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ORIGINAL ARTICLE – ENDOCRINE TUMORS

A Meta-analysis of the Effect of Prophylactic Central Compartment Neck Dissection on Locoregional Recurrence Rates in Patients with Papillary Thyroid Cancer

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ABSTRACT

Background. It is not known whether prophylactic central compartment neck dissection (pCCND) in conjunction with total thyroidectomy decreases rates of locoregional recurrence in patients with papillary thyroid cancer (PTC).

Methods. A meta-analysis was performed of reported recurrence rates of clinically node-negative PTC in patients treated with total thyroidectomy (TT) alone, or TT and pCCND. The primary outcome was locoregional recurrence of PTC.

Results. Eleven studies capturing 2,318 patients met the inclusion criteria. Overall, the recurrence rate for patients undergoing TT/pCCND was 3.8 % [95 % confidence interval (CI) 2.3–5.8]. In the six comparative studies, which included 1,740 patients, 995 patients undergoing TT and 745 patients undergoing TT/pCCND, the overall recurrence rate was 7.6:7.9 % in the TT group and 4.7 % in the TT/pCCND group. The relative risk of recurrence was 0.59 (95 % CI 0.33–1.07), favoring a lower recurrence rate in the TT/pCCND arm. The number of patients that would need to be treated (NNT) in order to prevent a single recurrence is 31. The relative risk for permanent hypocalcemia was 1.82 (95 % CI 0.51–6.5) and for permanent recurrent laryngeal nerve injury was 1.14 (95 % CI 0.46–2.83).

Conclusions. There was no difference in recurrence or long-term complication rates between patients undergoing TT or TT/pCCND. There was a trend toward lower recurrence rates in TT/pCCND patients, with a NNT of 31 patients. On the basis of these data, routine pCCND might be considered in the hands of high-volume surgeons treating patients with clinically node-negative PTC.

According to the American Thyroid Association guidelines on the management of patients with differentiated thyroid cancer, one of the initial goals of surgery in patients with DTC is to "minimize the risk of disease recurrence and metastatic spread … adequate surgery is the most important treatment variable." With level A evidence, the guidelines recommend that near-total or total thyroidectomy (TT) be performed for patients with thyroid cancer >1 cm.[1] Because regional lymph node metastases are present in 20–90 % of patients with papillary thyroid cancer (PTC), preoperative cervical ultrasound with fine needle aspiration biopsy of suspicious lymph nodes and therapeutic neck dissection for patients with clinically involved lymph nodes is recommended.[1–3]

The role of prophylactic central compartment lymph node dissection at the time of initial surgery remains controversial.[4–6] Given the overall excellent survival rates and the potential morbidity of reoperative cervical surgery, locoregional recurrence is an important issue in the management of patients with PTC, particularly because serum thyroglobulin assays and cervical ultrasound technologies are increasingly sensitive in the detection of recurrent disease.[7–9] Although lymph node metastases may be associated with higher rates of locoregional recurrence and decreased survival, particularly in older patients and those with multiple metastases and/or extracapsular nodal extension, it is unclear if

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prophylactic central compartment neck dissection reduces rates of recurrent PTC in the central compartment.[10–22]

The majority of studies examining the effectiveness of prophylactic central compartment neck dissection are single-institutional, retrospective studies, and a randomized, prospective trial is thought to not be feasible, given the prohibitively large sample size required.[23] Previous meta-analyses have been performed, but have included patients undergoing thyroid lobectomy and/or patients with papillary microcarcinoma.[24–26] To our knowledge, this study represents the most current and methodologically rigorous meta-analysis on the effects of pCCND on locoregional recurrence rates in adult patients with PTC.

METHODS

A systematic review was performed in accordance with the guidelines proposed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[27]

Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, EMBASE, and MEDLINE In-Process & Other Non-Indexed Citations electronic databases were searched using a combination of the following MeSH terms: Thyroid neoplasms, Carcinoma papillary, Lymph node excision, Neck dissection, Thyroidectomy, and keywords: "central neck," "level 6," "prophylactic," "routine," "papillary thyroid cancer," "lymph node dissection," "lymphadenectomy" with limits "human" and published in the English language in the last decade.

Two reviewers (KC and TSW) independently performed each step of the study selection process (Fig. 1). Titles and abstracts from the electronic search results were scanned for potential relevance. Full text articles were retrieved for any study that was considered potentially relevant by either reviewer. Studies with primary data comparing TT to total thyroidectomy with prophylactic central compartment neck dissection (TT/pCCND) were selected to undergo data extraction and methodological quality assessment. Articles were excluded if they included patients <18 years, with clinically or radiologically suspicious lymph nodes, or completion thyroidectomy, had no primary data on locoregional recurrence, or were focused on patients with papillary microcarcinoma. Letters to the editor, abstracts, and meeting proceedings also were excluded. Studies that reported a mix of patients were included if sufficient data were provided to extract patients meeting the inclusion criteria. If there was disagreement on the potential relevance of an article, discussion between the reviewers took place until a consensus was achieved. Consultation with arbitrators (SAR and JAS) was undertaken when a deciding

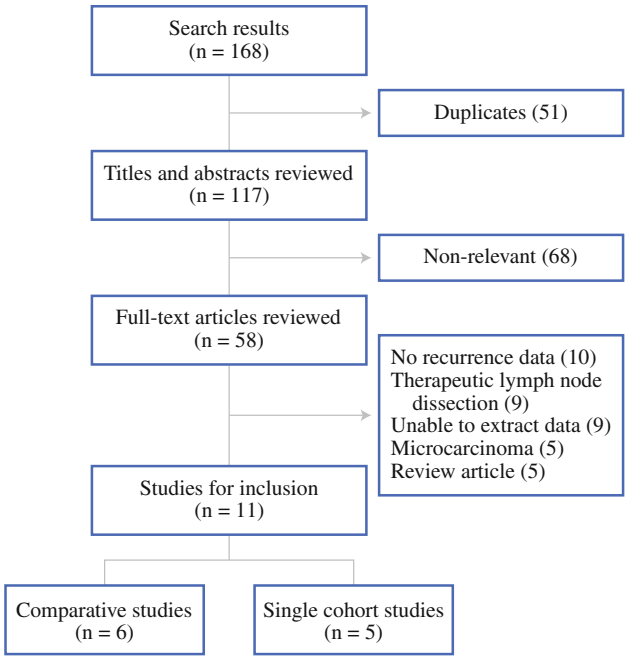

FIG. 1 Flow diagram of article selection process

opinion was needed. References of selected articles were reviewed for additional studies of relevance.

Two reviewers independently assessed the methodological quality of each study using the Methodological Index for Non-Randomized Studies criteria (MINORS), a 12-point scale validated for both comparative and non-comparative studies.[28] Intraclass correlation coefficient mixed-model analysis was performed to calculate the level of agreement in quality assessment between the two reviewers. An intraclass correlation coefficient with 95 % confidence intervals (CI) is reported. Data were extracted from the selected studies using a standardized template. All relevant study variables were collected, including author, journal, year of publication, study type, sample size, tumor size, MACIS score, length of follow-up, and postoperative complications. Methods for outcomes assessment were recorded as reported by the study authors. The primary outcome of interest was disease recurrence and was calculated for both comparative and single cohort studies. Secondary outcomes were postoperative complications of transient and permanent hypocalcemia, recurrent laryngeal nerve (RLN) injury, and postoperative hemorrhage; secondary outcomes were calculated only for comparative studies.

Use of a random effects model of inverse variance to pool the relative risk data from the included studies with the comparison group was planned a priori in the presence of heterogeneity; otherwise, a fixed effect model was employed. A random effect model formally takes study heterogeneity into account as part of its calculation. An

alpha error of 0.05 was considered a criterion for statistical significance. The random effects model using Der Simonian and Laird was used to pool the weighted proportion of recurrence from single group studies. Relative risk with 95 % CI for studies with comparison group and weighted pooled estimates of proportion with 95 % CI are presented. StatsDirect 2.7 (StatsDirect Ltd., UK) and Review Manager (version 5.1, www.cochrane.org) were used for data analysis. Weighted mean was calculated to summarize the mean age from the studies.

Heterogeneity among studies was tested using the Cochran's Q-statistic test with a p value of <0.1 for statistical significance. Cochran's Q-statistic assesses whether the observed differences in results are due to chance alone. An I^2 also was calculated to quantify heterogeneity between studies. I^2 describes the proportion of the variability in effect estimates that is due to heterogeneity rather than chance. An I^2 of <25 % represents low heterogeneity, 25–50 % moderate heterogeneity, and more than 50 % high heterogeneity.

RESULTS

A total of 11 studies, including 2,318 patients, met inclusion and exclusion criteria and were incorporated into the meta-analysis for locoregional recurrence; six studies were comparative between TT and TT/pCCND, and five were single cohort studies of patients undergoing TT/pCCND (Table 1). Meta-analysis for the secondary outcome of postoperative complications included the five comparative studies with available data on rates of postoperative morbidity. For the 11 studies, assessment of study quality by the two reviewers revealed an interrater reliability of 93.5 % (95 % CI 77–98). A funnel plot revealed symmetrically distributed plots, indicating the absence of publication bias.

Mean quality scores were 11.5 [maximum score, 16; standard deviation (SD) 2.4] for noncomparative studies and 16.1 (maximum score, 24; SD 1.8) for comparative studies on the MINORS scale. The majority of comparative studies used a historical control group or failed to demonstrate baseline equivalency. Of the 11 studies, only four studies were performed prospectively, and only one study provided a sample size calculation.

Weighted mean patient age was 46.7 (SD 4.6) years for TT and 50.5 (SD 4.2) years in the total thyroidectomy and prophylactic central compartment neck dissection (TT/pCCND) group ($p < 0.001$). There was no difference in gender between the groups (75 vs. 75.4 %; $p = 0.739$). Tumor size ranged from 0.2 to 11.0 cm in the TT group and 0.2 to 9.0 cm in the TT/pCCND group. The duration of follow-up ranged from 12 to 144 months for the TT group and 3 to 159 months in the TT/pCCND group.

TABLE 1 Summary of 11 studies included in the meta-analysis

Study	Procedure	*n*	Tumor size, cm[a]	Follow-up, months	Criteria for recurrent PTC	Recurrence, *n* (%)
Sywak et al.[16]	TT	391	2.3 (95 % CI 1.8–2.9)	70 (median)	Serum Tg cervical US	22 (5.6)
	TT/pCCND	56	2.0 (95 % CI 1.5–2.3)	24.5 (median)		2 (3.6)
Son et al.[15]	TT/pCCND	114	Ipsilateral 1.1 (SD 0.8); bilateral 1.4 (SD 0.9)	24.2 (mean)	Serum Tg or TgAb	9 (7.9)
Koo et al.[19]	TT/pCCND	111	1.6 (range 0.2–4.8)	24.4 (mean)	NR	0 (0)
Costa et al.[14]	TT	118	1.5 (range 0.1–10)	64 (mean)	Serum Tg cervical US	8 (6.8)
	TT/pCCND	126	1.7 (range 0.1–6)	47 (mean)		9 (7.1)
Hughes et al.[13]	TT	65	2 (median)	27.5 (mean)	Serum Tg cervical US/ WBS	3 (4.6)
	TT/pCCND	78	1.9 (median)	19.1 (mean)		4 (5.1)
Moo et al.[12]	TT	36	2.0	37.2 (mean)	Serum Tg and TgAb US/ CT/WBS histology	6 (16.7)
	TT/pCCND	45	1.4	37.2 (mean)		2 (4.4)
Roh et al.[20]	TT/pCCND	184	1.5 (SD 1.2)	46 (mean)	NR	1 (0.5)
Laird et al.[21]	TT/pCCND	118	1.91	16 (mean)	Serum Tg	3 (2.5)
Lang et al.[11]	TT	103	1 (range 0.2–11)	27.1 (median)	Serum Tg cervical US	3 (2.9)
	TT/pCCND	82	1.5 (range 0.2–9)	25.5 (median)		3 (3.7)
Lang et al.[22]	TT/pCCND	109	range 0.4–6	31.2 (median)	Serum Tg cervical US	5 (4.6)
Barczynski et al.[10]	TT	282	NR	128(mean)	Serum Tg cervical US/ WBS cytology/histology	37 (13.1)
	TT/pCCND	358	NR	126(mean)		15 (4.2)

PTC papillary thyroid cancer, *TT* total thyroidectomy alone, *CI* confidence interval, *SD* standard deviation, *NR* not reported,, *pCCND* prophylactic central compartment neck dissection, *Tg* thyroglobulin, *US* ultrasonography, *TgAb* thyroglobulin antibody, *WBS* whole body scan, *CT* computed tomography

[a] Tumor size reported as mean unless otherwise indicated

Overall, the recurrence rate of patients undergoing TT/pCCND in both the single cohort and comparative studies was 3.8 % (95 % CI 2.3–5.8). These studies were largely heterogeneous with an I^2 of 64 % (Fig. 2). The six comparative studies, which included 1,740 patients, 995 patients undergoing TT and 745 patients undergoing TT/pCCND, had small heterogeneity ($I^2 = 38$ %). The relative risk of recurrence for patients undergoing TT/pCCND was 0.59 (95 % CI 0.33–1.07). Pooled recurrence rates were 7.9 % (79 of 995) in the TT group and 4.7 % (35 of 745) in the TT/pCCND group, favoring pCCND (Fig. 3). The number of patients that would need to be treated (NNT) in order to prevent a single recurrence would be 31.

Meta-analysis also was performed for complications related to thyroidectomy (Fig. 4). Transient and permanent hypocalcemia and transient RLN injury were reported for a total of 1,495 (877 TT and 619 TT/pCCND) patients. The relative risk was 2.52 (95 % CI 1.95–3.25, $I^2 = 0$ %) for temporary hypocalcemia and 1.82 (95 % CI 0.51–6.5) for permanent hypocalcemia, with increased study heterogeneity ($I^2 = 33$ %). Transient RLN injury was reported in 66 patients overall, 24 in the TT group and 34 in the TT/pCCND group, for a relative risk of 1.44 (95 % CI 0.59–3.55). Permanent RLN injury was reported in 21 of 1,353 patients, with a relative risk of 1.14 (95 % CI 0.46–2.83). The I^2 for studies reporting transient and permanent RLN injury was 20 and 0 %, respectively. Only three studies had information available for comparison of rates of postoperative hematoma. Of 775 patients, the relative risk was 1.06 (95 % CI 0.17–6.67), with an I^2 of 26 %.

DISCUSSION

A compartment-oriented therapeutic neck dissection is recommended for patients with a diagnosis of PTC and preoperative clinical suspicion of metastatic central compartment lymphadenopathy.[1,3] Controversy exists, however, around the role of routine, prophylactic CCND in patients with no preoperative suspicion for metastatic lymphadenopathy. Some studies have favored routine pCCND and have demonstrated lower postoperative serum thyroglobulin levels and reduced rates of central neck recurrence, while other studies have demonstrated no difference in recurrent PTC and have argued

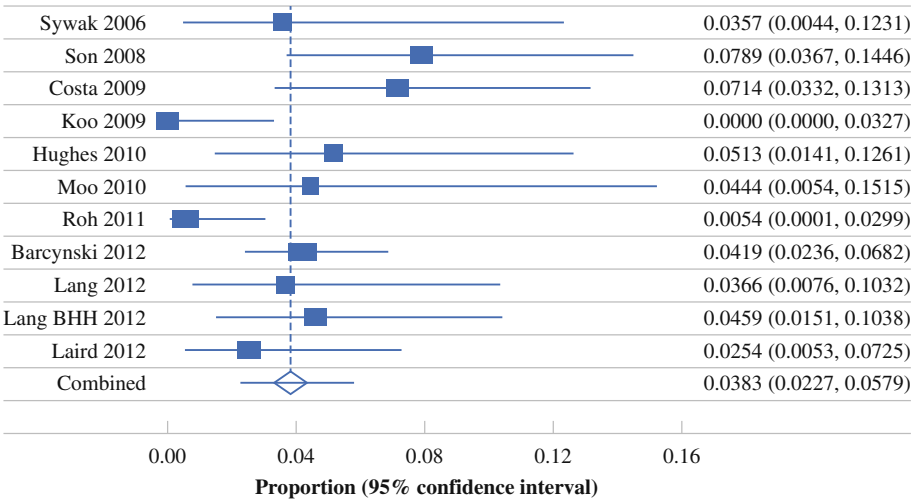

FIG. 2 Forest plot for recurrent papillary thyroid cancer. The *x*-axis represents the proportion of patients with recurrent disease

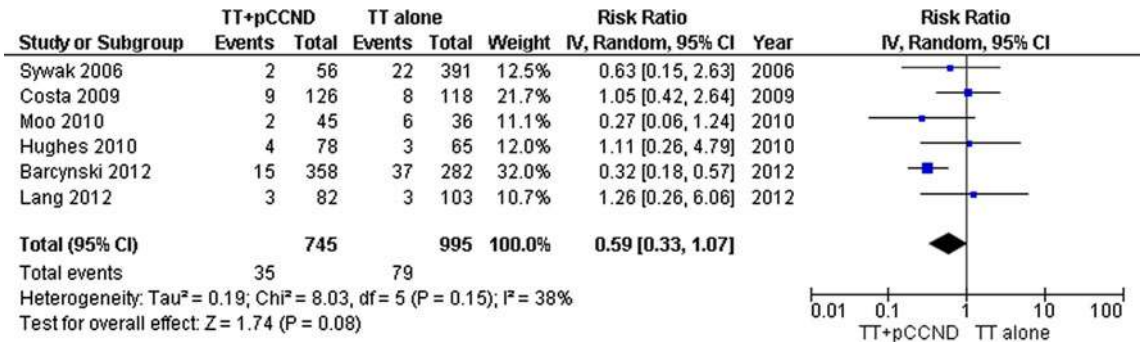

FIG. 3 Forest plot for recurrent papillary thyroid cancer in the six comparative studies

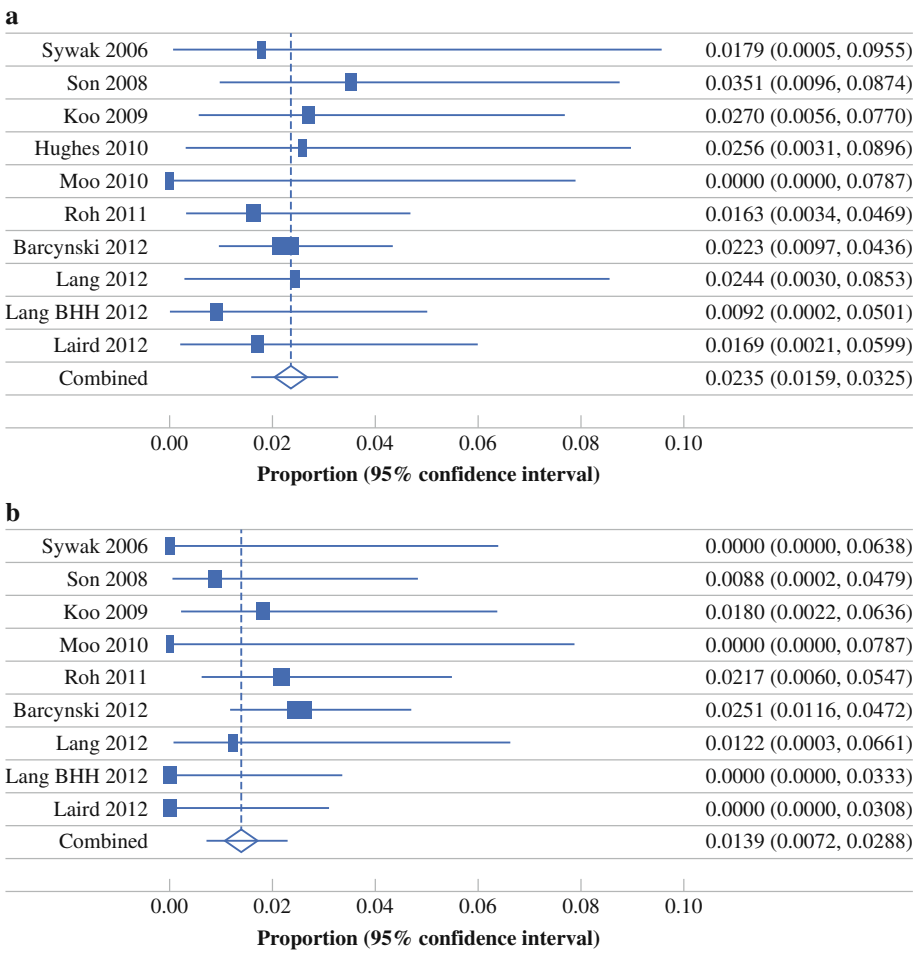

FIG. 4 Forest plot for postoperative complications. **a** Permanent hypoparathyroidism. **b** Permanent recurrent laryngeal nerve injury (paralysis). The *x*-axis represents the proportion of patients with the described complication

that upstaging of disease as a result of detection of central neck lymphadenopathy leads to subsequent overuse of adjuvant radioactive iodine therapy.[4–6,10–16,29]

The results of this meta-analysis suggest that patients who have undergone TT/pCCND may have a lower risk of recurrent PTC than those who have undergone TT alone. In the six studies comparing TT to TT/pCCND, recurrence rates were 7.9 % in the TT group and 4.7 % in the TT/pCCND group, for a relative risk of 0.59, although this did not reach statistical significance (95 % CI 0.33–1.07). Interestingly, when TT/pCCND patients in the five single cohort studies were included in the analysis of recurrence after TT/pCCND, the overall recurrence rate decreased to 3.8 %. This suggests that when performed routinely by experienced endocrine surgeons, pCCND may be associated with a lower risk of recurrent PTC, a finding not previously reported in other systematic reviews and meta-analyses.[4,24–26] On the basis of the calculated risk reduction, the number of patients that would need to be treated to achieve a lower recurrence rate is 31. Given that no difference was identified in secondary outcomes of permanent hypoparathyroidism and RLN injury, stronger consideration might be given to routine pCCND in patients with PTC, particularly when the surgery is performed by surgeons with a high-volume of thyroid cancer patients in their practice.

The feasibility of a prospective randomized controlled trial of pCCND in patients with clinically node-negative PTC was recently evaluated and estimated to require 5,480 patients in order to achieve statistical power for the detection of recurrent disease, and several thousands more for detection of endocrine-specific complications.[23] Given the prohibitively large sample sizes required, it was not deemed feasible to perform. Because the majority of other studies examining recurrence and morbidity in patients undergoing pCCND are single-institutional, retrospective studies, meta-analyses such as the current study are important methods for evaluating optimal management algorithms for patients with DTC. Several previous meta-analyses have been published but have differed in inclusion and exclusion criteria compared to the current study; they have included children, patients undergoing thyroid lobectomy, and/or focused on patients with papillary microcarcinoma.[24–26]

To our knowledge, this study represents the most current literature review of adult patients undergoing TT for PTC. Despite the rigorous literature search and explicit inclusion

and exclusion criteria utilized, the study is limited by the quality of available data in the published literature. Although postoperative radioactive iodine administration is an important adjunct in the treatment of DTC, its use was not analyzed in this meta-analysis because of institutional variations in protocol. The current study does include fewer patients than other recently published meta-analyses; however, this may reflect more rigorous exclusion criteria, as the current analysis includes only studies focused on adult patients with tumors >1 cm in size. Last, our analysis includes comparative and single cohort studies, which may limit direct comparisons by surgeon and institution. However, given the experience of many surgeons who routinely perform prophylactic central compartment neck dissection, the inclusion of these studies was critical in order to avoid selection bias of included studies.

In summary, this meta-analysis did not identify significant differences in the rates of locoregional recurrence or of permanent complications in patients undergoing pCCND for PTC compared to patients undergoing TT alone. There was, however, a trend toward lower recurrence rates in patients after pCCND. Although a NNT of 31 must be placed in a broader context, it does raise the possibility that surgeons who treat a high volume of patients with thyroid cancer and routinely perform pCCND might demonstrate lower rates of recurrent disease in patients with PTC. Multi-institutional, retrospective studies with longer follow-up periods are necessary to provide further clarity to the issue of prophylactic central compartment neck dissection and its potential benefits for patients with clinically node-negative PTC.

DISCLOSURE The authors declare no conflict of interest.

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