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Review

Is prophylactic central neck dissection necessary for cN0 differentiated thyroid cancer patients at initial treatment? A meta-analysis of the literature

La dissezione linfonodale profilattica del compartimento centrale del collo è necessaria come trattamento iniziale nei pazienti affetti da carcinoma differenziato della tiroide cN0? Meta-analisi della letteratura

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SUMMARY

Central lymph node metastases are common in patients with differentiated thyroid cancer (DTC). The management of preoperatively node-negative (cN0) DTC is still under debate. The aim of this study was to analyse the difference in recurrence and surgical complications between thyroidectomy (TT) alone and TT combined with prophylactic central neck dissection (pCND) as initial treatments to DTC patients with cN0 and evaluate the clinic significance of pCND for these patients. PubMed, Ovid, Cochrane Library, and Web of Science databases were systematically searched using multiple search terms. Twenty-three articles with 6,823 patients were identified. The quality of evidence was assessed by Jadad quality scores and the Newcastle-Ottawa Quality assessment scale. The results showed that compared with patients who underwent TT alone, patients who underwent TT plus pCND had a significant higher rate of transient recurrent laryngeal nerve injury ($p = 0.023$), transient hypocalcaemia ($p < 0.01$) and permanent hypocalcaemia ($p<0.01$). There was a trend towards lower central neck recurrence rate in TT plus pCND ($p < 0.01$). Combined TT and pCND as initial treatment for DTC patients with cN0 may reduce the risk of recurrence, but increases the incidence of some complications. Methodologically high-quality comparative studies are needed for further evaluation.

KEY WORDS: Differentiated thyroid cancer • Prophylactic central neck dissection • cN0 • Meta-analysis

RIASSUNTO

Le metastasi ai linfonodi del compartimento centrale del collo sono comuni nei pazienti affetti da carcinoma differenziato della tiroide (DTC). La gestione dei pazienti con stadiazione preoperatoria cN0 è ancora dibattuta. L'obiettivo di questo lavoro è stato quello di analizzare le differenze in merito a ricorrenza e complicanze chirurgiche tra tiroidectomia (TT) isolata e TT associata a svuotamento linfonodale profilattico del compartimento centrale del collo (pCND) come trattamenti iniziali di pazienti con DTC cN0, e di valutare l'importanza clinica del pCND per questi pazienti. I database PubMed, Ovid, Cochrane Library e Web of Science sono stati analizzati scrupolosamente, e sono stati identificati ventitré articoli per un totale di 6823 pazienti. La qualità di evidenza è stata valutata tramite lo score di Jadad e tramite la Newcastle-Ottawa Quality assessment scale. I risultati hanno mostrato che i pazienti sottoposti a TT e pCND, se paragonati ai pazienti sottoposti a TT isolata, hanno avuto un tasso significativamente più alto di lesioni transitorie del nervo laringeo inferiore ($p = 0,023$), di ipocalcemia transitoria ($p < 0,01$) e di ipocalcemia permanente ($p < 0,01$). Inoltre è stato rilevato un trend in diminuzione per quel che riguarda il tasso di ricorrenza nei pazienti sottoposti a TT e pCND ($p < 0,01$). La tiroidectomia totale associata allo svuotamento del compartimento centrale del collo come trattamento iniziale per quei pazienti con cN0 potrebbe ridurre il rischio di ricorrenza di malattia, ma aumenta l'incidenza di alcune complicanze. Si rendono necessari ulteriori studi di maggior qualità metodologica.

PAROLE CHIAVE: *Carcinoma differenziato della tiroide • Svuotamento profilattico del compartimento centrale del collo • cN0 • Meta-analisi*

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Introduction

Well differentiated thyroid cancer (DTC) represents most cases of thyroid cancer, the incidence of which continues to increase. Papillary thyroid carcinoma (PTC) is the most common type of DTC and its incidence is increasing in developed countries, particularly in the United States and Western Europe [1 2]. Despite its relatively good prognosis with a 10-year cancer-specific survival above 90%, locoregional recurrence is a major cause of disease morbidity [3]. There are some regional lymph node compartments to which thyroid cancer is likely to metastasise, such as the central, lateral and mediastinal. Some studies have reported that the central compartment is the most common because it is located adjacent to the lower pole of

the thyroid. At present, a growing number of surgeons are performing routine central neck dissection at the time of total thyroidectomy (TT) for PTC [4-6].

Although LNM has no major impact on survival, it has been suggested that the presence of nodal involvement is commonly associated with extrathyroidal invasion and an increased rate of recurrence and distant metastasis. A therapeutic central neck dissection is recommended in patients with LNM in the central neck identified on cervical ultrasonography or at the time of surgery. Nevertheless, the role of prophylactic central neck dissection (pCND) in the absence of suspected cervical metastases on preoperative ultrasound (cN0) is still uncertain [5 7]. Many physicians consider pCND to have the potential benefits that can improve the accuracy of staging, enable better selection of patients for radioactive iodine (RAI) treatment and decrease postoperative recurrence in patients with cN0 PTC. Current American Thyroid Association (ATA) guidelines state that pCND may be performed in PTC patients with cN0, especially for T3 or T4 tumours [8]. European consensus does not recommend central dissection because there is no evidence that it improves recurrence or mortality rates [9]. However, these recommendations are grade C (expert opinion), and the controversy is still sustained due to the lack of prospective comparative studies with high levels of evidence.

Currently, the value of pCND for DTC patients with cN0 has been investigated in a number of trials worldwide. A definitive conclusion has not been reached. Thus, the aim of this study was to evaluate the clinical significance of pCND and provide surgeons additional information for clinical decision making.

Materials and methods

Search strategy

A systematic search was developed for all English language literature published from January 2000 to July 2015. The comprehensive search was performed using the electronic databases PubMed, Ovid, Cochrane Library and Web of Science. We used the following terms: differentiated thyroid cancer OR papillary thyroid cancer AND prophylactic central neck dissection AND (cN0 OR negative lymph node) OR complication OR recurrence OR hypocalcaemia OR hypoparathyroid OR (recurrent laryngeal nerve palsy OR recurrent laryngeal nerve injury). The search strategy was slightly adjusted according to the requirement of different databases. Review articles and bibliographies of other relevant identified investigations were hand-searched to identify additional studies.

Inclusion and exclusion criteria

The goal of pCND is to remove all lymphatic tissue en bloc. The area of dissection is bound superiorly by the hyoid bone, inferiorly by the suprasternal notch, laterally by the medial borders of the carotid sheath and dorsally by the prevertebral fascia. The lymph nodes that are removed include the prelaryngeal, pretracheal and paratracheal nodes. Also removed are nodes found along the RLN. Particular attention is given to identifying and preserving the RLN and parathyroid gland.

All clinical studies were required to meet the following criteria for this study: (1) proven diagnosis of DTC; (2) patients who performed pCND had no clinically apparent central LNM at presentation by neck ultrasonography as well as clinical exam; (3) clinical comparative trials, comparison of adverse outcomes of TT plus pCND to TT alone; (4) the studies had to report on at least one of the clinical outcomes mentioned below: hypocalcaemia, recurrent laryngeal nerve (RLN) injury and recurrence; (4) either one of the higher quality or the most recent study was included when two studies were published by the same institution or authors. The following articles were excluded: (1) studies exploring the results of lateral cervical node dissection or modified neck dissection instead of pCND; (2) TT with pCND was not performed as the initial treatment; (3) letters, comments, expert opinions, reviews, or case reports; (4) measured outcomes were not clearly presented in the literatures or it was impossible to extract the appropriate data from the articles.

Data extraction and quality assessment

Two reviewers reviewed each article independently. Discrepancies between the two reviewers were resolved through discussion, and when this did not resolve the differences, a third person made a final decision. The authors, publication years, country of investigators, sample size, follow-up period, clinical complications and postoperative recurrence were extracted. The quality of randomised controlled trials (RCTs) was evaluated using Jadad quality scores [10], and included secure methods for randomisation, allocation concealment, patient and observer blinding, and loss to follow-up. The studies were divided into a low quality group (score < 4) and a high quality group (score ≥ 4). The quality of observational studies was performed using the Newcastle-Ottawa Quality assessment scale [11 12]. Briefly, the overall star assessed three main categories on the following: selection of cohort, comparability of cohort and ascertainment of outcome. A trial can be awarded a maximum of 1 star for each numbered item within the selection and outcome categories. A maximum of 2 stars can be given for comparability. The total number of star was accumulated, with more stars reflecting a better methodological quality.

Statistical analysis

For dichotomous outcomes, we expressed the results using risk ratios (RRs) with 95% CIs. Heterogeneity between studies was tested qualitative by Q-test statistics with significance set at $p < 0.10$ and quantitatively tested by I^2 statistics, with I^2 more than 50% indicating large in-

consistency. A random effect model was used to calculate pooled RRs in the case of significant heterogeneity ($p < 0.10$ or $I^2 > 50\%$), otherwise, a fixed effect model was used. A $p < 0.05$ was considered statistically significant. Publication bias was estimated by visually assessing the asymmetry of Begg's funnel plot. Furthermore, Egger's test was also performed to provide quantitative evidence of publication bias [13,14]. Sensitivity analysis was performed by sequentially omitting individual study to check the stability of the result. Statistical analyses were performed using STATA version 12.0 software (Stata Corporation, College Station, Texas, USA) and Microsoft Excel 2010.

Results

Description of studies

The initial search strategy yielded 327 potentially relevant studies, 273 of which were excluded after the initial review of their titles and abstracts. After further consideration of the 54 remaining studies, 23 articles [4-7,15-33] were included in our study. The total number of patients included was 6,823, ranging from 83 to 1,087 patients per study. The rate of central LNM in TT combined with pCND ranged from 16.7% to 82.3%. Seventeen studies reported that patients received postoperative RAI [5-7,15-18,20-22,24-27,30,32,33]. Among the 23 articles, 7 were conducted in Italy [4,17,18,27,28,32,33], 5 in the United States [5,6,19,21,26], 4 in Korea [16,20,25,29], 2 in Australia [15,22], 1 in Columbia [7], 1 in UK [23], 1 in China [24], 1 in Poland [30] and 1 in France [31]. The characteristics and methodological quality assessment are shown in Table I.

Methodological quality of the studies

The quality of one RCT included was evaluated according to the Jadad scale, and one study was low quality according to the scores. Each of the remaining 22 eligible studies included in our meta-analysis was assessed for quality according to the Newcastle-Ottawa Quality scale. For quality, scores ranged from 0 to 9, and studies with scores of 6 or more were rated as high quality. The quality of all studies included varied from 4 to 8, with a mean of 6; 17 studies obtained scores of 6 or more in methodological assessment, indicating that they were of high quality (Table I).

Meta-analysis findings

A meta-analysis of combinable data was carried out to analyse the postoperative complications and recurrence, and the main results are shown in Table II. Eight studies reported data on haemorrhage, 15 studies reported data on transient RLN injury, 14 studies reported data on permanent RLN injury, 19 studies reported data on transient hypocalcaemia, 19 studies reported data on permanent hypocalcaemia, 13 studies reported data on postoperative recurrence,

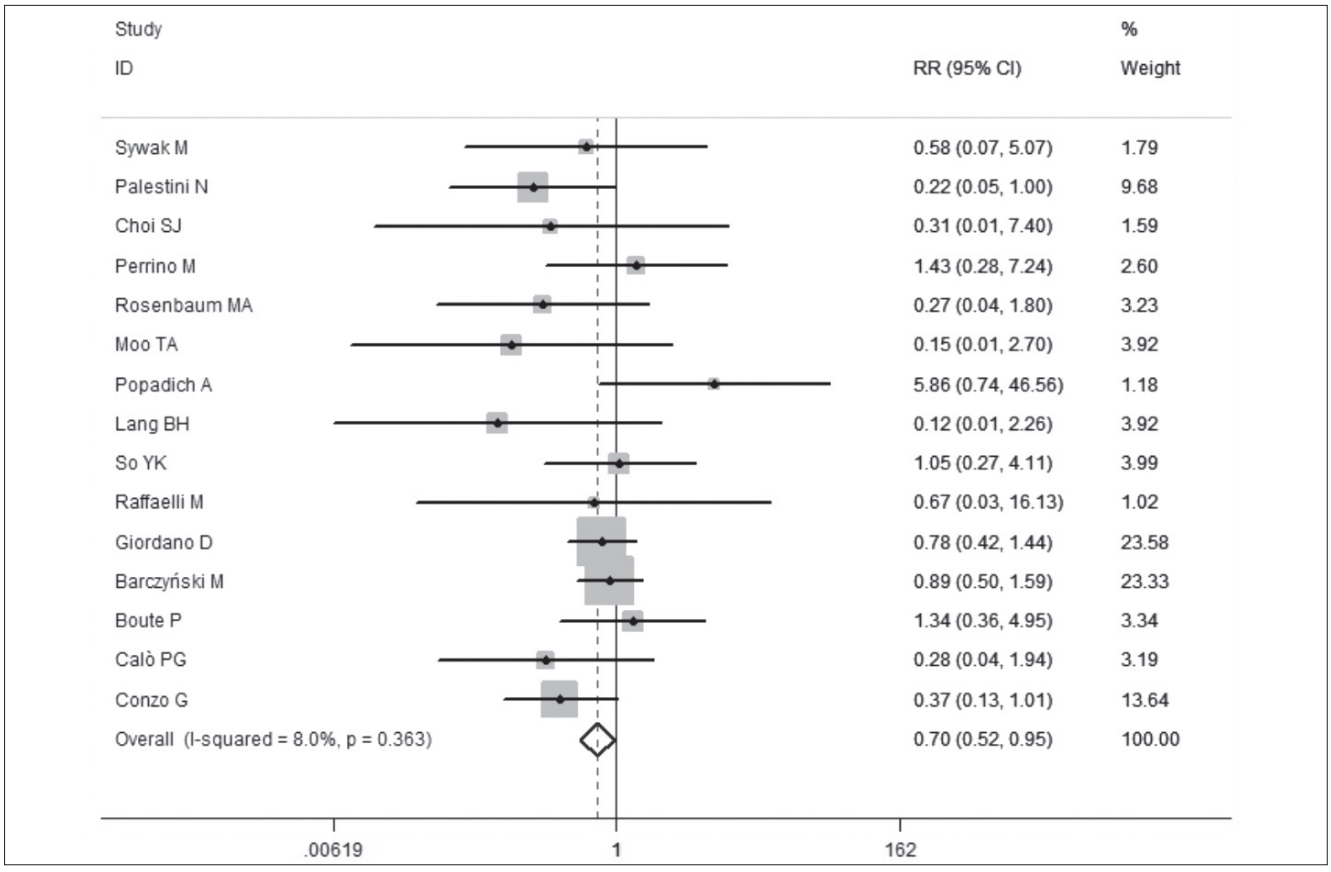

Fig. 1. Forest plot of risk ratio for transient RLN injury.

nine studies reported data on central neck recurrence and 10 studies reported data on lateral neck recurrence. When the data were pooled, transient RLN injury ($p = 0.023$) (Fig. 1), transient hypocalcaemia ($p < 0.01$), permanent hypocalcaemia ($p < 0.01$), postoperative recurrence ($p < 0.01$) and central neck recurrence ($p < 0.01$) were identified as statistically significant. Specifically, the pooled RRs (95% CIs) were as follows: 0.71 (0.521, 0.953) for transient RLN injury, 0.59 (0.531, 0.663) for transient hypocalcaemia, 0.61 (0.463, 0.801) for permanent hypocalcaemia, 1.78 (1.372, 2.302) for postoperative recurrence ($p < 0.01$) and 3.37 (2.028, 5.588) for central neck recurrence.

Sensitivity analysis and publication bias

A single study involved in this meta-analysis was deleted to reflect the influence of the individual data set to the pooled RRs, and the corresponding pooled RRs were not substantially altered. Begg's funnel plot and Egger's test were performed to access the publication bias of literatures. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (Fig. 2). Next, the Egger's test was used to provide statistical evidence of funnel plot symmetry (Fig. 3). Similarly, the results did not suggest any evidence of publication bias.

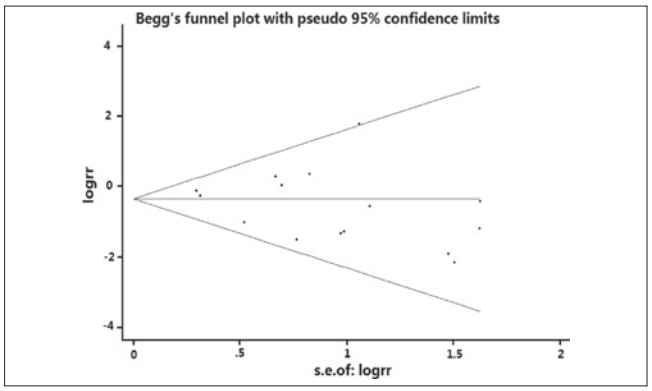

Fig. 2 Begg's funnel plot for visual assessment of overt publication bias for transient RLN injury.

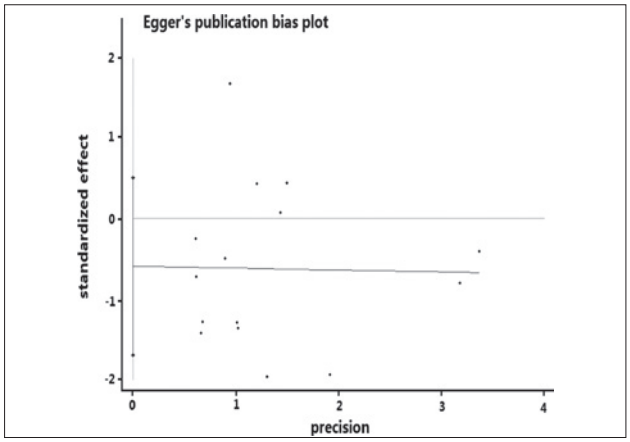

Fig. 3 Egger's publication bias plot showed no publication bias for transient RLN injury.

Discussion

Patients with DTC generally have excellent prognosis; however, it frequently tends to metastatise and often early to regional lymph nodes. About 80% of PTC patients have micrometastases in the central lymph nodes at diagnosis [4 34]. It remains difficult to identify which patients have central LNM before surgery due to the reduced sensitivity of ultrasound (especially in the central compartment) for nodal disease before TT [35 36]. Thus, the value of pCND in patients with cN0 is a matter of debate. In previous studies, some physicians described their experience of treating DTC in patients with pCND, and demonstrated that it had a tendency to upstage approximately 35% of patients, as detecting metastatic nodal disease moves N stage from N0 to N1a [21]. Improved staging might be useful for patients with tumours ≤ 1 cm and is the main advantage of pCND, which nevertheless remains a debated topic, because pCND can cause upstaging and potential overtreatment with the risk of treatment morbidity. In this study, our results showed that cN0 patients in TT plus pCND group had a relatively high incidence of central LNM, but the rate varied widely from 16.7% to 82.3%. We assume the reason may be the heterogeneity in surgical technique, especially in the setting of pCND in which the extent of surgery may vary by location and perceived risk factors. Simultaneously, it might also be a reflection of the quality of preoperative ultrasound evaluation and probably be a result of the quality of histological examination in different countries.

In contrast to other tumours, most DTC patients survive for more than 10 years, and might not have detectable LNM or recurrence until many years after initial surgery. Evaluating survivals as endpoints is difficult in clinical practice. The natural history of DTC would be for some patients to perform multiple neck operations that may result in a negative impact on quality of life. Thus, assessing the number of postoperative recurrences might be more realistic for patients with cN0. The rationale for pCND is based on the assumption that patients have high rates of metastases and regional recurrence in the central neck and that reoperation for central neck recurrence is difficult and carries an increased risk of hypocalcaemia and unintentional RLN injury [6 7 15 27]. However, improvements in survival and locoregional recurrence rates have not been consistently demonstrated with pCND. Although some studies have reported a decrease in neck recurrence after pCND, others do not demonstrate any effect [37-40]. In this study, pCND did show some advantage related to locoregional recurrence in cN0 disease. We found that TT plus pCND as initial treatment to DTC may reduce the risk of recurrence. Although there was variability in the rate of

Table I. Main characteristics of studies included.

Author	Country	Year	Design	Number of patients	Adverse events	Central LNM rate in TT+pCND	Follow-up	Number of postoperative RAI treatment	Quality of score
Sywak M [15]	Australia	2006	RT	TT: 391 TT+CND: 56	Hypocalcaemia, haemorrhage, RLN injury, recurrence	38%	TT: 70 months TT+CND:24.5 months	TT: 391 TT+CND: 56	8/9
Palestini N [4]	Italy	2008	RT	TT: 148 TT+CND: 157	Hypocalcaemia, haemorrhage, RLN injury	42%	NA	None	6/9
Choi SJ [16]	Korea	2008	RT	TT: 53 TT+CND: 48	RLN injury, recurrence	37.5%	24.4 months	TT: 53 TT+CND: 48	8/9
Costa S [17]	Italy	2009	RT	TT: 118 TT+CND: 126	Recurrence	47%	TT: 64 months TT+CND: 47 months	TT: 62 TT+CND: 87	6/9
Zuniga S [7]	Columbia	2009	RT	TT: 130 TT+CND: 136	Recurrence	82.3%	6.9 years	TT: 55 TT+CND: 79	7/9
Perrino M [18]	Italy	2009	RT	TT: 159 TT+CND: 92	Hypocalcaemia, RLN injury, recurrence	75.8%	69.2 months	140	6/9
Sadowski BM [19]	United States	2009	RT	TT: 130 TT+CND: 180	RLN injury, recurrence	46.7%	38.8 months	None	5/9
Roh JL [20]	Korea	2009	RCT	TT: 49 TT+CND: 148	Hypocalcaemia, recurrence	52.7%	36 months	TT: 49 TT+CND: 148	2
Rosenbaum MA [5]	United States	2009	RT	TT: 88 TT+CND: 22	Hypocalcaemia, RLN injury, recurrence	77%	TT:3.8 years TT+CND:2.8 years	TT: 56 TT+CND: 18	7/9
Hughes DT [21]	United States	2010	RT	TT: 65 TT+CND: 78	Hypocalcaemia, haemorrhage, RLN injury, recurrence	62%	TT: 27.5 months TT+CND: 19.1 months	TT: 56 TT+CND: 72	6/9
Moo TA [6]	United States	2010	RT	TT: 36 TT+CND: 45	Hypocalcaemia, RLN injury, recurrence	33%	3.1 years	TT: 36 TT+CND: 45	5/9
Popadich A [22]	Australia	2011	RT	TT: 347 TT+CND: 259	Hypocalcaemia, haemorrhage, RLN injury, recurrence	49%	TT: 50 months TT+CND: 32 months	TT: 347 TT+CND: 259	6/9
Mitra I [23]	UK	2011	RT	TT: 78 TT+CND: 49	Hypocalcaemia	59.2%	NA	None	5/9
Lang BH [24]	China	2012	RT	TT: 103 TT+CND: 82	Hypocalcaemia, haemorrhage, RLN injury, recurrence	54.9%	TT: 27.1 months TT+CND: 25.5 months	TT: 63 TT+CND: 62	6/9
So YK [25]	Korea	2012	RT	TT: 113 TT+CND: 119	Hypocalcaemia, haemorrhage, RLN injury, recurrence	37%	TT: 45.4 months TT+CND: 44.7 months	TT: 92 TT+CND: 101	6/9
Wang TS [26]	United States	2012	RT	TT: 37 TT+CND: 66	Hypocalcaemia, RLN injury	40.8%	21 months	TT: 12 TT+CND: 29	6/9
Raffaelli M [27]	Italy	2012	PT	TT: 62 TT+CND: 124	Hypocalcaemia, RLN injury, recurrence	35.5%	25.1 months	TT: 37 TT+CND: 90	8/9
Giordano D [28]	Italy	2012	RT	TT: 394 TT+CND: 693	Hypocalcaemia, RLN injury	NA	9 months	None	7/9
Hyun SM [29]	Korea	2012	RT	TT: 87 TT+CND: 65	Recurrence	44.6%	51.31 months	None	4/9
Barczyński M [30]	Poland	2013	RT	TT: 282 TT+CND: 358	Hypocalcaemia, RLN injury, recurrence	30.2%	TT: 128.8 months TT+CND: 126.4 months	TT: 79 TT+CND: 231	7/9
Boute P [31]	France	2013	RT	TT: 22 TT+CND: 61	Hypocalcaemia, RLN injury	16.7%	NA	None	5/9
Calò PG [32]	Italy	2013	RT	TT: 169 TT+CND: 46	Hypocalcaemia, haemorrhage, RLN injury, recurrence	30.4%	93 months	197	7/9
Conzo G [33]	Italy	2014	RT	TT: 390 TT+CND: 362	Hypocalcaemia, haemorrhage, RLN injury, recurrence	41.8%	9.5 years	652	8/9

RT: retrospective trial
PT: prospective trial
RCT: randomised controlled trial
TT: thyroidectomy
TT+pCND: thyroidectomy plus prophylactic central neck dissection
RLN: recurrent laryngeal nerve
LNM: lymph node metastasis
NA: not available
RAI: radioactive iodine

Table II. Statistical results of postoperative complications and recurrence between TT and TT+pCND groups.

	N	Cases	RR (95% CI)	Analytical model	P value
Haemorrhage	26	2885	0.66 (0.322, 1.353)	FEM	0.256
Transient RLN injury	175	5281	0.71 (0.521, 0.953)	FEM	0.023
Permanent RLN injury	75	5337	1.19 (0.748, 1.883)	FEM	0.467
Transient hypocalcaemia	1287	5851	0.59 (0.531, 0.663)	FEM	< 0.01
Permanent hypocalcaemia	204	5850	0.61 (0.463, 0.801)	FEM	< 0.01
Postoperative recurrence	261	4205	1.78 (1.372, 2.302)	FEM	< 0.01
Central neck	85	3422	3.37 (2.028, 5.588)	FEM	< 0.01
Lateral neck	88	3381	1.28 (0.840, 1.952)	FEM	0.250

FEM: fixed effects model
REM: random effects model
RLN: recurrent laryngeal nerve

recurrence among the individual series, there was a significant trend toward less recurrence in the central compartment in patients who underwent TT plus pCND compared to those who had TT only (1.0% *vs* 3.6%, $p < 0.01$). However, there was no significant difference in the rate of lateral recurrence whether or not a pCND was performed ($p = 0.25$). The biological behaviour of LNM may not always be predictable. While central LNM is often high, the recurrence rate remains low (0-15%), even in patients who underwent TT [7 41]. It has not been possible to explain this difference, but it might be related to the extreme aggressiveness of cancers, in which recurrence would not only depend on local procedures such as pCND.

The indication for pCND in PTC patients with cN0 is less well defined and remains controversial. The revised ATA guidelines were published with a modification in the recommendation for central neck dissection, and recommendation 27B was modified to state that "pCND may be performed with PTC with cN0, especially for T3 or T4 tumours" [8]. However, the strength was lowered to C, meaning that this was based on expert opinion. Although current guidelines offer varying recommendations for central neck dissection in the prophylactic setting, the decision for pCND is mostly at the discretion of the surgeon [7 21 24]. In some studies, patients who underwent pCND were generally more likely to have more risk factors, such as larger tumour size, extrathyroidal extension and multifocality which might have been easily detectable during surgery [7 24]. Ma et al. in their study identified several predictive factors for central LNM in cN0 patients, and proposed that certain risk factors, such as tumour size and extrathyroidal extension, could be considered in preoperative clinical decisions regarding the necessity of pCND in cN0 PTC patients [42]. We look forward to obtaining more information from larger samples for a better comprehension of treatment and authentication accuracy in a population-based collective of patients in the near future.

A benefit of pCND is accurate pathological assessment of nodal status, and these data may make it possible to take a selective approach in the use of postoperative RAI. A comprehensive literature review by Sawka et al. reported that there was no benefit from RAI in reducing cause-specific mortality or recurrence in DTC with early stage [43]. Sywak et al. also showed that there was no significant difference in recurrence in cN0 patients [15]. In accordance with previous results, we found that there was no significant difference between the two groups in terms of postoperative recurrence for patients who had adjuvant RAI. On the other hand, because of upstaging, it is expected that more patients would require RAI ablation and inevitably might be subjected to potential drawbacks from radiation, such as recurrent sialoadenitis, salivary gland swelling and increased risk of second primary malignancies in the long term [44-46]. Although RAI ablation is not recommended for patients with PTC in the absence of high-risk features according to the revised ATA guidelines [8], studies have yet to clarify whether these upstaged patients are overtreated. Whether current changes in decisions regarding RAI administration based on pCND have a long-term effect on outcomes for these patients remain to be seen.

Even with the benefits from pCND, central lymph node dissection inevitably results in a higher rate of RLN injury and hypocalcaemia than no dissection. Recent studies of lymph node dissection in DTC reported the development of transient hypocalcaemia in 14% to 60%, and permanent hypocalcaemia in 3% to 11%. This study showed that the rate of temporary hypocalcemia was indeed significantly higher when a pCND was performed (25.1% *vs* 14.3%, $p < 0.01$). This result is not unexpected, because more extensive dissection in the central neck may interfere with the blood supply to the parathyroid glands, particularly the inferior parathyroid glands. Simultaneously, a pCND did result in a significant increase in the incidence of permanent hypocalcaemia in our study (4.7% *vs* 1.7%, $p = 0.03$). Although the symptoms related to permanent hypocalcaemia may appear to be more acceptable in terms of quality of life than the voice disorders related to RLN injury, permanent hypocalcaemia can be difficult to treat and may require life-long calcium and vitamin D supplements. In terms of RLN injury, analysis of our data

suggests that pCND at the time of initial surgery was associated with a significantly higher rate of transient RLN injury. However, there was no significant difference in permanent RLN injury between the two groups.

The results of this study should be interpreted with caution because of some limitations. First, the studies included are not the highest-quality evidence, and such data might lead to less powerful results. Second, the number of patients in several studies is small, and most of the studies included were conducted in European and North American countries, which may not reflect the real situation. Third, the follow-up period in several studies included was relatively short. Because DTC has the characteristics associated with slow-growth, some patients might not have detectable LNM until many years after initial surgery. This might be a bias for clearly evaluating postoperative recurrence. Publication is a major concern for all forms of meta-analysis, and positive results tend to be accepted by journals, while negative results are often rejected or not even submitted. Although this study does not support publication bias, it should be noted that it could not completely exclude such biases. For example, our meta-analysis was restricted to papers published in English, which probably led to bias and might not allow a reliable conclusion.

Conclusions

In summary, pCND may result in the excision of occult central LNM for patients with cN0 DTC. Compared with TT alone, combined pCND by experienced surgeons may decrease the postoperative recurrence rate in this population. Nevertheless, pCND carries a greater risk of some complications, such as transient RLN injury, and transient and permanent hypocalcaemia. Balancing surgical morbidity and long-term benefits as well as better patient selection to undergo pCND are key. This study should be further updated whenever new and strong evidence is available.

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