META-ANALYSIS
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Morbidity Outcomes of Prophylactic Central Neck Dissection with Total Thyroidectomy versus Total Thyroidectomy Alone in Patients with Node-Negative Papillary Thyroid Cancer: A Meta-Analysis of Observational Studies

ABSTRACT

Objective: The primary objective of this meta-analysis is to compare locoregional recurrence, vocal cord paralysis and permanent hypoparathyroidism in patients with thyroid papillary carcinoma without neck node metastases, after total thyroidectomy with and without prophylactic central neck dissection.

Methods: Two independent reviewers performed a detailed literature search of MEDLINE (PubMed), HERDIN and Cochrane Library electronic databases to assess research studies until 2018 for inclusion. The primary endpoints of locoregional recurrence, permanent hypoparathyroidism and vocal cord paralysis were included in the assessment.

Design: Meta-analysis of retrospective cohort studies
Setting: University Hospitals and Tertiary Referral Centers
Participants: Patients with node-negative papillary thyroid cancer who underwent either total thyroidectomy alone or total thyroidectomy with prophylactic central neck dissection (either unilateral or bilateral).

Results: This meta-analysis showed that there is a significantly increased risk for locoregional recurrence in the total thyroidectomy alone group (1.96% TT with pCND VS 2.60% TT, RR=0.62, 95% CI=0.40-0.95, p=.03), permanent hypoparathyroidism in the total thyroidectomy with prophylactic central neck dissection group (5.72% TT with pCND vs 3.34% TT, RR=2.19, 95% CI=1.62-2.98, p=.00001) and no significant difference for vocal cord paralysis between the 2 groups (RR=1.56, 95% CI=0.86-2.84, p=.14).

Conclusion: This meta-analysis revealed that performing pCND in patients with node-negative PTC increases the risk of morbidity for hypoparathyroidism but not for vocal cord paralysis. More importantly, the incidence of recurrence is decreased in the pCND group which may have implications on the overall survival of patients. The benefit of performing pCND may outweigh the risk but the role of prophylactic CND in the treatment of patients with PTC with clinically negative lymph nodes is still debatable in terms of overall survival.

Keywords: *thyroidectomy, complications; neck dissection; papillary thyroid carcinoma; lymph node dissection; recurrence; vocal cord paralysis; hypoparathyroidism*

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Among the thyroid malignancies, papillary thyroid carcinoma (PTC) is the most common type accounting for about 80 - 90% of all thyroid cancers worldwide.[1-4] The consensus on the appropriate treatment of patients with papillary thyroid cancer has undergone paradigm shifts over the years yet there are still points of controversy.[3-6] Currently, the most widely debated subject in the management of PTC is whether a prophylactic central neck dissection (pCND) should be done in patients who are clinically node-negative.[5] Elective or prophylactic central neck dissection (PCND) has been proposed in the treatment of PTC without clinical and ultrasound evidence of lymph node metastasis in the neck (cN0).[7] A central neck dissection (CND) consists of removal of all lymph nodes and fibrofatty tissue between the common carotid arteries laterally from the hyoid bone superiorly to the innominate artery inferiorly.[8] The rationale of this procedure is to remove clinically non-detectable pathologic lymph nodes to reduce the rate of recurrent disease and the morbidity associated with re-operation.[9] On the other hand, some studies report that there is no oncologic benefit, as no difference has been shown in preablation radioiodine uptake in the neck whether or not pCND was performed.[8]

Although most management guidelines agree in performing CND routinely for patients with clinically evident nodal disease, the role of prophylactic central neck dissection remains controversial in patients who are clinically node-negative. The American Thyroid Association management guidelines recommend PCND in clinically node-negative (cN0) PTC patients especially in those with a tumor size larger than 4 cm or those with extrathyroidal extension.[8] At the same time, a European consensus statement on pCND endorsed by the European Thyroid Association in 2006 stated that there is no evidence that pCND improves recurrence or mortality rates, but it does allow an accurate staging of the disease that may guide subsequent treatment and follow-up.[8] Proponents of pCND also support its routine use as it has the advantage of increasing accuracy in TNM staging of pathologic lymph nodes.[8,10] On the other hand, those against the routine use of pCND claim that the clinical impact of occult micrometastases has yet to be demonstrated and it may lead to an overstaging of disease without clear evidence of reduction in recurrence or added benefit to survival. It was also found that the overall complication rate was significantly higher in patients treated with total thyroidectomy and pCND compared to total thyroidectomy alone.[4] The commonly reported complications included vocal cord paralysis or recurrent laryngeal nerve injury and hypothyroidism, with a noted higher risk of permanent hypoparathyroidism if bilateral neck dissection was done.[11-13] Interestingly, the overall recurrence rate and survival rate did not significantly differ between the two groups in these studies.[11-14] From the results of these studies, it seems evident that the incidence of morbidity is clearly and consistently proportional to the extent of surgery. This result is not unexpected however, since more extensive dissection in the central neck during surgery may interfere with the blood supply to the parathyroid glands, particularly the inferior parathyroid glands.[8] Despite these complications, those that favor pCND argue that it reduces the need for reoperation in central recurrence, which can exhibit more aggressive behavior and may lead to greater morbidity.

The primary objective of this meta-analysis is to provide evidence of prophylactic central neck dissection in the management of papillary carcinoma of the thyroid without clinically apparent neck node metatases, specifically to compare rates of oncologic control and morbidities after total thyroidectomy with and without prophylactic neck dissection in patients with thyroid papillary carcinoma.

METHODS

Protocol and Registration

This meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. A protocol for this meta-analysis has been registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO) under the registration number CRD42019125369.

Eligibility Criteria

For all the studies, the population included patients with papillary thyroid carcinoma without lymph node metastasis (N0 neck). The intervention would be total thyroidectomy combined with central neck dissection and the comparator is total thyroidectomy alone, with locoregional recurrence and morbidities as vocal cord paralysis and hypoparathyroidism. The inclusion criteria of eligible studies were: (1) retrospective cohort design to ensure homogeneity, (2) studies with more than 10 patients, (3) patients with PTC and no lymph node metastasis preoperatively, (4) studies having pCND + TT group and TT alone group; and (5) available data about recurrence and incidence rate of complications with a follow up period of at least 2 years. Exclusion criteria were as follows: (1) CND alone (2) thyroidectomy alone (3) lobectomy (4) pCND combined with lateral neck dissections/ other procedures (5) video-assisted or robotic techniques (6) revision operations, and (7) endoscopic procedures.

Information Sources and Search Strategy

Two independent authors searched MEDLINE (PubMed), HERDIN and the Cochrane Library electronic databases journal articles published in the English language from 2010 until 2018. The following keywords were used in all fields as search strategy: (1)

papillary thyroid carcinoma or papillary thyroid cancer or thyroid papillary cancer, (2) central neck dissection or central compartment neck dissection or central compartment lymph node dissection or central compartment node dissection; and (3) 1 and 2. The references of previous meta-analysis were also backtracked and assessed for eligibility. To ensure homogeneity in the scope of the studies, the limits used were any studies that included lateral neck, modified radical, hemithryoidectomy, or lobectomy in any of the titles, abstracts or keywords.

Study Selection and Data Collection Process

The abstracts were initially assessed for eligibility based on the specified criteria followed by a full-text analysis of the screened studies to resolve any uncertainty or conflict. A data form was used to extract all data we would evaluate. The following data on study characteristics were collected: first authorship, the publication year, the type of study, follow-up period, the number of patients in pCND + TT group and TT alone group, the number of patients having recurrence and the number of patients having surgical-related complications. Primary endpoints of the study included the rate of morbidity including permanent laryngeal nerve (RLN) injury, permanent hypoparathyroidism and locoregional recurrence. Recurrent laryngeal nerve injury was defined as a postoperative impairment of the motility of one or both vocal cords postoperatively. Permanent hypoparathyroidism was defined as persistent postoperative hypocalcemia 6 months after surgery requiring calcium and vitamin D supplementation. Locoregional recurrence was defined as either the cytological evidence of disease in the central or in the lateral compartment of the neck or the evidence of disease on follow-up ultrasound. Dichotomous variables were presented as relative risks with 95% confidence intervals.

Risk of Bias in Individual Studies

The quality of the cohort studies were assessed using the Newcastle-Ottawa quality assessment scale.[15] The quality was assessed based on representativeness, selection of non-exposed cohort, ascertainment of exposure, demonstration that outcome was not present at the start of the study, comparability of cohorts, assessment of outcome, follow-up period and adequacy of follow-up. The funnel plot method was also used to evaluate publication bias.

Summary Measures and Synthesis of Results

Statistical analysis was performed using Review Manager (RevMan) 5.3 software (Cochrane Collaboration, London, U.K.). Fixed effects models were used for the analyses. Heterogeneity across studies was assessed by χ^2 test and quantified with I^2 statistically with a $P<0.1$ and an $I^2>50\%$ was considered a significant difference. A pooled risk ratio (RR) with 95% confidence interval (CI) by the fixed effects model was used to estimate arms in studies included in this meta-analysis. In all tests, P value smaller than .05 was considered statistically significant.

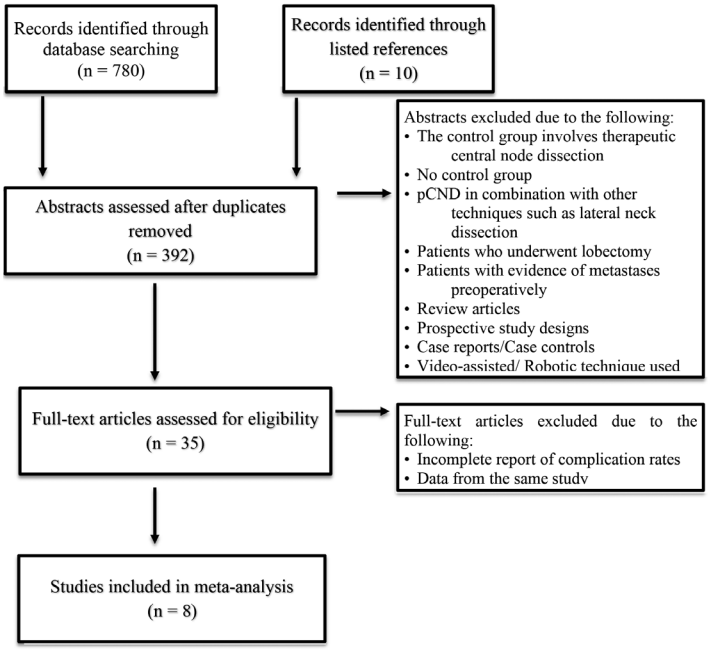

Figure 1. Flowchart of literature search

RESULTS

The flow chart of literature filtration is presented in *Figure 1*. A total of 780 publications were obtained from the initial search including 773 from PubMed, 1 from HERDIN and 6 from Cochrane Library electronic databases. Excluding the duplicates, unrelated topics, studies having no control group or TT alone group and studies combining other procedures, 35 full-text articles were assessed for eligibility. Finally, 8 retrospective studies with comparison between pCND + TT and TT alone were deemed eligible and included in this meta-analysis.

The basic characteristics of included studies are shown in *Table 1*. There were 8 retrospective cohort studies included which were published recently from 2010 until 2017. Among these hospital-based studies, a total of 13,429 cases were identified in this analysis, including 9,634 cases in the pCND+TT group and 3,795 cases in the TT alone group. Three of these included studies set the subgroup analysis and divided the pCND into unilateral pCND and bilateral pCND. For this meta-analysis, the data has been combined for unilateral and bilateral CND since most of the studies had pooled the data together in both

Table 1. Characteristics of Included Studies

Author	Study Design	Number of Patients: TT	Number of Patients: TT + pCND	Follow up period	Comparison of Outcomes: Permanent vocal cord paralysis: TT	Permanent vocal cord paralysis: TT + pCND	Permanent hypoparathyroidism: TT	Permanent hypoparathyroidism: TT + pCND	Locoregional Recurrence: TT	Locoregional Recurrence: TT + pCND
Calo, 2017 [5]	Retrospective cohort	103	30 unilateral 30 bilateral	46-72 months	1	3	2	1 unilateral, 1 bilateral	4	0
Dobrinja, 2017 [11]	Retrospective cohort	112	74	37-76 months	9	11	1	6	4	4
Giordano, 2017 [12]	Retrospective cohort	205	280 unilateral 124 bilateral	48-113 months	1	3	9	14 unilateral, 22 bilateral	12	14 unilateral, 6 bilateral
Kim, 2016 [13]	Retrospective cohort	2834	8735	62 months	0	2	17	38	6	12
Moo, 2010 [14]	Retrospective cohort	36	45	24 - 36 months	0	0	5	0	6	2
So, 2012 [17]	Retrospective cohort	113	119	45 months	2	1	2	7	1	2
Tartaglia, 2014 [15]	Retrospective cohort	284	63	60 months	8	1	27	16	0	2
Zhang, 2015 [16]	Retrospective cohort	108	134	60 months	1	1	0	2	9	3

* pCND = prophylactic central neck dissection, TT = total thyroidectomy

Table 2. Newcastle-Ottawa Scale for Cohort Studies

AUTHOR	Criterion: Publication Year	Cohort Selection	Cohort Comparability	Validity of Outcome Measure	Total
Calo et al.[5]		★★★	★★	★	6
Dobrinja et al.[11]	2017	★★★	★★	★★	7
Giordano et al.[12]	2017	★★★★	★★	★★	8
Kim et al.[13]	2016	★★★★	★	★★	7
Moo et al.[14]	2010	★★★★	★★	★★	8
So et al.[17]	2012	★★★★	★★	★★	8
Tartaglia et al.[15]	2014	★★★★	★	★★	7
Zhang et al.[16]	2015	★★★★	★	★	6

[1]A study can be awarded a maximum of one star for each numbered item within the selection and outcome category, and a maximum of two stars can be given for comparability. For the selection category, a star is awarded if the exposed cohort is representative; if the unexposed cohort is drawn from the same community as the exposed cohort; if exposure was ascertained by secure record and if it was demonstrated that the outcome of interest was not present at the start of the study. For comparability, one star is awarded if the study controls for the most important factor and another star can be awarded if the study controls for any additional factor. For outcome, a star is awarded if the assessment of the outcome is an independent blind assessment or by record linkage; if there was a long enough follow-up for the outcomes to occur; and if there was complete follow-up.

Table 3. Detailed Assessment using the Newcastle-Ottawa Scale for Cohort Studies

Author	Selection: Representativeness	Selection: Selection of non-exposed cohort	Selection: Ascertainment of Exposure	Selection: Demonstration that outcome of interest was not present at the start of the study	Comparability: Comparability of Cohorts	Outcome: Assessment of Outcome	Outcome: Was follow-up long enough for outcomes to occur	Outcome: Adequacy of follow up
Calo et al.[5]	✓			✓	✓	✓	✓	✓
Dobrinja et al.[11]	✓		✓	✓	✓	✓	✓	✓
Giordano et al.[12]	✓	✓	✓	✓	✓	✓	✓	✓
Kim et al.[13]	✓	✓	✓	✓	✓		✓	✓
Moo et al.[14]	✓ ✓	✓	✓	✓	✓	✓	✓	✓
So et al.[17]	✓	✓	✓	✓	✓	✓	✓	✓
Tartaglia et al.[15]	✓	✓	✓	✓		✓	✓	✓
Zhang et al.[16]	✓	✓	✓	✓			✓	✓

groups and were not specified. The scale distribution (0-10 stars) for the study quality ranged from 6 to 8 stars based on the Newcastle-Ottawa Quality Assessment Scale.[15] All the included studies demonstrated a relatively high quality as shown in *Tables 2* and *3*.

Risk of bias assessment is summarized in *Table 4*. Since the included studies shown in *Table 4* are retrospective and observational in design, evaluations of allocation concealment, blinding of participants and personnel, and blinding of outcome assessments are absent. Thus, the studies were judged to have a high risk of selection, information and confounding biases.

The post-operative morbidity outcomes of permanent vocal cord paralysis, permanent hypoparathyroidism and locoregional recurrence between the two groups are shown as forest plots of the risk difference in *Figures 2* to *4*. Risk of publication bias for each study is shown in *Table 4*.

The overall rate of vocal cord paralysis is 1.44% (44/3050), permanent hypoparathyroidism is 4.48% (183/4083) and locoregional recurrence is 2.3% (86/8376).

There was no significant difference in the incidence of permanent vocal cord paralysis between the TT alone group and the TT + pCND group (RR=1.56, 95% CI=0.86-2.84, p =.14, Fig 2A). There was no significant heterogeneity between studies (I^2=0% and P=.55). The funnel plot method confirmed no significant publication bias. *(Figure 2B)*

Permanent hypoparathyroidism was reported in all studies with no significant heterogeneity between studies with I^2=14% and P=.32. The rate of permanent hypoparathyroidism in the pCND+TT group was significantly higher than that in TT alone group (5.72% vs 3.34%, RR=2.19, 95% CI=1.62-2.98, p =.00001. (*Figure 3A*). A publication bias

Table 4. Risk of Bias Assessment Summary

Evaluated Item	Study							
	Calo, 2017	Dobrinja 2017	Giordano, 2017	Kim, 2016	Moo, 2010	So, 2012	Tartaglia, 2014	Zhang, 2015
Selection bias:Allocation concealment	-	-	-	-	-	-	-	-
Performance bias: Blinding of participants & personnel	-	-	-	-	-	-	-	-
Detection bias: Blinding of outcome assessment	-	-	-	-	-	-	-	-
Attrition bias: Incomplete outcome data	+	+	+	+	+	+	+	+
Reporting Bias: Selective reporting	+	+	+	+	+	+	+	+

Key: + = Low risk of bias, - = High risk of bias, ? = Unclear risk of bias

was shown in one study but was not present in the rest of the studies. *(Figure 3B)*

The overall locoregional recurrence was reported in all studies. There was no significant heterogeneity between studies with I^2=6% and P=.38. The rate of locoregional recurrence was statistically significantly lower in the pCND+TT group compared to the TT alone group (1.96% vs 2.60%, RR=0.62, 95% CI=0.40-0.95, p=.03). *(Figure 4A)* The funnel plot method confirmed no significant publication bias. *(Figure 4B)*

DISCUSSION

This meta-analysis found an increased risk for permanent hypoparathyroidism when central neck dissection was performed in addition to total thyroidectomy but no significant risk for vocal cord paralysis. There was also an increased risk for locoregional recurrence with total thyroidectomy was done alone. This meta-analysis is significant in guiding the current surgical management since it may elucidate on the role of pCND for important risk outcomes including vocal cord paralysis, post-operative hypoparathyroidism and locoregional recurrence. In addition to total thyroidectomy surgery, the recent evidence has grown to include the procedure of central neck dissection due to the increasing incidence of lymph node metastases in level VI nodes estimated to occur between 20 - 90% of cases.[5,15] In these cases, regional lymph node metastasis may be present at the time of diagnosis based on the preoperative ultrasound. However, imaging only reveals metastatic involvement of the central neck in only 50% of cases with pathologic lymph nodes found on definitive pathology.[18] Macroscopically positive nodal disease is present in 10 to 30% of patients and the incidence of the subclinical disease is reported in 40 to 70% of patients.[8] For PTC, the pattern of metastases usually spreads to the lymph nodes from central nodes, lateral nodes to the mediastinal nodes consecutively, and occurs more commonly in the ipsilateral central node of the primary tumor.[11] Because of this pattern, there are some studies that propose unilateral central neck dissection as an alternative approach to bilateral central neck dissection to decrease the risk of postoperative complications.[11,13] However, the evidence to favor this approach over the other is still inconclusive. Overall, there is limited evidence to support the commonly held belief that prophylactic CND is beneficial in the treatment of node-negative PTC. This meta-analysis was conducted to provide updated information on this ongoing debate. To our knowledge, the latest meta-analyses by Zhao *et al.* included only studies published from 2006 until 2016.[15] Different from previous meta-analyses and systematic reviews, we strictly included only retrospective cohort designs and excluded studies in which lobectomy, or lateral neck dissection was combined with pCND. This would provide more standardized results on the effect of pCND on morbidity.

However, analysis of preoperative staging, tumor size, presence of micrometastases which are important in comparing the 2 groups to assess homogeneity was not performed. This may lead to over- or underestimation of risk ratios.

An important issue of controversy is that the clinical impact of subclinical central lymph node metastasis is yet to be demonstrated. Preoperatively, it is standard practice to obtain an ultrasonographic examination to evaluate the central and lateral compartments of the neck for abnormal lymph nodes. Sonographic features raising suspicion for metastatic lymph nodes include: a diameter greater than 1 cm; loss of the normal fatty hilum; an irregular rounded contour; heterogeneous echogenicity; microcalcifications; hypervascularity; and cystic areas.[8] However, it is important to point out that preoperative imaging is not always reliable in detailing lymph node involvement. Lymph node metastasis is a known significant predictor of overall survival, especially in older patients. Zhang *et al.* further demonstrates an advantage of pCND in removing subclinical metastases and thus improving the recurrence rate and avoiding reoperation in their patients.[16] The retrospective study results of Giordano *et al.* on 610 patients show a similar rate of neck recurrence in all groups regardless of whether they underwent total thyroidectomy alone or total thyroidectomy with either ipsilateral or bilateral central neck dissection.[12] This finding suggests that lymph node micrometastasis seems not to affect the clinical outcome of patients with PTC.[12] Moreover, patients with PTC developing locoregional recurrence or distant metastasis can be treated effectively in most cases. This is similar to the results of Kim *et al*., the largest study on pCND to date, that found that pCND did not significantly decrease the risk of locoregional recurrence in cN0 PTC patients, even though

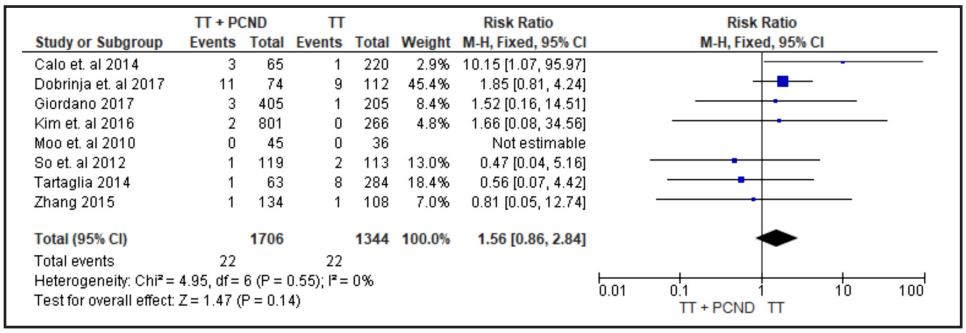

Figure 2A. Forest plot for permanent vocal cord paralysis events showing no significant difference between the pCND + TT versus TT alone groups.

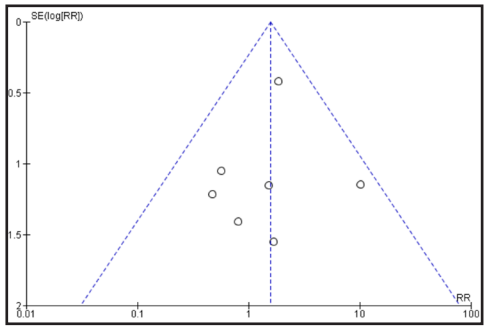

Figure 2B. Funnel plot analysis depicting publication bias for the studies comparing permanent vocal cord paralysis events

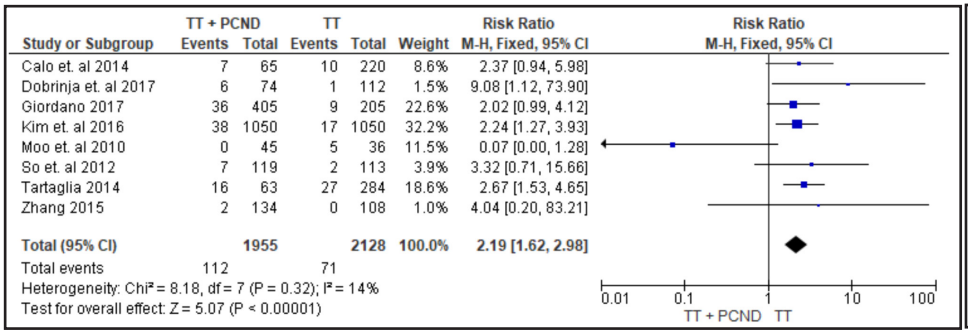

Figure 3A. Forest plot showing a higher incidence for permanent hypoparathyroidism events in the pCND + TT group versus TT alone group.

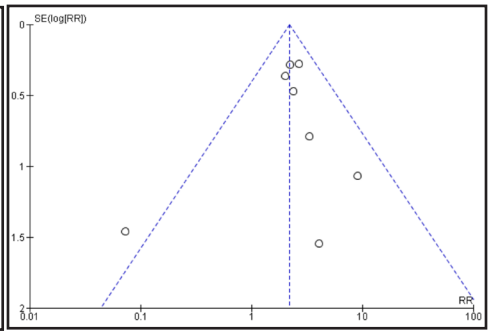

Figure 3B. Funnel plot analysis depicting publication bias for the studies comparing permanent hypoparathyroidism events

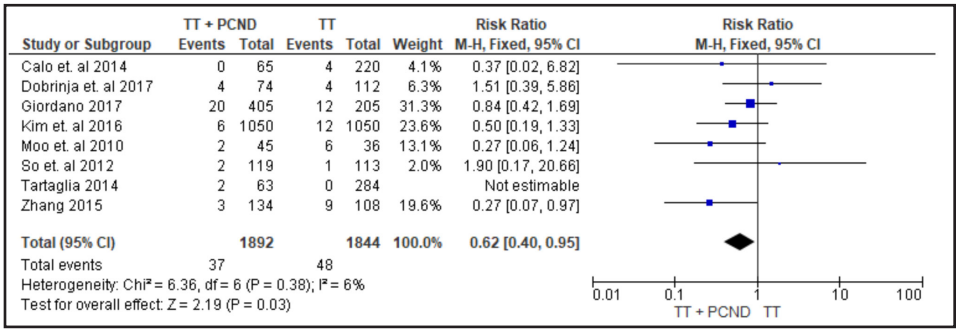

Figure 4A. Forest plot showing a higher incidence for locoregional recurrence events in the TT alone group versus pCND + TT group.

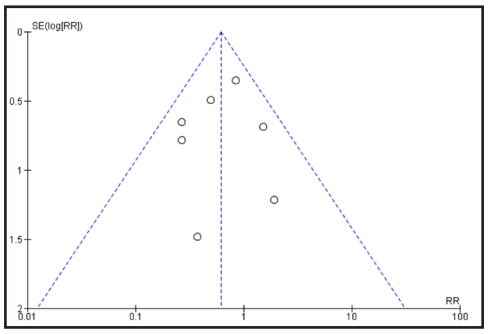

Figure 4B. Funnel plot analysis depicting publication bias for the studies comparing locoregional recurrence events

significantly higher numbers and doses of RAI were administered in the pCND group.[13] Although the previous study by Moo *et al.* revealed a higher recurrence rate for patients undergoing total thyroidectomy alone, this was not found to be statistically significant.[14] Overall, the meta-analysis by McHenry and Stulberg concludes that the potential benefit of pCND may be precise lymph node staging to help determine the need for radioiodine ablation although the effectiveness is still questionable due to the lack of high-level evidence.[8]

An important complication addressed in this meta-analyses is the risk of permanent hypoparathyroidism which is significantly higher in the TT + pCND group. This increased risk is to be expected as CND involves more surgical handling of the tissues which may contain the parathyroid glands. Accidental parathyroidectomy is a common event (15–35%) in this circumstance since identification and appropriate in situ preservation of the parathyroid glands particularly the inferior pair may be difficult.[3,17] There was no significant increased risk of permanent hypoparathyroidism in the study by Hartl *et al.* and So *et al.*[18-19] This finding is in contrast to the meta-analyses conducted by Chisholm *et al.* wherein there was an increased risk for transient hypoparathyroidism in the pCND group but not for permanent hypoparathyroidism.[20] Almost every comparative study included in this meta-analyses reported a higher incidence of postoperative hypocalcemia after prophylactic CND.[6,18,21-23] Conversely, the rate of permanent hypoparathyroidism significantly increased when bilateral but not ipsilateral, CND was done.[6]

Vocal cord paralysis or recurrent laryngeal nerve injury is another

complication common in thyroid surgery. Similar to the previous meta-analysis, most of these studies revealed no significant differences in the rates of temporary or permanent nerve injury in patients undergoing prophylactic CND compared to patients undergoing total thyroidectomy alone.[6,8,12,14-17,25-27] Giordano *et al.* also found no significant differences in recurrent laryngeal nerve injury for TT alone patients compared to those with combined ipsilateral or bilateral pCND.[25] The study by Kim *et al.* was the only other study that showed a significantly increased rate of temporary vocal cord palsy in pCND patients however these results may be skewed since the pre-operative and post-operative laryngoscopic examination was not performed in all patients.[13] The results of this meta-analyses are in agreement with the majority of the published studies.

In most retrospective studies, central lymph node metastasis has been shown to be associated with an increased risk of locoregional recurrence but not with overall survival.[3,17] In analyzing the most recent series, a similar recurrence rate was reported in patients who have undergone total thyroidectomy alone compared to those with an additional pCND operation.[28-29] The large-scale study by Kim *et al.* reports significantly higher numbers and doses of RAI administered in the pCND group, which implies that microscopically detected metastasis in PTC has little chance of evolving into clinically and prognostically significant disease.[13] Calo *et al.* also report similar locoregional nodal recurrence rates in patients who underwent TT alone or combined with either ipsilateral or bilateral CND.[5] It has been postulated that locoregional infiltration and multifocality were associated with a risk of recurrence.[4,5,8] In addition to these factors, Chang *et al.* also report that male sex, tumor size ≥ 0.5 cm, extrathyroidal extension, were associated with a significantly increased risk of recurrence.[30] On the other hand, Tartaglia *et al.* showed that even microcarcinomas <5 mm may be associated with metastatic disease as shown by their recurrence rate of 4.8% in 63 patients despite the CND and the post-operative radioactive iodine treatment.[17]

The results of this study are in agreement with the most recent reviews wherein there is a significantly increased risk for locoregional recurrence in the TT alone group compared to the TT + pCND group. However, the rate of recurrence does not equate with an effect on the survival rate. [11,13,15]

The most recent American Thyroid Association (ATA) guidelines stated that prophylactic CND could be considered in high-risk patients with advanced primary tumors and should be performed by experienced surgeons to avoid definitive complications.[6,21,28] To date, there is still no standardized system that determines those patients who can benefit from prophylactic CND. Many of the studies do not favor routine CND. In the Philippine setting, the latest Clinical Practice Guidelines for the management of well-differentiated thyroid cancer state that prophylactic central node dissection is not recommended because it does not improve overall and disease-free survival.[31] Furthermore, most of the studies recommend that the treatment should be tailored to the type of patient: for example, patients older than 45 years have larger tumors, with a greater propensity for regional metastasis and poorer response to radioiodine therapy.[11,21] On the other hand, Tartaglia *et al.* reveal that only extra-capsular extension may be considered a predictor of relapse based on their data.[17]

Thus, it is prudent to consider a prophylactic CND in the higher risk cohort for these patients. These include males >45 years of age and large tumor size, provided the surgeon has the appropriate level of expertise.[17] However, this procedure cannot be done routinely since the results of this systematic review show that pCND in combination with total thyroidectomy is associated with a higher risk of causing permanent hypoparathyroidism after surgery. Although the locoregional recurrence rate has been shown to be lower in this group, the survival rate and overall benefit is still not fully established.

Our study has several limitations. One is the inherent selection bias in a nonrandomized and non-blinded retrospective cohort design. There are only a few RCT study designs on pCND in the current literature, limiting its inclusion in the meta-analysis. Secondly, subgroup analysis was not done comparing unilateral and bilateral pCND since it was combined in some studies or not specified. Third, the follow-up period is also variable between the studies, which may also affect the reporting of recurrence in the cohorts. Fourth, there is a considerable difference in the number of patients for the pCND+TT group and TT alone group for some studies which may also lead to measurement bias. Thus, the authors recommend the inclusion of high-quality RCTs when feasible to further determine the impact of pCND on patient outcomes.

Although therapeutic CND is an important adjunct to total thyroidectomy for the treatment of PTC, the benefit of prophylactic CND remains to be established. Furthermore, it is also important to take into account the risk of morbidity related to the procedure. Similar to the trend seen in most studies, there is a significant increase in the risk for permanent hypoparathyroidism but not for vocal cord paralysis. Locoregional recurrence has been shown to be lower in the pCND group. The results of this meta-analysis show that the benefit of performing pCND may outweigh the risk but the role of prophylactic CND in the treatment of patients with PTC with clinically negative lymph nodes is still debatable in terms of overall survival. Thus, we conclude that more studies are warranted in order to establish a critical review of indications for the routine use of prophylactic CND with total thyroidectomy.

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