

Prophylactic central neck dissection for papillary thyroid carcinoma: the terms of the debate

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Abstract. An increasing interest in the management of central neck lymph nodes in the surgical treatment of papillary thyroid cancer is observed. While it is widely accepted that patients with clinically apparent lymph nodes metastases should undergo compartment-oriented neck dissection, controversy exists about the need for prophylactic central neck dissection. The main issues that have been raised are the following ones: the definition of the anatomic boundaries and terminology of central neck dissection, the value of the recommendations expressed by the most authoritative association, the arguments in favour and against the appropriateness of prophylactic neck dissection, the laterality of central neck dissection. This article aims at reviewing the literature on prophylactic central neck dissection for papillary thyroid cancer in order to clarify some issues and to offer the reader a clear and concise overview of this complex debate. (www.actabiomedica.it)

Key words: papillary thyroid carcinoma, lymph nodes metastases, prophylactic central neck dissection

Introduction

Papillary thyroid carcinoma (PTC) is by far the most common thyroid malignancy representing more than 90% of new thyroid cancer overall (1). Cervical nodal metastases are quite commonly observed in PTC, both in the central neck compartment and in the lateral one (2). The age-old debate about hemithyroidectomy versus total thyroidectomy for the treatment of PTC has now been replaced by the modern debate about the appropriateness of prophylactic central neck dissection (CND). It should be stated in advance that any discussion on this item is confounded by the lack of perspective trial and by the indolent natural history of this neoplasm. In the recent literature there has been a heated discussion from which a lot of arguments raised. Also the latest version of guidelines from the most authoritative association included preliminary recommendations on prophylactic CND. Nevertheless, the issue remains controversial or even it is getting more confused. The purpose of this review

article is to report the terms of the debate in a complete, schematic and clear fashion.

Literature search strategy

Data for this review were derived from pertinent articles identified from PubMed or as reference in relevant articles. Literature searches included the guidelines provided by the most authoritative national and international association in the field of thyroid disease and oncology. Guest editorial and letters to editor were also considered. Only papers published in English were used.

Anatomic boundaries and terminology of central neck dissection for thyroid cancer

Standard classification and terminology of neck dissection have been widely adopted after the report

published in 1991 by Robbins et al (3). Despite this original paper and subsequent updates, there remains controversy regarding CND: its inferior extent, validity of unilateral versus bilateral dissection, inconsistent terminology regarding indications such as routine rather than therapeutic versus prophylactic/elective. Due to the ongoing debate on the role of CND for papillary thyroid carcinoma, the need for a standardized classification and terminology was recognized. In 2009, the American Thyroid Association (ATA) published a consensus statement in order to define this issue (4).

Anatomic boundaries: the central compartment is 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 deep layer of the deep cervical fascia. The inferior extent of central neck dissection has been variably described as the sternal notch or the brachiocephalic (innominate) vasculature. Because the location of the thyroid gland is low in the neck near the thoracic inlet, the lymphatic drainage is contiguous with the anterior superior mediastinum that is accessible via a cervical approach. As a result, the inferior border of the central compartment is defined as the innominate artery on the right and the corresponding axial plane on the left. In terms of Robbins levels, it means that the central neck dissection should include the VI and VII levels.

Terminology: the central neck compartment contains the following lymph nodes basins: prelaryngeal (Delphian), pretracheal, right and left paratracheal nodes. At a minimum, CND should include the prelaryngeal, pretracheal and at least one paratracheal lymph node basin. This kind of dissection is called “unilateral central neck dissection”. When both the right and left paratracheal nodal basins are removed, the term “bilateral central neck dissection” has to be adopted. Isolated removal of only grossly involved lymph nodes (the so called berry picking) violates the nodal compartment entered without adequately addressing its disease and may be associated with higher recurrence rates and morbidity from revision surgery. A therapeutic CND implies that nodal metastasis is clinically apparent (preoperatively or intraoperatively)

or by imaging. A prophylactic CND implies that nodal metastasis is not clinically detected or by imaging. The importance of this distinction cannot be overemphasized since the impact of clinically detectable nodal metastasis may differ from microscopic nodal metastasis.

Indications for central neck dissection: what the guidelines say

According to the National Comprehensive Cancer Network guidelines (NCCN v.1.2010) CND has to be performed when lymph nodes are palpable or biopsy positive. If the nodes are negative, prophylactic CND can be considered but is not required in all cases. Features that could call for prophylactic CND are: age <15 and >45; radiation history; known distant metastasis; extrathyroidal extension; tumour >4 cm in diameter and aggressive histological variant. The recommendation expressed is based on lower-level evidence and there is nonuniform NCCN consensus but no major disagreement (5).

The American Thyroid Association guidelines (ATA, 2009) state that CND should be offered to clinical N+ patients. In patients with clinically uninvolved lymph nodes, ipsilateral or bilateral CND may be performed, especially for advanced primary tumours (T3 or T4). It is recognized that for patients with small, non-invasive tumors the balance of risk and benefit may favour simple near-total thyroidectomy with close inspection of the central compartment with compartmental dissection only in the presence of obviously involved lymph nodes. The level of this recommendation is an expert opinion based one (6).

In the British Thyroid Association guidelines (BTA, 2007) it is said that CND is to be performed in patients with clinically positive lymph nodes. Prophylactic CND should be performed in presence of any of the following features: male sex, age > 45 years, tumour greater than 4 cm in diameter, extracapsular or extrathyroidal disease, suspicious nodes encountered at surgery. This recommendation arises from expert committee reports or opinions and/or clinical experience of respected authorities, in absence of directly applicable studies of good quality (7).

The European consensus for the management of differentiated thyroid carcinoma endorsed by the European Thyroid Association in 2006 state that lymph nodes dissections should be performed in patients with pre-operative or intra-operative diagnosis of lymph nodes metastases. The benefits of prophylactic CND is deemed controversial. According to this task force, there is no evidence that the prophylactic CND improves recurrence or mortality rates, but it allows an accurate staging of the disease that may guide subsequent treatment and follow-up (8).

According to the American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi guidelines (AACE/AME, 2006), lymph nodes within the central compartment should be removed, especially if surgeon has specific training for and experience with thyroid surgical techniques. Patients with microcarcinoma (tumor < 1cm in diameter) and no evidence of lymph node involvement may avoid CND. This recommendation is considered an evidence based on the clinical experience, descriptive studies and expert consensus opinion (9).

Prophylactic central neck dissection: the issues in favour

To reduce the locoregional recurrences and to improve the survival. Cervical lymph node metastases are common in papillary thyroid carcinoma occurring in 20% to 50% of patients and micrometastases are even more common (10). One series found micrometastases in nearly 90% of the examined nodes (11). Although lymph node metastases are traditionally considered to have no clinically important effect on outcome in low risk patient, recent studies have shown that lymph node metastases represent a negative prognostic indicator with increased recurrences and decreased survival (10, 12, 13). It has been suggested that, due to the indolent behaviour of this neoplasm, a very long follow-up period is needed to identify recurrent disease. According to these findings, routine central neck dissection is useful to eradicate the disease.

Preoperative and intraoperative diagnostic limitations. Ultrasonography is the most sensitive method

for evaluating cervical lymphnodes (14), nevertheless the evaluation of central compartment neck nodes is considered to be quite difficult because of the presence of the thyroid gland, and most of these lymph nodes are quite small (15). It has been reported that preoperative ultrasound does not detect approximately 50% of metastatic lymph nodes in the central compartment (2, 16). Intraoperative macroscopic evaluation often fails in differentiating benign from metastatic lymph nodes, especially if the patient shows concomitant Hashimoto's thyroiditis where lymph nodes are diffusely enlarged (17-19).

Limitations of radioiodine ablation on lymph nodes metastases. The efficacy of radioiodine on lymph nodes metastasis may be limited. First, the tumour's ability to uptake ¹³¹I can be poor: 25 to 30% of tumors show scarce iodine uptake and this capacity decreases with age. Secondly, there are radiobiological constraints to be considered: only foci measuring less than 10 mm in diameter can be potentially destroyed (20).

To avoid revision surgery on central neck compartment. It is widely recognized that reoperation in the central neck compartment for recurrent disease has greater risk of recurrent laryngeal nerve injury and hypoparathyroidism (10). This supports a more aggressive initial surgery.

To achieve an accurate staging and determine postoperative treatment. Prophylactic CND allows the identification of occult lymph nodes metastases, resulting in a variation of the tumour stage. Furthermore, these findings may have implications on radioiodine administration. Recent studies reported that prophylactic central neck dissection modified the indication for radioiodine in a considerable amount of patient with pT1 tumours (21).

To improve the follow-up strategies. It has been demonstrated that CND is able to reduce the rate of postoperative detectable thyroglobuline level (19). This results in: less intense and simplified follow-up, considering the patient as disease free, avoiding further procedures such as fine needle aspiration or surgical explorations.

The issues against

Lack of evidence. To date, there is no perspective randomized controlled trial looking at the effect on outcome of prophylactic CND. Despite the increasing tendency to perform the prophylactic CND, no evidence based data demonstrating the efficacy of this procedure in reducing the recurrence rate and the disease specific mortality are present (10, 15, 17, 22).

Primum non nocere (first do no harm). Some studies which compare the morbidity between thyroidectomy alone and thyroidectomy with CND are available. No statistically significant differences have been found except for temporary hypoparathyroidism, which is more frequent in patients treated with CND. Therefore the Authors conclude that no increased permanent morbidities by performing the CND at the same time as thyroidectomy are observed (23). Nevertheless, if single results are examined, a clear tendency to increased laryngeal nerve palsy and permanent hypoparathyroidism in patients who underwent CND emerges. Furthermore, the likelihood of permanent morbidities resulting from CND may be higher in the hands of less-experienced surgeons than is reported in published series by experienced high-volume surgeons.

Micrometastases have doubtful prognostic relevance. Due to the large diffusion of prophylactic CND, a number of publications has been made about the high rate of micrometastatic disease found in electively dissected neck. However, the presence of microscopic nodal metastases has not been shown to have a major impact on patient's prognosis (10, 15). Moreover, microscopic nodal metastases have been frequently found also in lateral neck compartments (10). Thus, if we recommend routine CND in order to eradicate any microscopic disease, we should also dissect the lateral neck compartments.

Skip metastases are frequent. Generally, metastases first involve the nodes in the central compartment and then the lateral compartment (24). However, skip metastases leaping the central compartment have been reported in 11.2% to 19.7% of the cases (24). This as-

pect adds further doubts toward the efficacy of prophylactic CND in completely eradicating the neoplastic disease.

Staging, prognosis and ablation therapy. The relevance of micrometastatic disease has been already criticized above. It seems that the upstaging due to the discover of occult micrometastases has no prognostic implications. Secondly, even if it has been demonstrated that a considerable amount of pT1 patient will receive radioiodine in consideration of the elective CND, it remains still unclear if this will be of some benefit for the patients.

The problem of incidental carcinomas. We often do not know whether a patient harbors a cancer until after thyroidectomy and final pathology is available. If routine CND is advocated, how we behave with a postoperative unexpected diagnosis of cancer? It is difficult to justify reoperating the central neck compartment for a prophylactic dissection with its attendant higher risk of morbidity and for which there is no proof of efficacy.

Ipsilateral or bilateral central neck dissection?

Going beyond the debate on prophylactic CND appropriateness, another controversial item regards the ipsilateral or bilateral extension of the CND. The guidelines of the most authoritative associations do not provide any recommendation about this topic. Only in the latest American Thyroid Association guidelines (ATA, 2009) the laterality of central neck dissection is mentioned, but no indications are expressed. Two recent papers investigated this issue obtaining similar results as follows (25, 26). Tumours with maximal diameter greater than 1 cm are associated with a statistically significant higher rate of ipsilateral central nodes metastases at multivariate analysis. The presence of ipsilateral central lymph nodes metastases is a potential independent predictor of synchronous contralateral central metastases. Papillary thyroid cancers smaller than 1 cm in diameter (i.e. microcarcinomas), even if multifocal, do not generally have nodal metastases in the central compartment

controlateral to the primary tumour. These preliminary data may lead to the following remarks: 1) bilateral prophylactic CND is to be considered in tumours greater than 1 cm; 2) controlateral central neck dissection is recommended when ipsilateral central nodes metastases are founded; 3) in patients with papillary microcarcinoma prophylactic CND may be avoided. We caution that these studies investigated this item from an oncologic point of view. However, also the functional aspect has to be considered since the decision to electively dissect both sides of central neck compartment should take into account the higher risks of hypoparathyroidism and laryngeal nerves injury.

Conclusions

“The general lack of a great body of material for prolonged follow-up studies emphasizes the need for extreme caution in making all-inclusive pronouncements of a prognostic nature about a form of cancer in which the most noteworthy attribute is the extreme chronicity” (27). We believe that these 1950s quotes are perfectly applicable to the recent diffusion of routine prophylactic CND for papillary thyroid cancer. Like some other Authors, we believe that risk group stratification is extremely important in order to state appropriate criteria for prophylactic CND. The guidelines of the most authoritative associations suggest some features that could call for prophylactic CND: age < 15 and > 45 years, male sex, radiation history, tumour greater than 4 cm in maximal diameter, extracapsular or extrathyroidal disease, aggressive histological variant, known distant metastases. Some of these features cannot be known at the time of preoperative planning. Therefore, intraoperative findings as well as frozen pathology may have major relevance. As a consequence, the informed consent should include information about possible variations of surgical procedures and related risks. The future is represented by the clinical implementation of molecular biology. It has been demonstrated that BRAF positivity predicts for poor prognosis and a higher probability of nodal spread (28).

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