neck (82%-94%) than in the CNC (30%-60%)[6,22,23]. Detection of LN metastasis in the CNC using US remains difficult even in expert hands beacuse of the abnormal LN are often small in size or microscopic and frequently located deep inside the neck or just posterior to the sternum, where the overlying thyroid gland often hinders adequate visualization[21,23,24]. Kouvaraki *et al*[25] demonstrated that physical examination will miss macroscopic LN metastases in 39% of patients with PTC when a complementary neck US was performed. Although it is well accepted that intraoperative inspection underestimates the presence of pathologically detected nodal metastases, specially microscopic, a recent study documented the reliability of the surgeon to accurately determine the need for tCNCD based on a combination of preoperative US and intraoperative node inspection[26]. Neck computed tomography or magnetic resonance imaging may be appropriate for the assessment of cervical nodal status in centers where experience with neck US is lacking.

A prophylactic, elective or routine CNCD (*pCNCD*) implies resection of LN that are neither apparent clinically nor by imaging methods (cN0) with the theoretical goal of removing undetected metastatic disease and then decreasing persistent local disease. The actual role of pCNCD in PTC remains a major topic of debate and will be widely discussed in this paper.

At a minimum, CNCD should include the prealryngeal, pretracheal and at least one paratracheal LN basin (usually the ipsilateral). LN "plucking" or "berry picking" implies removal only of the clinically involved LN rather than a complete nodal group within the compartment. This LN "plucking" is not recommended because violates the nodal compartment entered without adequately addressing its disease and may be associated with higher recurrence rates.

Finally, every operative record of CNCD should indicate if it has been uni- or bilateral. When bilateral, prelaryngeal, pretracheal and paratracheal right and left nodal groups are removed; for the unilateral CNCD, the difference is that only one paratracheal (right or left) nodal basin is resected.

Thymectomy (uni or bilateral) is usually performed during the CNCD to provide a good clearance of LN level Ⅶ and has been a matter of debate. Huang *et al*[27] recently published a comparative analysis of the incidence of

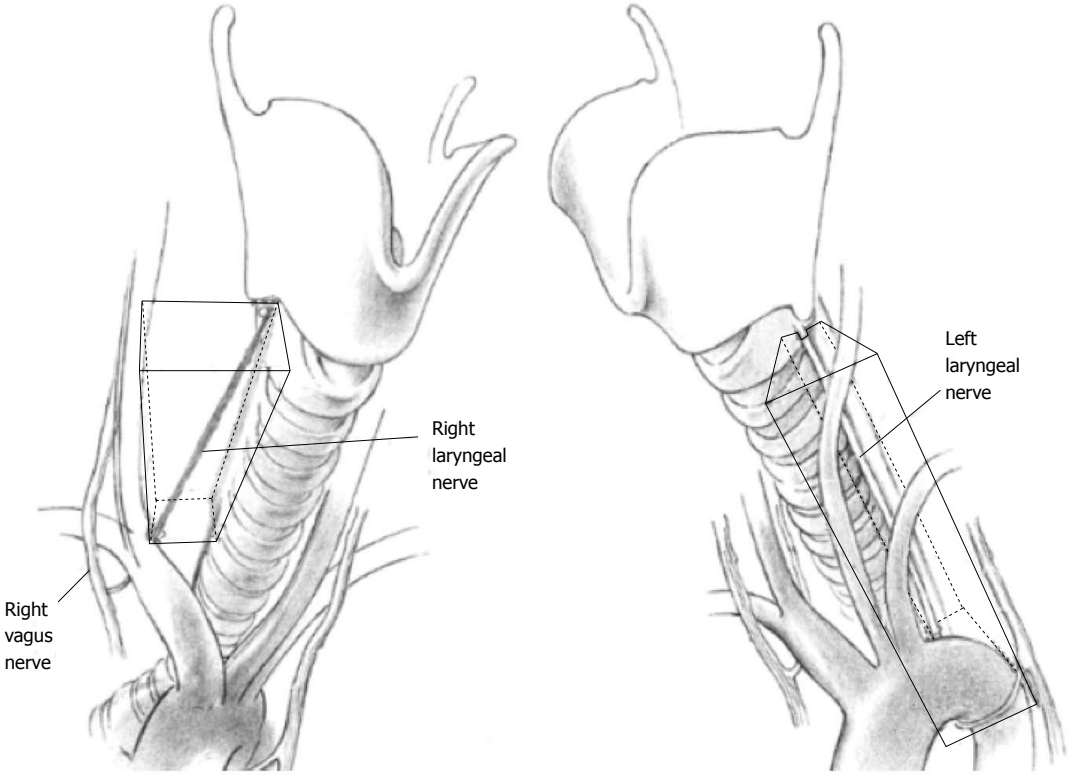

Figure 2 The way of recurrent laryngeal nerves in the central neck compartment.

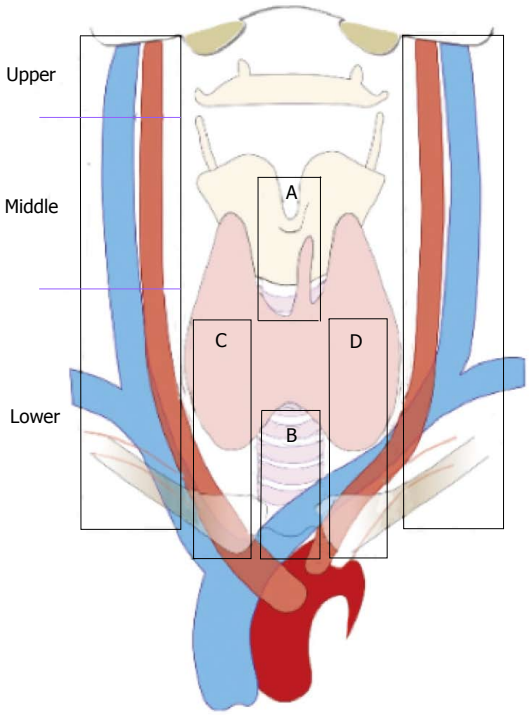

Figure 3 Boxes A, B, C and D representing lymph nodes in the central neck compartment (prelaryngeal, pretracheal and left/right paratracheal).

LN metastases in the thymus in two groups of patients undergoing CNCD with unilateral (n = 73) and bilateral (n = 82) thymectomy for PTC. A very low rate of LN micrometastasis was found in both groups (2.7% *vs* 3.6%, and always ipsilateral to the tumor) and the bilateral group presented a higher rate of transient (but not permanent) hypoparathyroidism (HP) (13.7% *vs* 52.4%). With this results, it seems clear that bilateral thymectomy during the CNCD does not provide a better carcinologic resection as no contralateral thymic metastases were found. The unilateral thymectomy with TT during the CNCD may represent an effective strategy for reducing the rate of postoperative hipocalcemia[27].

THERAPEUTIC CENTRAL NODAL COMPARTMENT DISSECTION

A general consensus exists among the different endocrine/thyroid scientific societies about TT + Therapeutic central neck compartment dissection (tCNCD) being the "gold standard" for the treatment of patients with cN1 PTC. Multiple historical and retrospective series have demonstrated that positive nodal metastases of PTC correlates with increased rates of persistent/recurrent disease and lower overall survival. Then, the rationale of removing grossly evident nodal disease along with any adjacent subclinical disease includes reducing the risk of recurrence and potentially increasing survival.

The first important reference in the medical literature defining the negative impact of age and LN involvement in local recurrence of differentiated thyroid cancer was reported in the classical paper of Harwood *et al*[9]. Globally, tumor recurrence and mortality rates were in 32%/24% and 14%/8% for LN(+) and LN(-) patients, respectively. In patients with more than 40 years old, mortality related

to the tumor was 41% and 15%, respectively, for LN(+) and LN(-) cases[9]. These results were confirmed by Tubiana *et al*[10] (*n* = 546) and Sellers *et al*[11] (*n* = 76), who published both of them series with more than 34 years of follow-up in which age older than 45-50 years old and the presence of cervical LN metastases (specially if palpable) were negative prognostic factors for poorer survival and higher locoregional recurrence[10,11]. Wada *et al*[28], in a retrospective study of 259 patients with PT microcarcinoma and routine CNCD found that recurrence was 16.7% for cN1 (*n* = 24) and only 0.43% (*n* = 235) for cN0 (this latter did not differ with a control group of non-performed CNCD, 0.65%).

Lundgren *et al*[12], in a large popullation-based control-case study, reported a 2.5-fold higher disease-related mortality in patients with differentiated thyroid cancer and LN metastases. Zaydfudim *et al*[13], in a review of the Surveillance, Epidemiology and End Results (SEER) registry found an increased risk of death in patients with PTC aging 45 years or older and having nodal metastasis, with no difference in survival in patients younger than 45 years with or without nodal metastasis. The review of the SEER by Podnos *et al*[29] described a survival at 14 years of 82% for node-negative patients and 79% for node-positive ($P < 0.0001$) being this difference also remarkable in the group with age 45 years or younger (96% N0 *vs* 90% N1). Ito *et al*[30] reviewed retrospectively 759 patients with PTC and found a 63% of central LN metastases which independently predicted worse disease free survival.

National Cancer Comprehensive Network, version 2.2014, establishes that "clinically positive and/or biopsy-proven nodal metastases should be treated with a formal compartmental resection. In the central neck, this is achieved through a unilateral or bilateral level Ⅵ dissection"[31]. The British Thyroid Association and the Royal College of Physicians, in the third edition of their guidelines in the management of thyroid cancer (2014), recommended that "overt disease in the central compartment discovered prior to/at surgery should be treated by a therapeutic level Ⅵ/Ⅶ node dissection"[32]. The ATA, in the 2009 revised Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer says in recommendation number 27 that "therapeutic central-compartment neck dissection for patients with clinically involved central or lateral neck LN should accompany TT to provide clearance of disease from the central neck"[33]. The Société Française d'Oto Rhino Laryngologie clearly defines the role of tCNCD, with recommendation number 7 being as follows: "when facing cN1 LN disease in the central compartment, it is recommended to avoid performing a berry picking and it is always preferred a compartment oriented central dissection when technically feasible"[34]. Finally, recommendation number 18 of the German Association of Endocrine Surgeons Guidelines is very convincing treating the role of tCNCD: "for clinically node-positive PTC, whatever the size of the thyroid primary, central compartment dissection should be combined with TT *to* diminish the risk of locoregional recurrence and improve survival"[35].

As it can be observed, there is a lot of surgical literature of low evidence level confirming the negative association between LN metastases and recurrence or survival in PTC. Nonetheless, it is also important to remark that data demonstrating improved survival and/or long-term recurrence risk among differentiated thyroid cancer patients treated with tCNCD are also lacking.

PROPHYLACTIC CENTRAL NODAL COMPARTMENT DISSECTION

Although it was longly abandoned at the end of the last century, the debate over the usefulness of prophylactic central neck compartment dissection (pCNCD) has been renewed over the past 10-15 years. During this period, the most important endocrine/thyroid medical and surgical societies have treated this topic in their published guidelines and, curiously, have been changing and swinging their recommendations about the indication of performing pCNCD in PTC. It must be considered that no level of evidence 1 information from prospective randomized trials is available in the literature and that the highest evidence reported is level 4 from retrospective studies comparing contemporaneous cohorts of patients treated with TT with or without pCNCD associated.

The main points for discussion about performing pCNCD are: rates of recurrence free survival and mortality; postoperative thyroglobulin (Tg) levels; importance of accurate staging; and, safety.

It is unknown what the natural history is in patients with PTC with microscopic LN involvement or subclinical nodal metastases (cN0). It is doubtful that they would eventually develop into clinically significant recurrences in the future as the studies of Wada *et al*[28] and Gemsenjäger *et al*[36] reported, the latter with only 17% of LN involved in pCNCD dissection and only 3.44% of nodal recurrence with no deaths related.

An example of how this issue is controversial can be appreciated in the different conclusions of recently reported meta-analysis. The good prognosis of PTC and its natural evolution has resulted in the inability of several studies to demonstrate a difference between TT+pCNCD compared with TT alone because of the short term follow-up. The one published by Lang *et al*[37] included 3331 patients and reported a 35% reduction in the risk of locoregional recurrence for patients with pCNCD (4.7% *vs* 8.6%) but it is not posible to know how much of this reduction is related to an increased rate of patients who underwent postoperative RAI-131 ablation (71.7% *vs* 53.1%). A previous meta-analysis published by Zetoune *et al*[38]. found no difference in recurrence rates favouring pCNCD, and Wang *et al*[16] also failed to evidence a significant difference between TT+pCNCD and TT, but they observed a trend toward a lower local recurrence (4.7% *vs* 7.9%). In Table 1 it can be seen that recent guidelines of the most important endocrine scientific societies about

Table 1 Recommendations of the different international endocrine and thyroid societies about prophylactic central nodal compartment dissection

Scientific Thyroid Society	Year	Recommendations about prophylactic central neck compartment dissection
European Society of Endocrine Surgeons[36]	2014	Recommended in T3 or T4 tumors; age > 45-yr or < 15-yr; male sex; bilateral or multifocal tumors; and, evidence of involved lateral LN
British Thyroid Association[32]	2014	Central compartment neck dissection is not recommended for patients without clinical or radiological evidence of lymph node involvement. May be considered for patients: PTC non-classical type; > 45-yr; multifocal tumors; > 4 cm; and extra-thyroidal extension on US, but benefit is unclear
National Comprehensive Cancer Network (NCCN version 2.2014)[31]	2014	Consider prophylactic CNC dissection in patients with known distant metastases; bilateral nodularity; extrathyroidal extension; tumor > 4 cm; poorly differentiated histology (although the level of evidence is low, NCCN considers the intervention as appropriate)
Japanese Society of Thyroid Surgeons and Japan Association of Endocrine Surgeons[40]	2014	Previous 2010 JSTS/JAES guidelines recommended routine bilateral central node dissection in patients who underwent total thyroidectomy. At present guidelines, it is not routinely considered and the indication may depend on institutional policy and surgeons' skill levels, joining ATA phylosophy
Société Française d'Oto Rhino Laryngologie et de Chirurgie de la Face et du Cou[34]	2012	In patients cN0, the diagnostic value of surgical exploration of the CNC is weak. Two different strategies are recommended: a compartment oriented CNC or not performing any surgical tecnique. Nonetheless, in patients with T3/T4 tumors prophylactic CNC dissection is strongly recommended
European Society of Medical Oncology Clinical Practice Guidelines[38]	2012	The benefit of prophylactic central node dissection in the absence of evidence of nodal disease is controversial. There is no evidence that it improves recurrence or mortality rate, but it permits an accurate staging of the disease that may guide subsequent treatment and follow-up
American Thyroid Association[33]	2009	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)
German Association of Endocrine Surgeons[35]	2013	The clinical benefit regarding locoregional recurrence and survival after prophylactic compartment dissection for clinically node-negative PTC > 10 mm is unproven although occult lymph node metastases are common in this setting. To prevent the risk of surgical complications from outweighing a conceivable oncological benefit, prophylactic lymph node dissection is not advised unless the requisite surgical expertise is available

PTC: Papillary thyroid carcinoma; CNC: Central neck compartment; NCCN: National Comprehensive Cancer Network; ATA: American Thyroid Association; JSTS: Japanese Society of Thyroid Surgeons; JAES: Japanese Association of Endocrine Surgeons; LN: Lymph nodes.

pCNCD are dim and use very vague expressions[31-35,39-41]. A global analysis of this table led us to consider pCNCD only in selected group of patients with recognized factors of higher locoregional recurrence (specially T3/T4 tumors, bilateral or multifocal tumors and age older than 45 years). Some reports agree that the mutation of BRAF V600E is associated with tumor aggressiveness, a poor prognosis, resistance to postoperative RAI therapy and the need for a more extended surgery. However, the potential role of the preoperative assessment of BRAF V600E mutation status in decisions regarding whether to perform pCNCD remains controversial. When the necessity of pCNCD in patients with PTC is preoperatively determined, we should recommend to perform pCNCD if BRAF V600E mutation and other conventional clinical risk factors are coexistent[42]. All these data suggest that the benefit provided by a pCNCD in cN0 patients may only be limited in terms of recurrence and that a prospective study with a very long follow-up, homogenous population and rigurous inclusion criteria is needeed. Nonetheless, a randomized controlled trial will hardly be performed because it has been estimated to cost $20000000 and would need 5840 patients to achieve statistical power[43].

As it would be expected, pCNCD has not shown any cancer-specific survival benefit. Costa *et al*[44], in a study on a group of 244 PTC who underwent TT+pCNCD or TT alone, did not find any difference in recurrence rates (6.3% *vs* 7.7%) or survival even when 47% of pCNCD showed LN involvement. Zuniga *et al*[45] also had a rate of 82.3% patients with LN involved after pCNCD but similar 5-year disease-free survival (88.2% *vs* 85.6%) was obtained for this cohort when compared to that having only TT. The most recent controversy has been provided by Barczyński *et al*[46], who has published the first paper in the literature showing a benefit not only for local recurrence (5.5% *vs* 12.4%) but also for specific disease survival (98% *vs* 92.5%) for patients with PTC having TT + pCNCD (n = 358) in comparison with those who had only TT (n = 282). Major bias in this study are its retrospective nature and that patients considered at risk in any group had RAI treatment.

Complete remission of PTC is defined by normal US and negative Tg levels in blood in the follow-up. Theoretically, pCNCD will result in higher rate of undetectable levels of Tg, facilitating follow-up and cancer surveillance and being a good surrogate for recurrence. Nonetheless, this difference may be overlaped by administration of postoperative RAI.

Lang *et al*[47] examined the results of surgical treatment of 185 patients PTC having TT + pCNCD (n = 82) or only TT (n = 103). The first group had lower median postoperative Tg levels (0.5 μg/L *vs* 6 μg/L) and higher rate of athyroglobulinemia (51.2% *vs* 22.3%) both of the differences with $P < 0.05$. When RAI was indicated by clinical or histological risk criteria, similar values with no significative differences were achieved six mo later. The only explanation posible is that residual microscopic disease not treated by pCNCD surgery in the TT-alone group was ablated by radioiodine administration. So *et al*[48], in a similar study comparing 113 patients having

TT alone with 119 undergoing TT+pCNCD found that the latter had significative lower levels of Tg (1.07 ng/mL *vs* 2.24 ng/mL), but this difference disappeared when low-dose RAI ablation was given and 3 years locoregional control was similar in both groups (96.5% *vs* 98.3%). Sywak *et al*[49] used Tg levels in an attempt to support pCNCD in his study of 447 PTC patients cN0 undergoing TT alone (n = 391) or TT+pCNCD (n = 56) and having RAI ablation following a similar algorithm. Mean postablation Tg levels were lower in the pCNCD (0.4 mg/L *vs* 9.3 mg/L, $P < 0.02$) and also was the rate of undetectable Tg levels (72% *vs* 43%, $P < 0.001$). However, no significant differences were found in locoregional recurrence rates (3.2% *vs* 5.6%) or cancer-specific mortality rates (0% *vs* 0%) despite a shorter median follow-up duration (25 mo *vs* 70 mo) in the pCNCD group. It can be thought that the impact of performing pCNCD to obtain an analytical control of the disease is more theoretical than really useful[49].

Performing a pCNCD provides the most real and adequate TNM staging for PTC and upstages 30%-50% of patients from cN0 to pN1. Then, patients aging 45 yr or older and having tumors staged as TNM Ⅰ (T1N0) or Ⅱ (T2N0) become TNM Ⅲ (T1 or T2 with N1a/b). The immediate consequence of stage migration is a different rate of overall cancer-specific survival (85%-90% for stage Ⅲ, 95% for stage Ⅰ). In addition, pN1 patients will be included in the ATA group of intermediate risk of recurrence and will receive RAI ablation at higher dosis, while T1 or T2 with cN0 patients are usually included in the low risk of recurrence group and receive lower dosis of RAI ablation. A recent systematic review published by Sawka *et al*[50] showed, however, that there is no benefit from RAI in reducing disease-specific mortality or recurrence in early stages (T1/T2). Bonnet *et al*[51] reviewed the records of 115 patients with PTC < 2 cm (T1) and cN0 undergoing pCNCD, considering the ATA guidelines and indicating RAI ablation for T1 PTC only if LN involvement existed. LN metastases were found in 42% and, globally, 58% of patients received RAI treatment (age < 18 years, aggressive cell types on pathology and vascular or capsular invasion were the other indications diferent than LN+ for RAI ablation). LN status modified the indication of RAI treatment in 30.5% of patients (14.65% were T1a tumors, < 1 cm, which resulted in pN0 and 15.85% were T1b tumors, between 1-2 cm, which resulted in pN1). Morbidity was limited to a 0.9% of permanent HP and the same percentage of RLN palsy. One year follow-up revealed 97.4% of patients with normal neck US and undetectable Tg levels, concluding the authors that, for T1 PTC, a pCNCD may change the need for RAI ablation without increasing the standard rate of complication or the risk of local recurrence[51].

Hughes *et al*[52] observed that patients with TT + pCNCD had higher dose of RAI than those with only TT (150 *vs* 30 mCi, P = 0.01), and Moo *et al*[53] found similar results (102.7 *vs* 66.3 mCi, P = 0.002). In both series, there was no difference in the rates of central neck recurrence or survival between both groups. Then, pCNCD allows better staging and stratification with more patients in early stage recieving higher dose of RAI ablation. Nevertheless, neither local recurrence rates nor survival are affected, some patients who will have no oncological benefit are exposed to potential side effects of RAI and, finally, health care costs are increased.

Safety can not be used nowadays to justify not performing a pCNCD in patients with PTC. CNC resection means wide dissection and sometimes gentle manipulation of the RLNs (which may result in temporary or permanent dysphonia up to 1%-3%) and clearance of all the fatty and lymphatic tissue aorund the parathyroid glands (which may be unintentionally removed o devascularised causing permanent or transient HP in, respectively, 2%-5% and 10%-50% respectively).

Lang *et al*[37] found that patients with pCNCD were 2.5 times more likely to have temporary HP than those undergoing TT alone in a systematic review reporting short-term results of patients operated for PTC. A recent meta-analysis about adverse effects of TT compared with TT + pCNCD included 1132 patients from 5 retrospective studies and found that there was one extra case of transient HP for every 8 (most exactly, 7.7) pCNCD performed. However, there was no increased risk of permanent HP and RLN injury[54]. Although some isolated series have reported higher rates of temporary RLN lesions with pCNCD (always with non-significant values of "*P*"), to date no studies have shown an increased risk of permanent RLN injury[55-57].

If pCNCD is not performed, the patient is at risk for central recurrence and may require a second operation in order to remove persistent or recurrent nodal disease. Because of the presence of fibrosis and scar tissue, re-operation may be associated with higher morbidity than pCNCD done at the first surgery. Segal *et al*[58] reviewed 503 patients retrospectively operated on for PTC, and the 48 requiring reoperation had higher complication rates of permanent RLN injury (25% *vs* 8%) and permanent HP (8.3% *vs* 5%). Simon *et al*[59] reported 77 patients undergoing a second surgery for recurrence out of a total of 252 primarily operated PTC, also being rates of permanent RLN palsy (6.8% *vs* 2.6%) and HP (3.9% *vs* 1.7%) higher for the re-operative group. On the other hand, Shen *et al*[60] found similar results in all the parameters analysed related to morbidity between first time performed pCNCD (n = 189) and re-operated patients (n = 106) with PTC (permanent HP, 0.5% *vs* 0.9%; permanent hoarseness, 2.6% *vs* 1.9%; and, transient hoarseness, 4.8% *vs* 4.7%).

As a conclusion, when an extensive review of the literature is done there seems to be no arguments favouring routine or pCNCD as an universal rule for patients with PTC. The guidelines and consensus documents of the most important medical and surgical societies are in the direction of selecting subgroups of patients with high risk of recurrence for pCNCD, specially T3 or T4 tumors, multifocal/bilateral tumors and patients with BRAF V600E mutation detected in the preoperative setting. In the rest

of PTC, which are the majority, TT must be considered an oncological proper treatment providing the best overall survival.

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