REVIEW ARTICLE

Prophylactic Central Neck Dissection in Clinically Node-Negative Differentiated Thyroid Carcinoma: An Overview

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ABSTRACT

Although therapeutic central neck dissection is recommended for patients with differentiated thyroid cancer with cervical lymph node metastasis, the effectiveness of prophylactic central neck dissection following total thyroidectomy in patients with clinical node-negative differentiated thyroid cancer remains controversial. There are many arguments in favor and many against the execution of prophylactic central neck dissection.

The authors review the most recent literature and illustrate the latest published guidelines, focusing on the currently hottest and most debated points.

Authors conclude that there is still no consensus on the role of prophylactic central neck dissection in clinically node-negative differentiated thyroid carcinoma. Prophylactic central neck dissection is associated with higher rates of hypoparathyroidism and recurrent laryngeal nerve injury with uncertain benefits. So, in the absence of involved lymph nodes, prophylactic central neck dissection should be avoided, reserving it to high-risk patients with advanced primary tumors; prophylactic central neck dissection should be performed by high-volume surgeons to avoid definitive complications.

Key words: differentiated thyroid cancer; papillary thyroid carcinoma; cN0; central lymph node metastasis; neck dissection; central neck dissection; prophylactic central neck dissection.

1. Introduction: Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy and the most common malignant neoplasm of the thyroid gland[1]. The incidence of thyroid cancer has increased dramatically in the last few decades (almost 310% between 1950 and 2004)[2,3] and it is surmised to become the third most common cancer in women of all ages by 2019[3]. It continues to be the most rapidly increasing cancer (>5% per year in both men and women) with an estimated 64,300 new cases diagnosed in the United States in 2016[4].

Papillary thyroid carcinoma (PTC) is the most common histopathological subtype of thyroid carcinoma, accounting for about 80-85% of thyroid cancers[2,5-8].

The prognosis for treated DTC patients is excellent with 10-year survival rates exceeding 90% in the past few decades[1,4,5] and 15-year survival rates of >87%[9]; unfortunately, even for clinically node-negative DTC, regional lymph-node metastases occur in up to 20-80% of cases mostly in the central compartment of the neck (level VI) comprising the prelaryngeal (Delphian), pretracheal, and paratracheal nodal basins[1,3,4,8,10-14]; micrometastases are reported in 40-90% of cases[15,16].

The presence of nodal disease confers increased risk of recurrence but has traditionally been thought to have no impact on overall survival[10,17-19]. Recent studies have indicated that regional lymph node metastases (LNM) increase the risk of loco-regional recurrence (LRR) and have an adverse effect on survival, especially in older patients (age >45 years) [5,6,10,20-23]. In a recent large population-based study, LNM was shown to be associated with increased risk of mortality[6,9]. Prognosis is negatively impacted if five or more metastatic lymph nodes are identified during neck dissection[10]. Other studies have demonstrated that occult LNM increase LRR but does not affect disease-specific survival[3,10].

This contributes to a high LRR rate as the primary problem for clinical node-negative patients, and could reach 15-30%, seriously affecting patients' postoperative quality of life[1,5,6,24]. The presence of LNM at diagnosis was found to be associated with a 4.2-fold and 6.2-fold higher risk of LRR and cervical lymph node recurrence, respectively[9]. Prophylactic central node dissection (PCND) may improve disease-specific survival and decrease LRR and postoperative thyroglobulin (Tg) level[1,15-17].

The inability to diagnose LNM accurately by preoperative ultrasonography (US) (low sensitivity) or intraoperative inspection, the high incidence of LNM, the decreased risk of LRR and need for reoperation and its morbidity, the improved ability to justify radioactive iodine (RAI) treatment, the better Tg surveillance, and the failure of 131I ablation in approximately 30% of cases are considered factors that favor PCND[15]. Arguments in favor of PCND are also the detection of subclinical LNM in up to 60% of patients, with possible advantages of long-term outcome, increased morbidity if re-operation becomes necessary when PCND is not performed and the lack of accurate histopathological staging without lymph node analysis[13].

Although therapeutic central neck dissection (CND) is recommended for patients with cN1 DTC, the effectiveness of PCND following total thyroidectomy (TT) in patients with clinical node-negative (cN0) DTC remains controversial[1,2,4,16,21,22,25].

2. Preoperative evaluation and central compartment staging

Clinical examination will detect metastases in approximately 10-15% of patients[23,26]. US and contrast-enhanced computed tomography (CT) are not sensitive in detecting metastatic central neck lymph nodes preoperatively because they are usually small and are obscured by the overlying thyroid gland[8].

Despite the high diagnostic accuracy in detecting the lateral LNM (with a sensitivity of 94%), preoperative US diagnosis of central LNM is technically difficult and often unreliable due to their proximity to the thyroid gland and air-filled trachea[14]; the diagnostic accuracy of US for cervical nodal metastasis in thyroid carcinoma is 63-70%[12] with a sensitivity of 26-84% and a specificity of 88-97%[2,3,7,12].

Identification of central compartment lymph nodes pre-operatively with US is user dependent and must be performed meticulously and by an experienced surgeon or radiologist[12]. Among the sonographic features of lymph nodes that are suspicious for metastatic disease, microcalcifications, cystic areas, short axis >5 mm, and peripheral vascularity are specific while peripheral vascularity and loss of fatty hilum are sensitive[27].

The sensitivity of a CT scan is low ranging from 39% to 66%[28] and its accuracy is about 66%[12]; combined US and CT approach shows a sensitivity of 48-54% and an accuracy of 66-69%[12]. This accuracy remains unsatisfactory for decision making[12].

Intraoperative detection of metastatic nodes by the surgeon has been demonstrated to be unreliable, less than 30% in some studies[12]. Patients with DTC often may have some component of coexisting lymphocytic thyroiditis, and therefore the presence of slightly enlarged or firm lymph nodes often does not correlate well with the presence of metastasis[12,20].

Fine needle aspiration cytology (FNAC) associate to Tg measurement is the more accurate diagnostic method for cervical LNM from DTC[29] when they are visible preoperatively.

Sentinel lymph node biopsy shows an inconsistent pattern of nodal spread, and, therefore, does not seem to be readily transferable to thyroid surgery[20]. Similarly, the role for frozen section evaluation of sampled lymph nodes to identify metastatic disease requiring CND remains uncertain[20].

3. Current guidelines and international consensus statements

The 2009 American Thyroid Association (ATA) guideline recommends therapeutic CND for any patients with clinically positive nodes and PCND for patients with T3 and T4 primary tumors without evidence of nodal metastases, or with known lateral LNM[14,22,28,30]. These general recommendations remained intact in the

2015 update, with the addition that PCND may be performed if the information gained will guide further steps in therapy[14,22]. The 2015 guidelines add a statement that it is appropriate to not perform a PCND for T1 or T2 tumors[2,7,12,14,22].

Consensus from European Society of Endocrine Surgeons (ESES) recommends that PCND should be risk-stratified, and patients with larger tumors, aged older than 45 years, age younger than 15 years, bilateral or multifocal tumors, or known involved lateral lymph nodes could receive PCND[7,12,14,31]. These European guidelines also highlight importance of PCND being done by surgeons in specialized centers[12,31].

The British Thyroid Association, in their 2014 guidelines, do not recommend routine PCND, citing high incidence of recurrent nerve damage and permanent hypoparathyroidism, and as such, they state that decision-making should be personalized; they do state that bilateral CND has a benefit over ipsilateral CND[12,14]. In the British guidelines, CND is recommended in patients with known involved lateral nodes[12].

In line with ATA guidelines, the Unità di Endocrino-Chirurgia (Endocrine Surgery Unit) guidelines state that prophylactic dissection should be performed in high-risk patients with advanced primary tumors (T3 or T4) by surgeons with high-volume caseloads to decrease definitive complications[15,20,22,28,32,33].

The National Comprehensive Cancer Network expert panel gives PCND a category 2B recommendation, stating that performance for patients with T3 or T4 tumors could be considered, but must be weighed against the increased risk of hypoparathyroidism and nerve injury[12,14].

In contrast, the Japanese Society of Thyroid Surgeons /Japanese Association of Endocrine Surgeons recommends routine use of PCND, based on increased risk of complications if surgery is needed for lymph node recurrence[12,14].

4. Surgical anatomy of the central compartment

To definite the anatomic boundaries of the central lymph nodes and their subgroups is significantly important for thyroid carcinoma. The central neck compartment is composed of level VI and level VI[12]. This consists of the region bounded superiorly by the hyoid bone, laterally by the carotid arteries, anteriorly by the superficial layer of the deep cervical fascia, and posteriorly by the pre-vertebral layer of the deep cervical fascia. The inferior border of the central compartment is defined as the innominate artery. This region includes the pre-laryngeal (Delphian), pre-tracheal, paralaryngeal and paratracheal lymph nodes[12,20]. Level VII contains the anterior superior mediastinal lymph nodes found below the level of the upper border of the sternal manubrium and above the innominate (brachiocefalic) artery[12,20]. The majority of the lymph nodes within the central compartment are located inferior to the larynx, and the most commonly involved central lymph nodes in thyroid carcinoma are the pre-laryngeal (Delphian), pre-tracheal, and the right and left paratracheal nodes[12,20,28].

Superior pole tumors may occasionally metastasize to parapharyngeal nodes deep to the sternohyoid and omohyoid muscles along the course of superior thyroid vasculature and to the retropharyngeal space[12].

4.1 Definition of a central neck lymph node dissection

The ATA consensus statement regarding the terminology and classification of the central neck[28] states that the CND contains the perithyroidal and paratracheal soft tissues as well as lymph nodes; it is limited superiorly by the hyoid bone, laterally by the common carotid arteries, anteriorly the by the superficial layer of the deep cervical fascia (and posterior aspect of the infrahyoid muscles), posteriorly by the deep layer of the cervical fascia (covering the prevertebral muscles and the oesophagus), and inferiorly by sternum and the innominate artery[14,18,20,28,31]. The term CND, as defined by the ATA consensus, implies removal of prelaryngeal and pretracheal lymphatic tissue and at least one paratracheal lymph node[28].

Lymph nodes found from the level of the sternal notch to the level of the innominate vein are described as level VII lymph nodes, some or all of which are often removed during CND[14]. PCND is defined as the complete excision of level VI and VII lymph nodes (based on the recognized anatomic continuity from the neck and superior mediastinum) [15].

5. Complications in CND associated with TT

Increased rates of postoperative complications have been reported in patients undergoing PCND, especially among low volume surgeons[1,12,15]. The complications associated with PCND include recurrent laryngeal nerve (RLN) injury with resulting voice dysfunction and parathyroid devascularization or removal with resultant temporary or permanent hypoparathyroidism[22].

The rate of transient RLN injury ranges from 0% to 7.3%, while rates of permanent unintentional RLN injury ranges from 0% to 5.9%[28,34,35].

Intraoperative neuromonitoring may be helpful in identifying a loss of signal on the first side that could suggest to stage completion thyroidectomy, especially in case of non-aggressive thyroid cancer[28,36].

Temporary hypoparathyroidism after CND occurs in 14% to 40% of cases in high volume centers[20,24]. In the literature the rates of transient hypoparathyroidism reported are extremely variable ranging from 8.7% to 86%, while rates of permanent hypoparathyroidism ranges from 0% to 16.2%[28,34,35].

Recent studies report that the overall prevalence of temporary hypocalcemia after TT with CND was significantly higher than after TT alone (31% vs 16%)[12]. The risk for postoperative hypocalcemia is between 2.0 and 2.7 times higher when CND is performed[10].

87-95% of temporary hypoparathyroidism caused by initial operation would recover in 6 postoperative months[1]. The higher rates of hypoparathyroidism with PCND are likely secondary to the close association of the inferior parathyroid glands to the level VI lymph nodes, and therefore, these parathyroid glands often are removed or devascularized during either a prophylactic or therapeutic procedure[18].

Inexperienced surgeons are associated with a greater rate of complications[19].

To decrease the risk of postoperative complications related to PCND, ipsilateral CND has emerged as an alternative approach to bilateral CND[1,24,34,37].

5.1 Complications in revision CND

Surgery for recurrent disease in the central neck compartment is a complex procedure, and specific data regarding surgical morbidity are scarce, mainly as a result of the limited number of patients requiring PCND[28]. Indications for revision surgery in central neck compartment include recurrent metastatic thyroid carcinoma to central compartment lymph nodes and inadequate initial surgery[28].

PCND is technically demanding because of the abundant scar tissue and distorted anatomy, which may lead to a higher risk of injury to the RLN and parathyroid glands. RLN may be, indeed, in a less predictable location after thyroidectomy; in addition, the parathyroid glands and RLN may be encased within fibrotic tissue, making them indistinguishable from the tumor[28].

Central neck LNM are usually detected during follow-up by means of increased serum Tg levels and by radiological examinations (US, RAI scan, or PET-CT), and subsequently confirmed with FNAC and contrast enhanced MRI or CT[28].

Several series have reported a higher incidence of permanent RLN palsy in PCND compared to primary setting procedures, with rates ranging from 1% to 12%[28] and an incidence of temporary and permanent hypoparathyroidism after revision surgery, ranging from 0.3% to 15%, and from 0% to 4.9%, respectively[23,28].

Due to the elevated complexities of revision surgery and known correlation between surgeon experience and outcomes, recurrent and persistent DTC should only be managed surgically by the most experienced thyroid cancer surgeons.

6. Risk factors for central compartment LNM

Factors increasing the risk of central LNM include tumor size > 1 cm, aggressive variants of DTC, extra-thyroidal extension, multifocality, age >45 years or <15, male gender, white race, familiarity, lymphovascular invasion and BRAFV600 mutation[1,5,10-12,15,16,18,19,21,38].

Age is one of the most important prognostic factors of DTC[3,8]. Patients older than 45 years are more often associated with poor prognosis and increased recurrence, as well as frequently reported for child <15 years[16]. Some studies have shown that cN0 patients ≤45 years old to have higher rate of central LNM than older patients and that ages younger than 45 years was an independent risk factor of central LNM in cN0 patients

with microcarcinoma[1,4,8,38]. Male gender is another significant risk factor for CLNM[1,4,19,38].

Tumor size is a very important factor in TNM staging, and large tumors are more prone to be aggressive[3,9,16]. The tumor size has been repeatedly confirmed as an independent predictor of both pathologic and clinical outcomes. LNM is known to increase with tumor size[16]; larger tumors (>1cm) were associated with an increased risk of central LNM[16,19]. Tumor size (>5mm) was also a significant predictive factor of central LNM in PTC microcarcinoma[8,16,38].

Multifocality and bilaterality have been reported to increase the rate of central LNM in PTC[8,9]. Lymphovascular invasion and extrathyroidal extension have been found to be associated with an increased risk of central LNM in DTC patients[8,38]. Capsular invasion in particular is associated with central LNM; the incidence of capsular invasion is higher in patients with central LNM than those without[8].

The presence of a BRAF V600E mutation has been associated in many studies with the aggressiveness of DTC (extrathyroidal invasion, LNM, and advanced stage) and also with disease-specific mortality when associated with other aggressive features, such as extrathyroidal extension[16,20]. However, BRAF V600E mutation analysis offers a very low positive predictive value (28%) for disease recurrence[20].

Cancer in the upper pole of thyroid are associated with higher rate of lateral neck node metastasis, while those in the lower pole have an increased risk of central node metastasis[8]. Cases of skip metastases to the lateral compartment (with the central being negative) can occur in up to 18% of patients, which occur more commonly in superior pole tumors[16,20].

An important limitation of risk factors for central compartment metastases is that they are based upon surgical histology which is not available until the post-operative period after the decision for central compartment dissection has been made[12].

7. Discussion

PCND might reduce LRR, improve disease-free survival, increase the number of patients with undetectable levels of Tg, and increase permanent hypoparathyroidism and RLN lesions[16].

Several prospective studies have demonstrated that PCND is able to decrease serum Tg levels and as a consequence, is associated with a greater rate of postoperative athyroglobulinemia[37]. Moreover, PCND can improve the accuracy of staging and selecting patients for RAI, and can decrease the risk for a reoperative procedure for recurrence[18,23,37,39].

PCND associated to TT increased the rate of adjuvant RAI treatment[1]. PCND led to 30% cN0 DTC patients upgrading their TNM staging, for whom RAI and long TSH suppression treatment were needed[1]. RAI is associated with potential morbidity, including salivary gland dysfunction, which can cause chronic dry mouth and throat, increased dental caries and loss of teeth, salivary gland swelling, and recurrent sialadenitis; it can also cause ageusia (loss of taste), xerostomia, lacrimal gland

dysfunction and nasolacrimal outflow obstruction, leukopenia, nausea, vomiting, pulmonary fibrosis, decreased sperm counts in men and ovarian dysfunction and menstrual irregularities in women, dysphagia, and second primary malignancies (0.5%)[11,16,40]. It is also associated with increased financial cost[40]. Higher morbidity rate, the uncertain significance of node-involvement, absence of proven benefits on survival, a consequent up staging and finally a RAI overuse with undesirable side effects are advocated against routine CND[16].

To reduce morbidity PCND must be performed by experienced hands[16].

The American Thyroid Association (ATA) assessed the feasibility of performing a randomized controlled trial to evaluate the benefit of prophylactic CLND[4,14]. This committee estimated that a clinical trial spanning 7 years with enrollement of 5840 patients, with a total study cost of approximately $20 million ($3425 per enrolled study subject) would be necessary[12,31]. The authors conclude that such a randomized controlled trial of PCND is not readily feasible[12].

8. Conclusions

There is still no consensus on role of PCND in clinically node-negative DTC. CND is associated with higher rates of transient hypoparathyroidism and RLN injury without safe and clear benefits.

So, in the absence of involved lymph nodes, prophylactic dissection should be avoided, reserving PCND to high-risk patients with advanced primary tumors; it should be performed by high-volume surgeons to avoid definitive complications.

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