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Impact of prophylactic central neck dissection on oncologic outcomes of papillary thyroid carcinoma: a review

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Abstract

Prophylactic neck dissection (PND) for papillary thyroid carcinoma (PTC) is controversial. Our aim was to assess current levels of evidence (LE) according to the Oxford Centre for Evidence-based Medicine (<http://www.cebm.net/?O=1025>) regarding the oncologic benefits of PND. Data were analyzed via MEDLINE key-words: PTC, differentiated thyroid carcinoma, PND, central lymph node metastases, central compartment, recurrence-free survival. There was conflicting evidence regarding the rate of reoperation for recurrence, with some studies showing a lower rate after PND with increased recurrence-free survival and a higher rate of undetectable pre- and post-ablation thyroglobulin levels (LE 4), whereas other studies did not show a difference (LE 4). Only one study (LE 4) showed improved disease-specific survival with PND. PND may improve recurrence-free survival, although this is supported by only a low LE. Current recommendations can only be based on low-level evidence.

Keywords

Lymph node metastasis; Prophylactic neck dissection; Papillary thyroid carcinoma; Recurrence-free survival; Radioactive iodine

Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, with an increasing incidence in part related to an improvement in screening for small tumors by neck ultrasound. It accounts for 80 % of all thyroid cancers and ranks as the sixth most common cancer in females [1, 2]. The high disease-specific survival rates obtained after PTC favor optimizing the evaluation of prognostic factors to avoid overtreatment and a too stringent follow-up. Lymph node status has been shown to be related to local recurrence and, for older patients, disease-specific survival [3, 4]. The complete surgical removal of known cervical lymph node metastases (CLNMs) via a compartment-oriented neck dissection is currently recommended. However, the role of systematic prophylactic neck dissection (PND) in the absence of suspected cervical metastases on preoperative ultrasound (cN0) remains

controversial. The most recent guidelines from the American Thyroid Association (ATA) in 2009 do not advocate PND, but guidelines from the Japanese Association in 2010 and from France in 2012 do [5, 6]. All of these recommendations are grade C (“expert opinion”) due to the lack of high level evidence in the field. The proponents of systematic PND have underlined its potential effect on recurrence-free survival and disease-specific survival. However, PND can also result in the, possibly unnecessary, upstaging of some tumors with occult lymph node metastases according to the UICC/AJCC staging classification [7], the ATA risk grouping [5] and even more recent classifications [8]. The opponents of systematic PND have emphasized that the prognostic role of occult micrometastases has not been demonstrated [9]. Thus, they suggest that overtreatment occurs in cases of systematic PND. PND may also involve greater morbidity in terms of transient hypoparathyroidism [9]. Nevertheless, the incidence of subsequent permanent complications has not been shown to differ between cases of systematic PND associated with total thyroidectomy (TT) and TT alone for experienced surgeons [10–14]. Furthermore, adjuvant treatment by radioactive iodine can be personalized according to lymph node status in patients who undergo TT/PND compared to TT alone [15].

The issue of PND for PTC has been debated for more than half a century and the use of elective/prophylactic lateral neck dissection has long been abandoned. However, the debate over the usefulness of prophylactic central compartment neck dissection has been renewed over the past 10–15 years. The major reasoning behind this issue is the increased use of pre-operative ultrasound and postoperative routine follow-up with thyroglobulin (Tg) and ultrasound, which are particularly sensitive. ATA, in their guidelines in 2006, recommended PND in patients with tumors larger than 1 cm. This clearly created considerable debate as to its value and increased risk of complications. Interestingly, in 2009, the revised guidelines recommended PND only in patients with locally advanced thyroid cancer, extrathyroidal extension or aggressive histology. This leads us to believe that a more critical analysis of the utility of PND should be undertaken, especially in light of possible complications related to hypoparathyroidism.

The purpose of this study was to review the available evidence in the literature to assess the impact of systematic PND in conjunction with TT on the oncologic outcomes of patients with PTC.

Materials and methods

The literature was reviewed using the National Library of Medicine database (<http://www.pubmed.gov>). A MEDLINE search was performed with special emphasis on PTC, TT, PND and recurrence using combinations of the following terms: papillary thyroid carcinoma, differentiated thyroid carcinoma, prophylactic central neck dissection, prophylactic lateral neck dissection, total thyroidectomy, lymph node metastasis, central compartment, recurrence-free survival, radioiodine treatment, thyroglobulin levels, disease-specific survival, recurrence rate, loco-regional recurrence, follow-up, reoperation. Articles published between 2000 and 2014 were retained. Due to the paucity of randomized data, articles were selected for this review with regard to the following criteria: evolution of concepts, development and refinement of techniques, intermediate and long-term clinical

outcomes, quality of the study and relevance. The levels of evidence (LE) was assessed according to the Oxford Centre for Evidence-based Medicine (Table 1) (<http://www.cebm.net/?O=1025>).

Results

No level of evidence 1 information from prospective randomized trials was available in the literature. The highest level of evidence reported was level 4, retrospective studies comparing contemporaneous cohorts of patients treated with TT as compared to PND and TT.

PND and recurrence-free survival

Recently, three retrospective (LE 4) studies have shown a benefit in terms of recurrence-free survival in cases of systematic central compartment PND associated with TT compared to TT alone (Tables 2, 3). Hartl et al. and Popadich et al. [12, 13] have shown a lower rate of reoperation in the central compartment, with median follow-ups of 2.6 and 6.9 years, respectively (LE 4). These reoperations were all due to recurrence in the central compartment (Table 3).

Barczynski et al. [10] also reported a lower recurrence rate at 10 years: 4.2 % for TT with central compartment PND compared to 13.1 % for TT without PND (LE 4). In accordance with these findings, Moo et al. [16] previously demonstrated a trend toward a benefit of central compartment PND (16.4 vs 4.4 %), although it did not reach statistical significance due to the small population included ($n = 81$) (LE 4). In addition, a recent meta-analysis published in 2013 demonstrated a lower recurrence rate in favor of the PND group (13 eligible studies with 3,331 patients) (LE 4) [17]. In fact, the natural evolution of PTC, which carries a good prognosis, resulted in the inability of several studies to demonstrate a difference between TT/PND and TT alone, possibly because of the short-term follow-up. Based on the available data, recurrence is rarely observed in studies with a mean follow-up of 2 years [18–23]. However, this meta-analysis included heterogeneous populations with cN1 PTC and one study including only microcarcinomas [24–26].

In contrast, Costa et al. [27] in 2009 found no difference in recurrence rates when performing PND (6.3 vs 7.6 %), but the mean follow-up, size and age significantly differed between the two groups. Nevertheless, all the recurrences were diagnosed for pN1 patients and corroborate PND as an accurate staging system. In 2010, a meta-analysis performed by Zetoune et al. [9] also found no influence of central compartment PND on recurrence-free survival (including 5 studies with 1,264 patients), although the included population was heterogeneous (LE 4). A larger meta-analysis including 11 studies with 2,318 patients, published by Wang et al. [28] in 2013 failed to demonstrate a significant difference between TT/PND vs TT alone although they observed a trend toward a lower recurrence rate (4.7 vs 7.9 %). They also suggested the positive impact of routine PND performed by experienced surgeons (3.8 % recurrence rate), in the studies in which PND was routinely performed. They included six comparative studies between TT and TT/PND and five cohorts of patients operated with TT/PND, with a more homogeneous population (cN0 PTC). All these meta-analyses were based on various inclusion criteria that lead to different study populations

with different confounding factors (tumor size, preoperative lymph node status, iodine treatment, initial surgery). These data suggest the necessity of a prospective study with a long-term follow-up, requiring rigorous inclusion criteria to study a more homogenous population [15].

Opponents of PND may note that the removal of occult micrometastases does not appear to affect the rate of recurrence [24, 29, 30]. However, in several studies, the central lymph node metastases that were found were primarily metastases larger than 1 cm, and these patients could, thus, have benefited from PND as much as patients classified as cN1 who receive therapeutic neck dissection [19, 31]. Furthermore, PND may identify pN0 populations with low-risk PTC that can receive lower radioiodine doses or no iodine and have less frequent postoperative follow-up visits [30]. Whether or not PND is an effective staging system for making postoperative decisions and correctly assessing tumor aggressiveness remains controversial.

Barczynski et al. [10] found that PND resulted in a lower recurrence rate in general but also improved 10-year disease-specific survival for T3 tumors (LE 4). Few studies have conducted as long a follow-up to determine the effect of PND on disease-specific survival [32].

PND and postoperative Tg levels

A normal ultrasound associated with negative Tg levels (after TT) defines complete remission [33]. PND associated with TT has been shown in many retrospective (LE 4) studies to increase the number of patients with undetectable Tg levels throughout the follow-up compared to TT alone (Table 3) [12, 13, 19, 34–36]. Additionally, for microcarcinomas, Choi et al. [25] showed higher Tg levels for patients who did not undergo PND (LE 4). These results contradict those of Hughes et al., [18] (LE 4) possibly due to the administration of postoperative radioactive iodine, which decreased Tg levels. Undetectable Tg levels were predictive of the absence of recurrence during long-term follow-up [37], which argues that even patients with T3–T4 tumors could be moved to the low-risk group when Tg is low and their neck ultrasound is normal (LE 4) [38, 39]. Many authors have argued that the postoperative characterization of the tumor and response to treatment should be considered in managing the long-term follow-up instead of considering only the preoperative characteristics [40, 41]. Performing central compartment PND may improve the identification of patients with a higher risk of recurrence and detectable postoperative Tg levels (LE 4) [21, 42]. Recently, Nascimento et al. [43] demonstrated that measuring the Tg level 1 year after post-ablative radioiodine treatment was not necessary when Tg was undetectable in the pre-ablative sample (LE 4). In this study, recurrence occurred only in patients diagnosed as pN1 by central compartment PND.

PND for accurate staging

Nodal status is an important prognostic factor in PTC, but prognosis seems to primarily depend on the number and size of the metastatic nodes [44]. PND is the most sensitive and specific means to determine nodal status in cN0 PTC to date [45, 46]. Ultrasound is the reference technique for PTC compared to computed tomography or magnetic resonance

imaging [47]. However, preoperative ultrasound has low to moderate sensitivity in detecting small central compartment lymph node metastases particularly in level VI, with sensitivities ranging from 35 to 50 % (LE 4) [48, 49]. The accuracy of ultrasound in the central compartment improves once the thyroid has been removed, in the follow-up setting. Ultrasound appears to have a higher sensitivity, ranging from 27 to 85 %, for the detection of lateral LNM with high variability among studies (LE 4) [45, 50]. Even with recent technological improvements in ultrasonography, the current preoperative evaluation of the central and lateral neck compartments is not as sensitive or specific as PND [48, 51]. In most studies, PND upstaged 30 to 50 % of patients undergoing PND of the patients from cN0 to pN1 [5, 8, 10, 12, 13, 18, 24, 31, 36]. This high frequency is the initial reason justifying PND. Furthermore, the size, number, extracapsular spread and location of CLNMs are predictive factors of recurrence that are only evaluable if PND is performed [8, 24, 52]. Several studies have proposed scales to determine the prognosis of PTC by considering CLNMs characteristics [8, 53]. Thus, a personalized strategy could be created case by case for postoperative adjuvant treatment and the frequency and duration of follow-up (LE 4) [43].

Whether micrometastases should be included in the pN1 status and, therefore, treated similarly to clinically apparent CLNMs remains a debatable issue. In some studies, the risk of recurrence for patients with micrometastases was found to be nearly the same as that of pN0 patients (LE 4) [8, 14, 24, 45]. Several teams have evaluated an alternative technique of sentinel node mapping and biopsy in thyroid cancer, reporting good accuracy. But this staging method is technically challenging and has not been shown to have a decreased rate of complications as compared to PND (LE 4) [54].

Among the proponents of PND, there is also debate regarding the type of PND that should be performed (i.e., unilateral or bilateral PND of the central compartment) [50, 55]. Unilateral central compartment PND is performed in many centers with no worse outcome as compared to bilateral central PND. It serves as an indicator of regional spread and a tool for selecting patients for further treatment with a lower morbidity rates than bilateral PND (LE 4) [11]. However, CLNMs can be found in 25 % of contralateral level VI PND (LE 4) [20, 56]. Thus, while a unilateral approach to PND could be a tool for staging the cervical nodes for the choice of subsequent treatment [20, 57, 58], unilateral ipsilateral PND may not be considered as a therapeutic step in patients with CLNMs. Chae et al. proposed a frozen section examination of the ipsilateral nodes to predict CLNMs on the contralateral side [57, 59]. In addition, however, skip metastases in contralateral level VI are present in 5 to 10 % of patients, except for PTCs <10 mm (LE 4) [31, 60].

PND safety

For experienced teams reporting their results, bilateral PND does not carry a higher risk of permanent recurrent nerve paralysis or hypoparathyroidism than TT alone (less than 1–2 %) (LE 4) [10, 12, 13]. Similarly, however, for experienced surgeons reporting their results, reoperation in the central compartment, after TT alone, does not increase the rate of permanent complications either (LE 4) [61, 62]. Thus, whether performed primarily or secondarily, central neck dissection is safe if performed by an experienced surgeon.

Although permanent complications appear to be equivalent, there are other data supporting the higher risk of temporary hypoparathyroidism with PND, but this is also level 4 evidence [9, 20, 42].

Predictive factors for central lymph node metastasis and PND

To elucidate the possible indications for PND, the risk factors for occult ipsilateral or contralateral CLNMs for patients with PTC and a clinically negative neck have been studied under different perspectives, but only level 4 evidence is available. In a prospective study carried out in 111 patients with PTC, Koo et al. [60] showed that tumor size was an independent risk factor for the presence of ipsilateral central lymph node metastasis, and the presence of ipsilateral central metastasis was the only independent predictor for the presence of contralateral central nodal metastasis (LE 4). Similar conclusions were reported by Kim et al. [63] (LE 4). Other factors associated with central nodal metastasis were male gender, extrathyroidal extension, and tumor multifocality [31, 63–67]. Studies of biological markers have mainly focused on the BRAF mutation (BRAF V600E mutation in exon 15 of the BRAF gene). Tufano et al. [68] performed a meta-analysis to investigate correlations of BRAF mutation status with PTC prognosis, including lymph node metastasis, extrathyroidal extension, distant metastasis, and stages III/IV. The overall prevalence of the BRAF mutation was 45 %, and the risk ratio in BRAF mutation-positive patients was 1.32 (95 % CI, 1.20–1.45; $Z = 5.73$; $p < 0.00001$) for lymph node metastasis (LE 4). The BRAF mutation also was significantly associated with PTC recurrence, extrathyroidal extension, and advanced stage, possibly offering new prospects for optimizing and tailoring initial treatment strategies to prevent recurrence [69].

PND in national and international guidelines

Most national and international societies recommend performing, at initial surgery, PND associated with TT for T3 and T4 PTC [5, 6, 70–74]. Other risks factors such as male sex, age older than 45 years or less than 15 years, extrathyroidal extension, multifocal and bilateral tumors are arguments for the International Association of Endocrine Surgery for complete initial TT with PND [71]. For smaller T1 and T2 tumors, PND is not systematically recommended except by the Japanese Society of Thyroid Surgeons and the French Society of Otolaryngology-Head and Neck Surgery [6]. As shown above, all of these recommendations are based on retrospective studies (LE 4) [15].

Different recommendations from specialist societies are shown in Table 4.

Conclusion

Although overall survival is not influenced by PND, it is not clear if recurrence-free survival is affected. Accurate pathologic lymph node staging by PND may influence the use of adjuvant radioactive iodine. If complete staging is the goal, based on the risk of positive nodes involving the contralateral aspect of level VI, PND should include bilateral dissection of level VI to secure an ultimate and comprehensive staging to grade patients in the appropriate prognostic groups. However, routine PND should be considered in the context of

an increased risk of complications, which is dependent on the surgeon's skill and experience.

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Table 1

Level of evidence, 2011

Level 1 (LE 1)	Local and current random sample surveys (or censuses)	Systematic review of: Cross-sectional studies with consistently applied reference standard and blinding Inception cohort studies Randomized trials Randomized <i>n</i> -of-1 trial with the patient raising the question about, or observational study with dramatic effect
Level 2 (LE 2)	Systematic review of surveys that allow matching to local circumstances ^b	Individual cross-sectional studies with consistently applied reference standard and blinding Inception cohort studies Randomized trial or observational study with dramatic effect Individual randomized trial or (exceptionally) observational study with dramatic effect
Level 3 (LE 3)	Local non-random sample ^b	Non-consecutive studies, or studies without consistently applied reference standards ^b Cohort study or control arm of randomized trial ^a Non-randomized controlled cohort/follow-up study ^b
Level 4 (LE 4)	Case-series ^b	Case-control studies Poor or non-independent reference standard ^b Poor quality prognostic cohort study ^b Historically controlled studies ^b
Level 5 (LE 5)	n/a	Mechanism-based reasoning

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^aLevel may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; level may be graded up if there is a large or very large effect size

^bAs always, a systematic review is generally better than an individual study

Table 2

Population characteristics in the 12 studies from the literature comparing TT vs TT/PND

Study (LE)	Study design	No of patients	Mean age TT vs TT/PND (years)	T classification	Follow-up TT vs TT/PND (months)
Lang et al. [17] (LE 2)	Meta-analysis	3,331	–	T1, T2, T3, T4	50.8 vs 45.2
Wang et al. [28] (LE 4)	Meta-analysis	2,318	46.7 vs 50.5	T1, T2, T3, T4	12–144 vs 3–159 ns
Barczynski et al. [10] (LE 4)	Retrospective	640	52.7	T1, T2, T3, T4	128 vs 126 ns
Popadich et al. [13] (LE 4)	Retrospective	606	48 vs 44	T1b, T2, T3, T4	50 vs 32 ns
Sywak et al. [36] (LE 4)	Retrospective	447	42.6 vs 39.1	T1b, T2	70 vs 24.5 ns
Zuniga et al. [32] (LE 4)	Retrospective	266	41.5 vs 42.9	T1, T2, T3, T4	6.1
Hartl et al. [12] (LE 4)	Retrospective	263	46 vs 47	T1b, T2, T3	74 vs 83 ns
Costa et al. [27] (LE 3)	Retrospective	244	52 vs 46	T2, T3, T4	47 vs 62
So et al. [35] (LE 4)	Retrospective	232	49.8 vs 49.2	–	45.4 vs 44.7 ns
Raffaelli et al. [20] (LE 3)	Prospective	186	42 vs 43.2	T1, T2, T3	25 vs 25.5 ns
Lang et al. [19] (LE 4)	Retrospective	185	50 vs 52	T1, T2, T3, T4	31.9 vs 28.2
Hughes et al. [18] (LE 4)	Retrospective	143	41.2 vs 46.8	T1a, T2	27.5 vs 19 ns
Moo et al. [16] (LE 4)	Retrospective	81	49.2 vs 45.7	T1, T2	37.2 vs 37.2

LE level of evidence, *TT* total thyroidectomy, *PND* prophylactic neck dissection, *ns* not significant

Table 3

Oncologic results and outcomes from the 12 studies comparing TT vs TT/PND

Study (LE)	No. of TT vs TT/PND	I ¹³¹ (%)	pN1 (%)	Recurrence (%) TT vs TT/PND	Pre-ablative negative Tg level (%) or means of Tg levels TT vs TT/PND (ng/mL)	Undetectable final Tg (%) TT vs TT/PND or means of Tg levels TT vs TT/PND (ng/mL)
Lang et al. [17] (LE 2)	TT: 1,739 TT/PND: 1,592	62	–	8.6 vs 4.7	–	–
Wang et al. [28] (LE 4)	TT: 995 TT/PND: 745 Central bilateral	–	–	7.9 4.7 ns	–	–
Barczynski et al. [10] (LE 4)	TT: 282 TT/PND: 358 Central bilateral	48.4	30	13.1 4.2 $p < 0.001$	89.4 94.4 $p = 0.018$	1.8 ng/mL 0.04 ng/mL $p = 0.005$
Popadich et al. [13] (LE 4)	TT: 347 TT/PND: 259 Central bilateral 22 % Unilateral 78 %	98	49	8.1 5 $p = 0.11$	– – $p = 0.025$	7.2 ng/mL 1.9 ng/mL ns
Sywak et al. [36] (LE 4)	TT: 391 TT/PND: 56 Central unilateral	100	38	5.6 3.6	– –	43 % 72 % $p = 0.001$
Zuniga et al. [32] (LE 4)	TT: 130 TT/PND: 136 Central bilateral	70	82.3	19 vs 14 ns	– –	– –
Hartl et al. [12] (LE 4)	TT: 91 TT/PND: 155 Central bilateral + lateral ipsilateral	100	52	20 7.7 $p = 0.005$	43 65 $p = 0.001$	84 % 93 % $p = 0.03$
Costa et al. [27] (LE 3)	TT: 118 TT/PND: 126 Central unilateral or bilateral	61	46.8	7.6 vs 6.3 ns	– –	– –
So et al. [35] (LE 4)	TT: 113 TT/PND: 119 Central bilateral	83	37	3.5 vs 1.7 ns	2.24 ng/mL 1.07 ng/mL $p < 0.022$	0.69 ng/mL 0.44 ng/mL ns
Raffaelli et al. [20] (LE 3)	TT: 62 TT/PND: 124 Central unilateral or bilateral	–	35.5	0 vs 0.8 ns	– ns	– –
Lang et al. [19] (LE 4)	TT: 103	67	54.9	2.9 vs 3.7	22.3	<0.5 ng/mL

Study (LE)	No. of TT vs TT/PND	I ¹³¹ (%)	pN1 (%)	Recurrence (%) TT vs TT/PND	Pre-ablative negative Tg level (%) or means of Tg levels TT vs TT/PND (ng/mL)	Undetectable final Tg (%) TT vs TT/PND or means of Tg levels TT vs TT/PND (ng/mL)
Hughes et al. [18] (LE4)	TT/PND: 82	86 vs 92	62	ns	51.2	<0.5 ng/mL
	Central unilateral				$p < 0.024$	ns
	TT:65			4.6	15	77 %
	TT/PND: 78			5.1	10	75 %
Moo et al. [16] (LE 4)	Central bilateral	70	33.3	ns	ns	ns
	TT: 36			16.7 vs 4.4	–	–
	TT/PND: 45			ns	–	–
	Central bilateral					

LE level of evidence, TT total thyroidectomy, TT/PND total thyroidectomy with prophylactic neck dissection, Tg thyroglobulin

Table 4

Recommendation of the different national and international thyroid associations

National and International thyroid association	Year	PND for T4 T3 tumors	PND for T2 T1 tumors
International Association of Endocrine Surgery [71]	2014	Recommended and if age >45 years or <15 years, male, bilateral or multifocal tumors	Not recommended
British thyroid association (http://www.british-thyroid-association.org/news/Docs/Thyroid_cancer_guidelines_2007.pdf)	2014	Personalized decision if age >45 years, multifocal tumor, extrathyroidal extension	Not recommended age <45 years, unifocal tumor, no extrathyroidal extension
National Comprehensive Cancer Network (http://www.nccn.org)	2013	Consider	Consider
French ENT Society (http://www.orlfrance.org/article.php?id=20)	2012	Recommended	Recommended (at least unilateral)
European Society for Medical Oncology [74]	2012	Controversial	Controversial
Japanese society of thyroid surgeons [6]	2011	Recommended	Recommended
Latin American Thyroid Society [70]	2009	Recommended	Not recommended
American Thyroid Association [5]	2009	Recommended	Not recommended
European Thyroid Association [72]	2006	Not recommended	Not recommended