European Journal of Surgical Oncology 44 (2018) 1671–1678

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Review

Decision making for the central compartment in differentiated thyroid cancer☆

João Gonçalves Filho [a, 1], Mark E. Zafereo [b, *, 1], Faisal I. Ahmad [b], Iain J. Nixon [c], Ashok R. Shaha [d], Vincent Vander Poorten [e], Alvaro Sanabria [f], Avi Khafif Hefetz [g], K. Thomas Robbins [h], Dipti Kamani [i], Gregory W. Randolph [i], Andres Coca-Pelaz [j], Ricard Simo [k], Alessandra Rinaldo [l], Peter Angelos [m], Alfio Ferlito [n], Luiz P. Kowalski [a]

[a] Head and Neck Surgery and Otorhinolaryngology Department, A C Camargo Cancer Center, Sao Paulo, Brazil
[b] Department of Head and Neck Surgery, MD Anderson Cancer Center, Houston, TX, USA
[c] Consultant Otorhinolaryngologist Head and Neck Surgeon NHS Lothian/ Edinburgh University, UK
[d] Head and Neck Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[e] Otorhinolaryngology-Head and Neck Surgery and Department of Oncology, University Hospitals Leuven, KU Leuven, Leuven, Belgium
[f] Head and Neck Surgeon, Department of Surgery, School of Medicine, Universidad de Antioquia-Fundacion Colombiana de Cancerologia-Clinica Vida, Medellin, Colombia
[g] ARM Center for Advanced Otolaryngology Head and Neck Surgery, Assura Medical Center, Tel Aviv, Israel
[h] Division of Otolaryngology - Head and Neck Surgery, Southern Illinois University School of Medicine, Springfield, IL, USA
[i] Division of General Otolaryngology and Thyroid and Parathyroid Endocrine Surgery, Mass. Eye and Ear, Boston, MA, USA
[j] Department of Otolaryngology, Hospital Universitario Central de Asturias, Oviedo, Spain
[k] Consultant Otorhinolaryngologist Head and Neck Surgeon Head and Neck Cancer Unit Guy's and St Thomas' Hospital NHS Foundation Trust London, London, UK
[l] University of Udine School of Medicine, Udine, Italy
[m] Professor of Surgery, Chief of Endocrine Surgery, University of Chicago Medicine, Chicago IL, USA
[n] Formerly Director of the Department of Surgical Sciences and Chairman of the ENT Clinic at the University of Udine School of Medicine, Udine, Italy

ARTICLE INFO

Article history:
Accepted 3 August 2018
Available online 13 August 2018

Keywords:
Thyroid cancer
Central compartment
Neck dissection
Thyroidectomy
Lymph node metastases
Level VI
Surgery

ABSTRACT

The central compartment is a common site for nodal spread from differentiated thyroid carcinoma, often occurring in patients without clinical or ultrasonographic (US) evidence of neck lymph node metastasis (cN0). However, the role of elective central compartment neck dissection (CND) among patients with DTC remains controversial. We performed a systematic literature review, also including review of international guidelines, with discussion of anatomic and technical aspects, as well as risks and benefits of performing elective CND. The recent literature does not uniformly support or refute elective CND in patients with DTC, and therefore an individualized approach is warranted which considers individual surgeon experience, including individual recurrence and complication rates. Patients (especially older males) with large tumors (>4 cm) and extrathyroidal extension are more likely to benefit from elective CND, but elective CND also increases risk for hypoparathyroidism and recurrent nerve injury, especially when operated by low-volume surgeons. Individual surgeons who perform elective CND must ensure the number of central compartment dissections needed to prevent one recurrence (number needed to treat) is not disproportionate to their individual number of central compartment dissections per related complication (number needed to harm).

Published by Elsevier Ltd.

Introduction

Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy and its incidence has continued to rise worldwide over the last 30 years, particularly papillary thyroid carcinoma (PTC) [1]. Although usually associated with indolent

☆ The paper was written by members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com).

* Corresponding author. 1515 Holcombe Blvd Unit 1445 MD Anderson Cancer Center, Department of Head and Neck Surgery Houston, TX 77030, USA.
E-mail address: MZafereo@mdanderson.org (M.E. Zafereo).

[1] The first two authors, JGF and MEZ, contributed equally in the preparation of the manuscript.

https://doi.org/10.1016/j.ejso.2018.08.005
0748-7983/Published by Elsevier Ltd.

behavior, excellent prognosis, and low mortality of 1%, there is high incidence of lymph node metastases, particularly in the central compartment (levels VI-VII), and relatively high incidence of recurrent disease following surgery (approximately 10–20%), the most common location being central compartment lymph nodes. Even for clinically node-negative DTC, the rate of occult lymph node metastases in the central compartment on histopathological examination is reported to be 20–90% [2–5].

Central neck dissection (CND) performed for removal of clinical or radiologically proven metastatic lymph nodes (cN1a) in the central compartment is termed 'therapeutic' CND [6]. There is a consensus that selective central compartment dissection should be performed in patients with lymph node metastases from DTC in the presence of clinical or ultrasound (US) evidence of nodal disease, with high resolution US being the most sensitive method of detection [7]. However, in the absence of ultrasonographically detectable lymph node metastases, performing an elective (or prophylactic) CND remains controversial [6,8]. Numerous studies have discussed the role of elective CND in patients with clinically node-negative (cN0) necks [2,6,8–13]. On the other hand, many authors question the potential benefit of elective treatment of clinically negative lymph node metastasis in the central compartment [3,14–16]. A third intermediate approach is to perform a frozen section analysis of ipsilateral central compartment excisional lymph node(s) at the time of thyroid surgery, with formal ipsilateral central compartment dissection in the event of intraoperative diagnosis of metastatic lymphadenopathy.

Despite the high rate of occult central nodal metastasis, there is a low rate of clinically meaningful metastases that ultimately influence patient outcomes, and it is a particular challenge to identify in which cases these occult lymph node metastases require intervention at the time of initial surgery. Therefore, the low rate of clinically meaningful metastases and the potential increased risk of complications with elective central compartment dissection provide the basis of an argument against an elective central neck dissection (CND), while the overall high rate of occult central compartment metastases, relatively high central compartment recurrence rates, and the surgical risk in the event that a reoperation is required for recurrent central compartment disease provide the basis of an argument in favor of elective CND. Differences in surgeon volume and experience represent another variable which makes it particularly challenging to inject uniform guidelines into this debate.

In this review, we outline the current literature in the controversy regarding elective CND, and we examine the variability of treatment guidelines from international medical organizations. We seek to provide a balanced review of contemporary literature and expert opinion, and to inject into the debate a call for the individual surgeon to examine their individual recurrence and complication rates in relation to the current literature.

Review strategy

An electronic search of PubMed database published in English language from January 2000 to June 2017, using the keywords "differentiated thyroid cancer" or "differentiated thyroid carcinoma" or "papillary thyroid cancer" or "papillary thyroid carcinoma" combined with "central lymph node metastasis" or "central compartment neck dissection" or "prophylactic central neck dissection" with limits "human" was conducted. The "related articles" function was used to broaden the search, and relevant references of the articles were also searched to identify additional studies. A total of 36 relevant studies were analyzed for systematic review.

The most recent guidelines on central compartment dissection for DTC, according to the American Thyroid Association (ATA) [7], National Comprehensive Cancer Network (NCCN) [17], European Society of Endocrine Surgeons (ESES) [18], British Thyroid Association (BTA) [19], Latin American Thyroid Society (LATS) [20], Brazilian Thyroid Consensus (BTC) [21], and the Japanese Society of Thyroid Surgeons/Japanese Association of Endocrine Surgeons [22] were also reviewed.

The benefits and complications of CND for DTC, as well as its impact on loco-regional recurrence rates were reviewed and discussed among the authors in order to come to consensus regarding the rationale for elective and therapeutic CND in the management of DTC.

Surgical anatomy of central compartment

The central neck compartment is composed of level VI and level VII. 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. 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 (brachiocephalic) artery. 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 [23–27]. However, 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. The mean size of nodes in the central neck is 3.5 mm, and the number of lymph nodes retrieved from a bilateral CND pathologic specimen is 13 ± 5 lymph nodes [11,26,28].

In 2009, the American Thyroid Association Surgery Working Group proposed for the first time a subdivision of the central compartment [26], which was later detailed by Orloff et al. [24]:

A) Pre-laryngeal (Delphian): the region between the hyoid bone and the cricoid cartilage;
B) Pre-tracheal: the region anterior to the trachea from the cricoid cartilage to the innominate (brachiocephalic) artery (includes level VII);
C) Right paratracheal lymph nodes;
D) Left paratracheal lymph nodes.

In 2014, Giugliano et al. [25], proposed a slightly different division of the central compartment in four areas (sub-compartments) where the clinically most important lymph nodes are usually found. These sub-compartments are:

A) Area A, the delphian and pre-thyroidal lymph nodes included in the adipose tissue present in a medial sub-platysmal space that develops from the median fascial folds. This area corresponds to the region of the neck commonly defined as the muscular linea-alba and is superficial to the thyroid capsule and cartilage;
B) Areas B/D, deep lymph nodes contained in the adipose tissue on the right (B) and left side (D) respectively; they are bound laterally by the neuro-vascular bundle of the neck, medially by the trachea, posteriorly by the esophagus, anteriorly by each lobe of the thyroid, cranially by the horizontal line delineated by the entry point of the recurrent laryngeal nerves (RLN) into the cricothyroid membrane and inferiorly by the brachiocephalic (innominate) trunk;

C) Area C, deep pre-tracheal nodes present in the adipose tissues bound superficially by the strap muscles, the pre-tracheal fascia at its deepest point, cranially by the thyroid isthmus and caudally by the brachiocephalic (innominate) trunk [25].

Preoperative evaluation and central compartment staging

Lymph node micrometastases in the central compartment are observed in many PTC patients [26]. Accurate pre-treatment assessment of nodal disease is critical in surgical planning, and US has been established as the initial diagnostic modality for thyroid nodules, and for pre-operative evaluation and staging of patients with DTC [29,30,31,33–37]. 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.

The diagnostic accuracy of US for cervical nodal metastasis in thyroid carcinoma ranges from 30 to 84% in sensitivity and 95–97% in specificity [30,38]. However, the sensitivity and specificity of US in detecting lymph node metastases vary according to the involved neck compartment [30,32]. Since preoperative physical examination and US evaluation of the central compartment may be limited, the role of intraoperative inspection is also important [29,37].

Hartl et al. studied 317 consecutive patients classified as cN0 by US and treated with routine prophylactic CND. Pathologic examination confirmed lymph node metastases in 35% of patients [39]. Wada et al. found 60% of 259 patients with PTC with no evidence of nodal disease on US or clinical examination had occult disease on pathological analysis [40]. In another study which included 358 patients with papillary thyroid carcinoma with no evidence of nodal disease based on negative physical examination, negative findings on preoperative neck US, and no lymphadenopathy evident at intraoperative inspection, lymph node metastases were found in 30% of the patients undergoing elective CND [41].

Raffaelli et al. (2012) published the final results of a prospective evaluation of patients with clinically node-negative PTC who underwent an elective CND and found micrometastases in 35% of patients [42]. Lee et al. (2015) studied the accuracy of US in the diagnosis of lymph node metastasis in 184 consecutive PTC patients. They observed that US had low sensitivity (39%) and high specificity (88%) in detecting central node metastases, with an accuracy of 70% (30).

Reasons for the relatively low accuracy of US in the diagnosis of central lymph node metastases include masking by the presence of the thyroid gland, and the relatively small size of lymph nodes in the central compartment [30]. Thus, some authors have studied the role of CT scan or combination of ultrasonography and CT scan in the preoperative evaluation of lymph node disease in patients with DTC. Lesnik et al. (2014) studied the diagnostic accuracy of US, CT, and both methods in preoperative detection of lymph node metastasis in patients with PTC. In this particular study, the sensitivity of a CT scan, although still low, was superior to US in the evaluation of the central compartment (50% vs 26%) in the presence of the thyroid gland, and greatest sensitivity (54%) was noted when the combination of US and CT scan was employed [36].

Recently, Kim et al. (2017) compared the diagnostic accuracy of US and CT for detecting central lymph node metastasis in a series of 3668 patients with PTC. They also studied the clinical impact of CT-detected central lymph node metastasis in patients considered clinically node negative on US. CT showed a significantly higher sensitivity (39% vs 28%), and accuracy (66% vs 63%) than US. Moreover, combined US and CT approach had a significantly higher sensitivity (48% vs 28%) and accuracy (69% vs 63%) than US alone. Nevertheless, this accuracy remains unsatisfactory for decision making [43].

It is also important to note that comparisons of sensitivity and specificity with ultrasound and CT imaging have been reported with pathologic determination of lymph node metastasis as the gold standard. However, the significance of micrometastases in DTC remains of significant debate, as often these micrometastases behave very indolently and may not affect prognosis nor require definitive treatment.

Rates and patterns of distribution of lymph node metastasis in central compartment

While regional PTC lymph nodes metastases in the central compartment are very common, the majority of pN1 patients have micrometastatic disease at the time of diagnosis [3,12,39,40]. The rates of preoperative clinically apparent lymph node metastasis in the central compartment have been reported to range from 10 to 30%, but microscopic metastasis has been reported in up to 67% in CND performed in clinically negative central necks [3,40–46].

Intraoperative detection of metastatic nodes by the surgeon has been demonstrated to be unreliable, less than 30% in some studies [47,48]. Patients with DTC often may have some component of coexisting thyroiditis, and therefore the presence of slightly enlarged or firm lymph nodes often does not correlate well with the presence of metastasis. Additionally, while the prelaryngeal and pretracheal lymph nodes are readily evaluable during routine thyroid surgery, most surgeons do not advocate for routine intraoperative evaluation of deeper paratracheal bed lymph nodes (which may require more dissection of the nerve, potential parathyroid compromise, and increase scarring in the paratracheal bed) in the absence of a formal dissection of the central compartment.

Wada et al. (2003) studied the frequency and pattern of lymph node metastasis from 259 papillary thyroid microcarcinomas and found metastasis in the central compartment in 64% of patients. Pretracheal involvement was found in 43%, while ipsilateral and contralateral paratracheal lymph nodes were involved in 36% and 19% of patients, respectively [40]. In a prospective study, Roh et al. (2008), systematically studied the pattern of lymph nodes metastasis in 52 patients with PTC and lymph nodes metastasis. In this study, the central compartment was divided into four nodal subsites: pretracheal, ipsilateral and contralateral paratracheal, and superior mediastinal below the sternal notch. During surgery, central nodal metastases were clinically suspected in 87% of patients, and metastasis was present in 90% (47 of 52 patients). Metastatic disease in the ipsilateral paratracheal bed was found in 85%, in the superior mediastinum in 46%, in the pretracheal area in 31%, and in the contralateral paratracheal bed in 9% of patients [49]. Koo et al. studied 111 patients who underwent central compartment dissection and found occult lymph node metastasis in 54%. Of these patients bilateral, unilateral ipsilateral, and unilateral contralateral lymph node metastases were present in 50% (30/60), 43% (26/60), and 7% (4/60) respectively [44].

In 2014, Eun et al. reported a prospective multicenter study of the distribution of central lymph node metastasis in 140 consecutive patients (cN0) undergoing prophylactic bilateral central neck dissection for PTC. In this study, nodal involvement in the central compartment was found in 36% of patients. Twelve (24%) patients had ipsilateral paratracheal lymph node metastasis, 17 (33%) had ipsilateral paratracheal and pre-tracheal lymph node metastasis, 14 (28%) had bilateral paratracheal lymph node metastasis, 9 (18%) had only pre-tracheal lymph node metastasis, and 8 (16%) had prelaryngeal lymph node metastasis [50]. In a recent study that analyzed pattern of central lymph node metastasis in 485 patients with unilateral foci of PTC undergoing elective bilateral CND, occult lymph node metastasis was found in 32% of patients. The most common subsite of central node metastases were the ipsilateral paratracheal lymph nodes (26%), followed by pre-tracheal (13%), pre-laryngeal (5%), and contralateral paratracheal lymph nodes (4%) [51].

The distribution of metastatic lymph nodes acquires importance when practices of central neck dissection are discussed and recommended. The comprehensive CND described in the ATA document, where all the levels are resected, may not be the most common procedure in current practice [7]. Many surgeons use a prophylactic "pretracheal central neck dissection", taking out the lymph nodes located between the recurrent laryngeal nerves, and inferiorly to the level of the thymus gland. With this approach, approximately 40% of potential lymph nodes may be left in situ in the central compartment, although the clinical significance of the undissected lymph nodes remains unclear.

Risk factors for central compartment lymph node metastasis

Many authors have analyzed factors associated with central lymph node metastasis and some have advocated for these risk factors to be considered in selection of patients for elective CND. Recently two large meta-analyses published by Sun et al. (2015) and Ma et al. (2016) studied the risk factors for central lymph node metastasis in patients with cN0 papillary thyroid carcinoma. The first meta-analysis had 9084 patients, and the factors on univariate analysis associated with increased risk of central lymph node metastasis included age <45 years, male gender, multifocal tumor, tumor size >2 cm, primary tumor in the central area, lymphovascular invasion, capsular invasion, and extrathyroidal extension [4]. In a second meta-analysis, 37,355 patients with cN0 papillary thyroid carcinoma were analyzed. The pooled univariate analysis indicated that age <45 years, male gender, tumor size >1 cm, multifocality, bilaterality, extracapsular invasion, angiolymphatic invasion, aggressive histopathologic subtype, and BRAF mutation were associated significantly with central compartment lymph node metastasis [5].

Most risk factors for nodal disease are therefore high risk features and as such are used to justify treatment intensification by many groups (i.e. prophylactic central neck dissection). However, age <45 years is in fact a low risk disease feature, which runs contrary to the ethos that high risk features support a more aggressive approach. Another limitation of some 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. Additionally, given the high frequency (30–70%) of micrometastasis to central compartment nodes, almost any risk factor may appear statistically significant in analyses with significant sample size, and the actual clinical significance of micrometastases remains a matter of debate. As such, prognostic factors for micrometastases to the central neck determined by univariate analysis may not actually represent independent prognostic factors associated with clinically meaningful metastasis. Finally, higher risk of central compartment metastases does not necessarily correlate with higher risk of recurrence in the central compartment following surgery. With the high frequency of metastasis, it may be expected to have a higher rate of nodal recurrence in patients who are not submitted to CND, but up to now, this has not been able to be demonstrated.

Surgical technique – central compartment neck dissection

The central neck compartment and its limits, as defined by Robbins et al. (2002 and 2008) [52,53] in their studies regarding the levels of the neck, and by the American Thyroid Association Surgery Working Group (2009) [54], and detailed by McAlister et al. (2014) [55], comprise the central lymph nodes in the region limited by the hyoid bone superiorly, the innominate artery inferiorly, and the carotid arteries laterally [55]. Notwithstanding this definition, variability in the description of the central compartment neck dissection has been found. Roh et al. (2008) defined the superior limit of dissection as the level of the superior thyroid arteries [49]. Similarly, Grant et al. (2010) in their study with 421 patients undergoing CND utilized the thyroid cartilage to define the superior extent of the dissection [56]. Nevertheless, Holostenco and Khafif (2014) studied prospectively the upper limits of central neck dissection in 27 patients who underwent 31 paratracheal dissections. The surgical specimens were divided into upper and lower paratracheal regions, separated by the nerve curve line (corresponding to the level of the cricoid cartilage). In this study, the authors observed that all upper paratracheal surgical specimens were devoid of lymph nodes, metastatic cells, or other lymphatic structures [57].

In the practice of many surgeons, CND begins with recurrent laryngeal nerve (RLN) identification, dissection and preservation throughout its entire course in the tracheoesophageal groove, followed by a lateral to medial dissection of the paratracheal lymph nodes. The carotid artery is delineated as the lateral border of the dissection, with attention to potential lymph nodes posterior to the common carotid where metastatic lymph nodes can be identified close to the inferior thyroid artery origin. During the dissection, the parathyroid glands must be identified and preserved by retracting tributaries of the inferior thyroid artery laterally, or by autotransplantation of inferior parathyroid glands when preservation of the blood supply is not possible. The superior parathyroid glands can generally be preserved in situ along with their blood supply posterior to the superior aspect of the recurrent laryngeal nerve, as there are relatively fewer lymph nodes in this area. In-depth knowledge of the anatomical relations and variations of parathyroid glands and their vascular supply are of great importance to avoid devascularization and inadvertent removal of parathyroid glands [58–60].

The RLN must be carefully dissected throughout its paratracheal course. On the right side where the nerve runs more in an anteroposterior plane due to its course around the subclavian artery, the paratracheal specimen may be retracted medially and pulled deep to the RLN. Alternatively, the lymph nodes medial and lateral to the RLN may be resected as separate specimens, but it remains critically important to remove the lymph nodes deep to the right RLN. On the left side, the RLN is posteriorly in the prevertebral fascia due to a more inferior and posterior curve around the aortic arch, and the lateral compartment lymph nodes can generally be dissected medially and anteriorly over the RLN. Once the dissected specimen is pulled medial to the RLN, it is dissected away from the trachea while the tissues are retracted upwards so that mediastinal contents are elevated and resected along with the specimen. Usually thymic tissue serves as a good indicator of the lowest extent of the dissection. This part of the dissection must be done very carefully because a tortuous right carotid artery, innominate artery or (rarely) subclavian artery may be exposed in patients posing a risk of injury. The thymus itself rarely contains metastatic nodes, and may contain inferior parathyroid tissue, and thus generally should not be included in the specimen [61].

Concomitant performance of CND along with thyroid surgery increases the rates of the more frequent complications of surgery such as RLN injury and hypoparathyroidism. First, the number and location the parathyroid glands are variable, and one or more – most likely inferior - parathyroid glands may be found among resected paratracheal lymph nodes because their identification and distinction from the lymph nodes may be difficult. If not incidentally resected, the glands may be devascularized. While loss of a single parathyroid gland will not cause hypoparathyroidism, when CND is combined with total thyroidectomy, it is important to preserve as much parathyroid tissue as possible. In case of an isolated parathyroid gland remaining within the paratracheal bed, a small frozen section biopsy, if available, may serve the double purpose of confirming the histology of the gland and establishing whether the parathyroid tissue has blood supply; as the gland should bleed at the biopsy site. If there is no bleeding, and the biopsy confirms parathyroid tissue, then the gland should be excised, cut into small pieces, and implanted in adjacent muscle such as the sternocleidomastoid muscle. Reimplanted parathyroid tissue has a better chance of functioning than devascularized in situ parathyroid tissue.

The rationale and outcomes of central compartment neck dissection

Some studies have reported that an elective central lymph node dissection reduces the risk of recurrences in the central compartment [41,64–66,68–70]. However, other studies have compared recurrence rates in the central neck compartment in patients with clinically node-negative PTC who underwent thyroidectomy alone with those who underwent thyroidectomy and elective CND. In these studies the variability in the recurrence rates in the central neck compartment ranged from 0 to 7.8% for thyroidectomy alone, and from 0 to 5.6% for thyroidectomy and elective CND [3,11].

Four recent large meta-analyses focusing on locoregional recurrence and surgical complications in patients with DTC after prophylactic CND were published [2,9,10,13]. The first, comprised 3558 patients, of whom 58% underwent total thyroidectomy (TT) alone, and 42% were underwent TT with elective CND. The overall prevalence of temporary hypocalcemia after TT with CND was significantly higher than after TT alone (31% vs 16%). Similarly, the cumulative prevalence of temporary RLN injury after TT with CND was higher than after TT alone (5.2% vs 2.9%), but this difference was not found to be statistically significant. Postoperative lymph nodal recurrence was also investigated, and prevalence of central neck recurrence was similar between TT with CND and TT alone (1.7% vs 2.3%), without any statistical significance [2]. In a second meta-analysis, the authors analyzed 3331 patients, 1592 (48%) underwent TT with elective CND and 1739 (52%) underwent TT alone. Overall postoperative morbidity was significantly higher in patients underwent TT with elective CND group (33%) than in the group with TT alone (18%). On the other hand, patients who underwent TT with CND presented with lower risk of locoregional recurrence than patients in the TT alone group (4.7% vs 8.6%). Nevertheless, this study did not differentiate clearly between locoregional recurrence in central compartment and/or lateral compartment [9].

Wang et al. evaluated 2318 patients with PTC in relation to the recurrence and complications associated with elective CND, and did not find significant differences in the rates of locoregional recurrences or of permanent complications in patients undergoing TT with elective CND compared to the patients who underwent TT only. This study projects that 31 patients would need to undergo elective CND to prevent a recurrence in a single patient [10]. Liang et al. (2017) analyzed 6823 patients and observed that there was a significant trend toward lower recurrence rate in the central compartment in patients who underwent TT with elective CND compared to those who had TT only (1.0% vs 3.6%). However, TT with CND also resulted in a significantly higher rate of RLN injury and postoperative hypocalcemia than TT only [13].

Recently, two prospective studies examining the benefit and risks of elective CND were published. Viola et al. (2015) in a randomized controlled study evaluated 181 patients with PTC without evidence of lymph node metastases (cN0), among these, 88 patients were treated with TT, and 93 patients were treated with TT with elective CND. The mean follow-up time for this study was 59 ± 7 months. The study confirmed a high prevalence of lymph node micrometastases (46%). Nevertheless, patients in both groups had a comparable outcome, with the similar percentage of disease free patients and of patients with biochemical and structural recurrence in each group. This result strongly supports the concept that lymph node micrometastases do not affect the clinical outcome of PTC patients. Postoperative complications were higher in patients who underwent TT with CND [46]. Lee et al. (2015) performed a prospective randomized study to evaluate the benefit of prophylactic CND in 257 patients with PTC who were clinically node-negative (cN0). Of these, 104 patients had TT alone, and 153 patients had TT with elective CND. The mean follow-up duration was 49 ± 16 months for patients undergoing a TT versus 55 ± 11 months for patients who had a TT plus CND. Micrometastasis was found in 23% of the patients who underwent elective CND. There was no significant difference in the disease recurrence rates between the two groups (3.9% in the TT versus 3.3% in the TT with elective CND). However, the complication rate in the TT with elective CND group was significantly higher than that in the TT only group [67].

It is important to note that studies which have demonstrated a protective effect of prophylactic CND can suffer from migration bias, commonly known as the Will-Rogers phenomena and very common in literature of gastric neoplasms and lymph node dissection. The prophylactic CND produces a sub classification of the cN0 patients who undergo total thyroidectomy, categorizing them into pN0 and pN1, with most of the pN1 having micrometastasis. Furthermore, patients with confirmed central compartment disease are more likely to undergo treatment with radioactive iodine, which makes it inherently more difficult to compare patients treated with elective CND versus observation. Additionally, when high numbers of patients are pooled in meta-analysis, insignificant clinical differences of 1–2% in nodal recurrence may be shown as highly statistically significant.

Despite variation in the recurrence rates in the central compartment among studies, the finding in the clear majority of studies endorse that no significant benefit can be attributed to elective CND. Beyond the issue of recurrence, some authors have argued the use of elective central compartment dissection as a staging method that can provide information that can impact decision to use radioactive iodine [2,39,42,62,63]. However, staging inherently refers to survival, and the inherent problem in studying survival in DTC is that very few patients ultimately die of disease. Therefore, the overwhelming majority of studies which have included a survival analysis have not been able to show any difference with regard to central compartment dissection.

Given the difficulty of identifying clinical and histopathological risk factors consistently associated with central lymph node metastasis, and the still unclear role of prophylactic CND in the management of DTC, there is a desire for prospective randomized controlled studies to answer this question [71]. With this in mind, the American Thyroid Association Surgical Affairs Committee presented the design and feasibility of a prospective randomized controlled trial to evaluate the use of routine prophylactic CND in terms of oncological and functional outcomes in cN0 PTC patients. This committee estimated that a clinical trial spanning 7 years with enrollment of 5840 patients, with a total study cost of approximately $20 million ($3425 per enrolled study subject) would be necessary. The authors concluded that such a randomized controlled trial of prophylactic central lymph node dissection is not readily feasible [71]. This study highlights the lack of power from which all prospective trials to date have suffered.

As previously discussed, increased rates of postoperative complications have been reported in patients undergoing elective CND, especially among low volume surgeons. Additionally, studies of complications with central neck dissection are difficult to interpret because of heterogeneity in the degree of central compartment dissection. Individual surgeons who perform elective CND must ensure the number of central compartment dissections needed to prevent one recurrence (number needed to treat) is not disproportionate to their individual number of central compartment dissections per related complication (number needed to harm). The most common complication among high volume surgeons associated with total thyroidectomy and central compartment dissection is temporary hypoparathyroidism and hypocalcemia. A moderate approach to the central compartment advocated by some high volume surgeons in order to limit the occurrence of temporary hypoparathyroidism and hypocalcemia is the use of intraoperative frozen section to guide intraoperative decision with regard to the performance of an elective CND and the extent of that dissection (whether unilateral or bilateral). However, it is well recognized that PTC micrometastases cannot reliably be ruled out based on the presence of one or two negative lymph nodes [72].

Current guidelines and international consensus statements

In a similar way that expert authors differ regarding their recommendations in regard to prophylactic CND, there is significant variation in the principle international guideline statements. The National Comprehensive Cancer Network (NCCN), in a category 2B recommendation, suggests that prophylactic CND may be considered for patients with T3 or T4 tumors, taking into consideration the risk of complications such as hypoparathyroidism and recurrent laryngeal nerve injury [17]. Similarly, in the 2015 ATA guidelines, elective central compartment dissection is suggested as a consideration for patients with T3 and T4 primary tumors without evidence of nodal metastases, or with known lateral lymph node metastasis. In addition, the ATA guidelines add a statement that it is appropriate not to perform a prophylactic for T1 or T2 tumors [7].

Various international consensus groups have also put forth guidelines and consensus statements. The 2013 s Brazilian Thyroid Consensus (Recommendation 32) indicates that in patients without suspected metastases on preoperative US, elective dissection of the central compartment lymph nodes may be considered when tumors are > 4 cm or there is grossly apparent extrathyroidal extension [21]. Similarly, the Latin American Thyroid Society reserves recommendation for elective CND for patients with a T3 or T4 classification [20].

The British Thyroid Association, in their 2014 guidelines, do not recommend routine prophylactic CND, citing high incidence of recurrent nerve damage and permanent hypoparathyroidism, but they suggest that CND may be considered in the spirit of personalized decision making. In the British guidelines, prophylactic CND is recommended in patients with known involved lateral nodes [19]. In contrast, the Japanese Society of Thyroid Surgeons/Japanese Association of Endocrine Surgeons advocate routine use of prophylactic CND, citing increased risk of complications if surgery is needed for lymph node recurrence [22]. The European Society of Endocrine Surgeons recommend that in patients with high-risk features, including T3-4 tumors, age <15 or >45, male gender, bilateral or multifocal disease, or known lateral neck lymph node metastases, prophylactic CND should be considered. These European guidelines also highlight importance of prophylactic CND being done by surgeons in specialized centers [18].

Conclusions and future directions

Although the presence of lymph node metastasis is very common in the central neck in patients with cN0 DTC, there is still no consensus on role of elective CND in this patient group. Therefore, an individualized approach is warranted. International consensus groups and guidelines have suggested that patients with large tumors (>4 cm) and extrathyroidal extension are more likely to benefit from elective CND at the time of thyroidectomy. On the other hand, these patients are higher risk for complications such as hypoparathyroidism and recurrent nerve injury, especially when operated by low-volume surgeons. Surgeons should consider their own operative experience when determining risk/benefit of an elective CND, especially keeping in mind the low risk of recurrence and minimal risk of death from disease among patients who are clinically N0 at the time of surgery. Individual surgeons must be familiar with their individual recurrence and complication rates, such that the number of central compartment dissections needed to prevent one recurrence (number needed to treat) is not disproportionate to their individual number of central compartment dissections per related complication (number needed to harm). Low-volume surgeons generally should err on the side of not routinely performing prophylactic CND, as experienced high-volume surgeons may still salvage these patients with low complication rates, in the rather rare (<5%) event of a central neck recurrence in a previously undissected central compartment.

Conflicts of interest

The authors have no conflicts of interest.

References

[1] Nixon IJ, Ganly I, Patel SG, Palmer FL, Whitcher MM, Ghossein R, et al. Changing trends in well differentiated thyroid carcinoma over eight decades. Int J Surg 2012;10:618–23.

[2] Shan CX, Zhang W, Jiang DZ, Zheng XM, Liu S, Qiu M. Routine central neck dissection in differentiated thyroid carcinoma: a systematic review and meta-analysis. Laryngoscope 2012;122:797–804.

[3] Ywata de Carvalho A, Chulam TC, Kowalski LP. Long-term results of observation vs prophylactic selective level VI neck dissection for papillary thyroid carcinoma at a cancer center. JAMA Otolaryngol Head Neck Surg 2015;141:599–606.

[4] Sun W, Lan X, Zhang H, Dong W, Wang Z, He L, et al. Risk factors for central lymph node metastasis in CN0 papillary thyroid carcinoma: a systematic review and meta-analysis. PLoS One 2015;10:1–17.

[5] Ma B, Wang Y, Yang S, Ji Q. Predictive factors for central lymph node metastasis in patients with cN0 papillary thyroid carcinoma: a systematic review and meta-analysis. Int J Surg 2016;289:153–61.

[6] Tartaglia F, Blasi S, Giuliani A, Sgueglia M, Tromba L, Carbotta S, et al. Central neck dissection in papillary thyroid carcinoma: results of a retrospective study. Int J Surg 2014;12:S57–62.

[7] Haugen BR, Alexander EK, Alexander KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;269:1–133.

[8] Wong KP, Lang BH. The role of prophylactic central neck dissection in differentiated thyroid carcinoma: issues and controversies. J Oncol 2011;29:1–12.

[9] Lang BH, Ng SH, Lau LL, Cowling BJ, Wong KP, et al. A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. Thyroid 2013;23:1087–98.

[10] Wang TS, Cheung K, Farrokhyar F, Roman SA, Sosa JA. A meta-analysis of the effect of prophylactic central compartment neck dissection on locoregional recurrence rates in patients with papillary thyroid cancer. Ann Surg Oncol 2013;20:3477–83.

[11] McHenry CR, Stulberg JJ. Prophylactic central compartment neck dissection for papillary thyroid cancer. Surg Clin North Am 2014;94:529–40.

[12] Gambardella C, Tartaglia E, Nunziata A, Izzo G, Siciliano G, Cavallo F, et al. Clinical significance of prophylactic central compartment neck dissection in the treatment of clinically node-negative papillary thyroid cancer patients. World J Surg Oncol 2014;19:247–52.

[13] Liang J, Li Z, Fang F, Yu T, Li S. Is prophylactic central neck dissection necessary for cN0 differentiated thyroid cancer patients at initial treatment? A meta-analysis of the literature. Acta Otorhinolaryngol Ital 2017;37:1–8.

[14] Nixon IJ, Ganly I, Patel SG, Morris LG, Palmer FL, Thomas D, et al. Observation of clinically negative central compartment lymph nodes in papillary thyroid carcinoma. Surgery 2013;154:1166–72.
[15] Liu J, Xu Z, Li Z, Zhang Z, Tang P, Liu S. Long-term outcomes of observation for clinically negative central compartment lymph nodes in papillary thyroid carcinoma. Eur Arch Otorhinolaryngol 2015;272:3801–4.
[16] Nixon IJ, Wang LY, Ganly I, Patel SG, Morris LG, Migliacci JC, et al. Outcomes for patients with papillary thyroid cancer who do not undergo prophylactic central neck dissection. Br J Surg 2016;103:218–25.
[17] NCCN, Thyroid carcinoma (version 1.2017). https://www.nccn.org/professionals/physician_ gls/pdf/thyroid.pdf. (accessed 31 Jan 2017).
[18] Sancho JJ, Lennard TW, Paunovic I, Triponez F, Sitges-Serra A. Prophylactic central neck disection in papillary thyroid cancer: a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbeck's Arch Surg 2014;399:155–63.
[19] Mitchell AL, Gandhi A, Scott-Coombes D, Perros P. Management of thyroid cancer: United Kingdom national multidisciplinary guidelines. J Laryngol Otol 2016;130:S150–60.
[20] Pitoia F, Ward L, Wohllk N, Friguglietti C, Tomimori E, Gauna A, et al. Recommendations of the Latin American Thyroid Society on diagnosis and management of differentiated thyroid cancer. Arq Bras Endocrinol Metabol 2009;53:884–7.
[21] Rosário PW, Ward LS, Carvalho GA, Graf H, Maciel RM, Maciel LM, et al. Thyroid nodules and differentiated thyroid cancer: update on the Brazilian consensus. Arq Bras Endocrinol Metabol 2013;57:240–64.
[22] Takami H, Ito Y, Okamoto T, Yoshida A. Therapeutic strategy for differentiated thyroid carcinoma in Japan based on a newly established guideline managed by Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons. World JSurg 2011;35:111–21.
[23] Pai SI, Tufano RP. Central compartment neck dissection for thyroid cancer. Technical considerations. ORL J Otorhinolaryngol Relat Spec 2008;70:292–7.
[24] Orloff LA, Kuppersmith RB. American Thyroid Association's central neck dissection terminology and classification for thyroid cancer consensus statement. Otolaryngol Head Neck Surg 2010;142:4–5.
[25] Giugliano G, Proh M, Gibelli B, Grosso E, Tagliabue M, De Fiori E, et al. Central neck dissection in differentiated thyroid cancer: technical notes. Acta Otorhinolaryngol Ital 2014;34:9–14.
[26] Carty SE, Cooper DS, Doherty GM, Duh QY, Kloos RT, Mandel SJ, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid 2009;19:1153–8.
[27] Iyer NG, Kumar A, Nixon IJ, Patel SG, Ganly I, Tuttle RM, et al. Incidence and significance of Delphian node metastasis in papillary thyroid cancer. Ann Surg 2011;253:988–91.
[28] Pereira JA, Jimeno J, Miquel J, Iglesias M, Munné A, Sancho JJ, et al. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. Surgery 2005;138:1095–100.
[29] Wang LY, Palmer FL, Thomas D, Shaha AR, Shah JP, Patel SG, et al. Preoperative neck ultrasound in clinical node-negative differentiated thyroid cancer. J Clin Endocrinol Metab 2014;99:3686–93.
[30] Lee YJ, Kim DW, Park HK, Kim DH, Jung SJ, Oh M, et al. Pre-operative ultrasound diagnosis of nodal metastasis in papillary thyroid carcinoma patients according to nodal compartment. Ultrasound Med Biol 2015;41:1294–300.
[31] Sadowski BM, Snyder SK, Lairmore TC. Routine bilateral central lymph node clearance for papillary thyroid cancer. Surgery 2009;146:696–703.
[32] Hwang HS, Orloff LA. Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. Laryngoscope 2011;121:487–91.
[33] Mizrachi A, Feinmesser R, Bachar G, Hilly O, Cohen M. Value of ultrasound in detecting central compartment lymph node metastases in differentiated thyroid carcinoma. Eur Arch Otorhinolaryngol 2014;271:1215–8.
[34] Moreno MA, Edeiken-Monroe BS, Siegel ER, Sherman SI, Clayman GL. In papillary thyroid cancer, preoperative central neck ultrasound detects only macroscopic surgical disease, but negative findings predict excellent long-term regional control and survival. Thyroid 2012;22:347–55.
[35] Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–214.
[36] Lesnik D, Cunnane ME, Zurakowski D, Acar GO, Ecevit C, Ecevit A, et al. Papillary thyroid carcinoma nodal surgery directed by a preoperative radiographic map utilizing CT scan and ultrasound in all primary and reoperative patients. Head Neck 2014;36:191–202.
[37] Oltmann SC, Schneider DF, Chen H, Sippel RS. All thyroid ultrasound evaluations are not equal: sonographers specialized in thyroid cancer correctly label clinical N0 disease in well differentiated thyroid cancer. Ann Surg Oncol 2015;22:422–8.
[38] Ahn JE, Lee JH, Yi JS, Shong YK, Hong SJ, Lee DH, et al. Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer. World J Surg 2008;32:1552–8.
[39] Hartl DM, Leboulleux S, Al Ghuzlan A, Baudin E, Chami L, Schlumberger M, et al. Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. Ann Surg 2012;255:777–83.
[40] Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003;237:399–407.
[41] Barczyński M, Konturek A, Stopa M, Nowak W. Prophylactic central neck dissection for papillary thyroid cancer. Br J Surg 2013;100:410–8.
[42] Raffaelli M, De Crea C, Sessa L, Giustacchini P, Revelli L, Bellantone C, et al. Prospective evaluation of total thyroidectomy versus ipsilateral versus bilateral central neck dissection in patients with clinically node-negative papillary thyroid carcinoma. Surgery 2012;152:957–64.
[43] Kim SK, Woo JW, Park I, Lee JH, Choe JH, Kim JH, et al. Computed tomography-detected central lymph node metastasis in ultrasonography node-negative papillary thyroid carcinoma: is it really significant? Ann Surg Oncol 2017;24:442–9.
[44] Koo BS, Choi EC, Yoon YH, Kim DH, Kim EH, Lim YC. Predictive factors for ipsilateral or contralateral central lymph node metastasis in unilateral papillary thyroid carcinoma. Ann Surg 2009;5:840–4.
[45] Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Clinical significance of metastasis to the central compartment from papillary microcarcinoma of the thyroid. World J Surg 2006;30:91–9.
[46] Viola D, Materazzi G, Valerio L, Molinaro E, Agate L, Faviana P, et al. Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical implications derived from the first prospective randomized controlled single institution study. J Clin Endocrinol Metab 2015;100:1316–24.
[47] Scherl S, Mehra S, Clain J, Dos Reis LL, Persky M, Turk A, et al. The effect of surgeon experience on the detection of metastatic lymph nodes in the central compartment and the pathologic features of clinically unapparent metastatic lymph nodes: what are we missing when we don't perform a prophylactic dissection of central compartment lymph nodes in papillary thyroid cancer? Thyroid 2014;24:1282–8.
[48] Ji YB, Lee DW, Song CM, Kim KR, Park CW, Tae K. Accuracy of intraoperative determination of central node metastasis by the surgeon in papillary thyroid carcinoma. Otolaryngol Head Neck Surg 2014;150:542–7.
[49] Roh JL, Kim JM, Park CI. Lateral cervical lymph node metastases from papillary thyroid carcinoma: pattern of nodal metastases and optimal strategy for neck dissection. Ann Surg Oncol 2008;15:1177–82.
[50] Eun YG, Lee YC, Kwon KH. Predictive factors of contralateral paratracheal lymph node metastasis in papillary thyroid cancer: prospective multicenter study. Otolaryngol Head Neck Surg 2014;150:210–5.
[51] Ji YB, Yoo HS, Song CM, Park CW, Lee CB, Tae K. Predictive factors and pattern of central lymph node metastasis in unilateral papillary thyroid carcinoma. Auris Nasus Larynx 2016;43:79–83.
[52] Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, et al. American Head and neck society; american academy of otolaryngology–head and neck surgery. Neck dissection classification update: revisions proposed by the american Head and neck society and the american academy of otolaryngology-head and neck surgery. Arch Otolaryngol Head Neck Surg 2002;128:751–8.
[53] Robbins KT, Shaha A, Medina J, Califano JA, Wolf GT, Ferlito A, et al. Committee for neck dissection classification, american Head and neck Society.Consensus statement on the classification and terminology of neck dissections. Arch Otolaryngol Head Neck Surg 2008;134:536–8.
[54] American Thyroid Association Surgery Working Group; American Association of Endocrine Surgeons. American Academy of Otolaryngology—Head and Neck Surgery 2009 Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid 2009;19:1153–8.
[55] McAlister ED, Goldstein DP, Rotstein LE. Redefining classification of central neck dissection in differentiated thyroid cancer. Head Neck 2014;36:286–90.
[56] Grant CS, Stulak JM, Thompson GB, Richards ML, Reading CC, Hay ID. Risks and adequacy of an optimized surgical approach to the primary surgical management of papillary thyroid carcinoma treated during 1999-2006. World J Surg 2010;34:1239–46.
[57] Holostenco V, Khafif A. The upper limits of central neck dissection. JAMA Otolaryngol Head Neck Surg 2014;140:731–5.
[58] Gonçalves Filho J, Kowalski LP. Surgical complications after thyroid surgery performed in a cancer hospital. Otolaryngol Head Neck Surg 2005;132:490–4.
[59] Abboud B, Sleilaty G, Braidy C, Zeineddine S, Ghorra C, Abadjian G, et al. Careful examination of thyroid specimen intraoperatively to reduce incidence of inadvertent parathyroidectomy during thyroid surgery. Arch Otolaryngol Head Neck Surg 2007;133:1105–10.
[60] Mohebati A, Shaha AR. Anatomy of thyroid and parathyroid glands and neurovascular relations. Clin Anat 2012;25:19–31.
[61] El Khatib Z, Lamblin J, Aubert S, Arnalsteen L, Leteurtre E, Caiazzo R, et al. Is thymectomy worthwhile in central lymph node dissection for differentiated thyroid cancer? World J Surg 2010;34:1186.
[62] Ferlito A, Rinaldo A, Silver CE, Shaha AR, Fliss DM, Rodrigo JP, et al. Paratracheal node dissection for well-differentiated cancer of the thyroid: indications, technique and results. Auris Nasus Larynx 2008;35:463–8.
[63] Choi JS, Kim J, Kwak JY, Kim MJ, Chang HS, Kim EK. Preoperative staging of papillary thyroid carcinoma: comparison of ultrasound imaging and CT. Am J Roentgenol 2009;193:871–88.
[64] Lin X, Chen X, Jiru Y, Du J, Zhao G, Wu Z. Evaluating the influence of prophylactic central neck dissection on TNM staging and the recurrence risk stratification of cN0 differentiated thyroid carcinoma. Bull Cancer 2016;103:535–40.
[65] Gemsenjäger E, Perren A, Seifert B, Schüler G, Schweizer I, U P. Lymph node surgery in papillary thyroid carcinoma. J Am Coll Surg 2003;197:182–90.

[66] Mao LN, Wang P, Li ZY, Wang Y, Song ZY. Risk factor analysis for central nodal metastasis in papillary thyroid carcinoma. Oncol Lett 2015;9:103–7.
[67] Zhang L, Liu Z, Liu Y, Gao W, Zheng C. The clinical prognosis of patients with cN0 papillary thyroid microcarcinoma by central neck dissection. World J Surg Oncol 2015;7:1–5.
[68] Lee DY, Oh KH, Cho JG, Kwon SY, Woo JS, Baek SK, et al. The benefits and risks of prophylactic central neck dissection for papillary thyroid carcinoma: prospective cohort study. Int J Endocrinol 2015;13:1–6.
[69] Qu H, Sun GR, Liu Y, He QS. Clinical risk factors for central lymph node metastasis in papillary thyroid carcinoma: a systematic review and meta-analysis. Clin Endocrinol 2015;83:124–32.
[70] Liu LS, Liang J, Li JH, Liu X, Jiang L, Long JX, et al. The incidence and risk factors for central lymph node metastasis in cN0 papillary thyroid microcarcinoma: a meta-analysis. Eur Arch Otorhinolaryngol 2017;274:1327–38.
[71] Carling T, Carty SE, Ciarleglio MM, Cooper DS, Doherty GM, Kim LT, et al. American Thyroid Association design and feasibility of a prospective randomized controlled trial of prophylactic central lymph node dissection for papillary thyroid carcinoma. Thyroid 2012;22:237–44.
[72] Robinson TJ, Thomas S, Dinan MA, Roman S, Sosa JA, Hyslop T. How many lymph nodes are enough? Assessing the adequacy of lymph node yield for papillary thyroid cancer. J Clin Oncol 2016;34:3434–9.