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# The Effect of Prophylactic Central Neck Dissection during Total Thyroidectomy on Locoregional Recurrence in Patients with Papillary Thyroid Carcinoma: An Updated Meta-Analysis

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## Abstract

**AIM:** The current systematic review was conducted to update the existing evidence regarding the association between prophylactic central neck dissection (pCND) and locoregional recurrence (LRR) in patients undergoing total thyroidectomy (TT).

**METHODS:** Studies were identified through systematic searches of electronic databases (PubMed, Scopus, Cochrane Library, and Clinical Trials.gov) between November and December 2022. The primary outcome was the unadjusted pooled estimate for LRR using an inverse variance – a weighted random-effects meta-analysis of odds ratios (ORs).

**RESULTS:** Twenty-two studies comparing pCND + TT and TT alone in cN0 PTC patients were analyzed. The meta-analysis included 6918 patients, 2796 cases in the combined group, and 3402 controls in the TT-alone group. The summary OR for overall LRR was not statistically significant, indicating a lack of additional benefit for pCND (OR = 0.76 95% CI [0.5–1.14], p = 0.18). Results were consistent for studies with an experimental or nonexperimental design. The rates of transient (OR = 1.81, 95% CI [1.36–2.41], p < 0.001) and permanent (OR = 2.56, 95% CI [1.72–3.8], p < 0.001) hypoparathyroidism were significantly higher in patients who underwent pCND. The rates of transient (OR = 1.71, 95% CI 1.24–2.35, p < 0.001) and permanent (OR = 2.12, 95% CI 1.29–3.45, p < 0.001) RLN nerve injury were also higher in patients who underwent pCND. Contradictory results were observed for adjuvant RAI with RCTs suggesting a lower need for postoperative RAI therapy.

**CONCLUSION:** The meta-analysis and the systematic review suggest that pCND was not associated with lower odds of LRR in patients with N0 PTC. Moreover, transient and permanent hypoparathyroidism and RLN injury were higher in patients undergoing TT + PCND. TT + pCND should not be routinely recommended except in high-risk patients due to the lack of benefit and lower safety profile than TT only.

## Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinomas and the least aggressive PTC is an epithelial tumor with follicular cell differentiation and distinctive nuclear features. The neoplasm appears as an irregular solid mass and cystic nature in rare cases. The etiology could be from radiation or genetic origin. PTC is most common in females, and the incidence of PTC has seen an upsurge in the last few decades. The prognosis was observed to be better in patients <55 years of age. Advanced technologies used in ultrasonography screening and fine-needle aspiration biopsy (FNAB) have facilitated the detection and diagnosis of PTC [1], [2].

Thyroid cancer is the most common type of endocrine tumor and is rapidly growing, with more than a 5% incidence rate per year in both males and females [3]. Besides, the incidence rate of papillary thyroid cancer (PTC) constituted the preponderance (80–85%) of these cases, with an estimated 60,000 cases yearly, and is still on growth [4]. The prognosis for treated PTC cases is excellent, with 10-year survival rates surpassing 90%. Nevertheless, locoregional recurrence (LRR) can be correlated with a lower rate of disease-free survival [5]. Previous research evaluating risk factors for locoregional recurrence in PTC reported that large tumor mass, presence of lymph node metastasis (LNM), a high number of metastatic LNs (Lymph Nodes), extrathyroid extension (ETE), older patients, multifocal cancer, and being a male are all significantly associated with locoregional recurrence and bad prognosis.

There is some degree of controversy when total thyroidectomy (TT) is combined with prophylactic central neck dissection (pCND). Numerous investigations preferred pCND due to its ability to inhibit locoregional recurrence. It also might be linked with decreasing postsurgical thyroglobulin (Tg) levels, increasing the dose of radioactive iodine (RAI) because of pathological

upstaging, and reducing the complication rate after the initial surgery. On the other hand, several studies have also investigated the potential advantages of TT combined with pCND compared with TT alone in reducing postoperative Tg levels, elevating the tumor stage, and reducing the LRR. A study reported that pCND does not help decrease short-term LRR in patients with no clinical evidence of nodal metastasis [6].

This debate is partially due to a lack of high-quality evidence confirming any reliable advantages of pCND in decreasing LRR. Given the low rates of recurrence and morbidity after thyroidectomy, novel research approximated that 5840 patients in a prospective, randomized, controlled trial would be required to have sufficient statistical power to discover a 25% reduction in the recurrence risk [7].

It is only recently that several randomized clinical trials (RCTs) investigated the effect of pCND on oncological and surgical outcomes. Thus, the current systematic review and meta-analysis were conducted to update the existing evidence regarding the effectiveness of pCND on LRR in PTC patients after TT.

## Methods

### *Development of meta-analysis protocol*

The PICOS format was used to define the research questions (Appendix 1). An initial review was performed to identify observational and experimental studies that assessed the efficacy and/or safety of pCND in PTC patients. In addition to previous systematic reviews, these studies were used to draft the keywords for systematic search to ensure the accuracy of the search process. In addition, the protocol for the current systematic review and meta-analysis was formulated based on these studies before data extraction and pooling of estimates to reduce bias.

### *Database search and Identification of trials*

The current systematic review was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA). EMBASE, PubMed, and Cochrane Library were searched for relevant studies. The keywords used for the search were: (“Papillary thyroid carcinoma” OR “PTC”) AND “thyroidectomy” AND (“lymph node dissection” OR “central neck dissection” OR “neck dissection” OR “pCND”). References of previous meta-analyses were also cross-checked against the final list of included studies [6], [8]. The author conducted the search process, and data extraction and disagreements were resolved by discussion and consulting two-independent reviewers.

### *Ethics approval*

The corresponding institutional review board approved all studies. Approval was not required for the current secondary data analysis. Informed consent was obtained from patients in all included studies.

### *Outcomes*

The primary outcome of the current meta-analysis was the inverse variance-weighed random-effects meta-analysis of odds ratios (ORs) for LRR. Secondary outcomes included the incidence of operative and postoperative complications. These were: postoperative radioiodine ablation (RAI), postoperative transient and permanent hypoparathyroidism, and operative recurrent laryngeal nerve injury (RLNI). All outcomes were recorded as counts and percentages.

### *Eligibility criteria*

The systematic review and meta-analysis were conducted according to the PRISMA guidelines. The following inclusion criteria were used: (1) Prospective or retrospective studies, (2) confirmation of PTC, (3) absence of lymph node metastasis based on preoperative imaging or inspection during surgery, (4) two mutually exclusive study arms (pCND + TT and TT alone), (5) each arm should include more than ten patients, (6) availability of data regarding LRR, (7) clear follow-up time. Only studies published between 2015 and 2022 were included in the current systematic review to provide updated evidence regarding the effect of pCND on the specified primary and secondary outcomes.

Studies that met any of the following criteria were excluded: (1) Therapeutic central neck dissection, (2) hemithyroidectomy, (3) combined central and lateral neck dissection, (4) thyroid cancers other than PTV, (5) studies not in English.

### *Data extraction*

The author and two independent reviewers screened, agreed on the included studies, and extracted the relevant data from the included studies. A standardized data sheet was used to extract the following data: The last name of the first author, publication year, country, study design (observational or experimental), tumor size, number of patients in each group (TT + pCND or TT), type of pCND (unilateral/ Bilateral), the incidence of locoregional recurrence, number of patients getting RAI ablation, site of locoregional relapse, and postoperative complications. The unadjusted estimates were extracted for the outcomes of interest.

### *Statistical methods*

The OR was used as the measure of effect size within each study. The OR and the corresponding 95% CIs were calculated from event numbers extracted from each study. The inverse-weighed random-effects model was used to pool estimates from the included studies. The primary analysis was an inverse variance random fixed-effect meta-analysis of ORs for LRR. The analysis was stratified by study design (observational vs. experimental). A treatment arm continuity correction was applied for studies with a zero cell count in one of the arms [9], [10]. This continuity correction was used to calculate individual study results with confidence limits and conduct the meta-analysis based on the inverse variance method.

### *Sensitivity analysis and publication bias*

Sensitivity (influence) analysis was performed using the leave-one-out method to investigate the source and possible causes of heterogeneity in case of moderate to substantial heterogeneity ($I^2 > 50\%$), and to test the robustness of the results. Forest plots were used to visualize the meta-analysis results. The effect size for RCTs was estimated using the per-protocol population of each trial. Funnel plots were used to assess publication bias, and Egger's test was used to test the asymmetry of funnel plots [11]. $p < 0.05$ was considered statistically significant. All analyses were performed using R v 3.6.3 [12].

## Results

### *Database search*

A total of 269 were initially retrieved using the adopted search terms (Figure 1). After excluding the duplicates, 134 full-text articles were assessed for eligibility, and further 112 studies were excluded. Thus, 22 studies were included in the qualitative and quantitative synthesis.

### *Study characteristics*

Five of the included 22 studies were RCTs. In addition, there were 13 retrospective cohorts, one prospective, and two case–control studies. The characteristics of the included studies (age, sex, mean tumor size, study design, and sample size) are shown in Table 1. The outcomes assessed in each study are also shown. In all studies, permanent hypoparathyroidism and laryngeal nerve injury (LNI) were defined based on a cutoff point of 6 months.

All the included studies were published during 2015–2021; four were in the US, nine were in Europe, seven were in Asia, and two were in Africa (Egypt). Among these 22 hospital-based studies, a total of 6198 cases were identified in this analysis, including 2796 cases in the pCND+TT group and 3402 cases in the TT-alone group. Two studies [28], [33] provided only propensity-matched data used in the current analysis, and two studies used historical controls [25], [32]. In one of the studies, all surgeries were performed by one surgeon [32]. One study classified the results by the laterality of the dissection [27]. The baseline criteria were not significantly different in any of the included RCTs. The follow-up time ranged from 6 to 113 months. The sample size in two RCTs was ~30 and ~50 in a third. The sample size in the remaining two RCTs ranged from 84 to 113, comparable to the sample size in the included nonexperimental studies.

Age and gender were comparable across the majority of the included studies. The tumor size was summarized in the majority of the studies using the mean, although two studies reported the median and percentage of patients with tumor size ranging from 1–4 cm. The mean tumor size was not reported in four studies (Table 1). There was variability in the use of postoperative RAI between studies, and one RCT used it initially in all patients [26].

### *Primary outcome*

The outcomes of the included studies are shown in Table 2. Only two studies did not report the incidence of LRR [27], [30]. Only nine studies reported the incidence of central and lateral locoregional recurrence, with zero incidences reported in four of these studies. Thus, a meta-analysis of central and lateral locoregional recurrence was not performed due to the small sample size of studies with non-zero events (n = 5).

The overall pooled estimate (Figure 2a) of unadjusted effects was not statistically significant (OR = 0.76 95% CI [0.5–1.14], p = 0.18), indicating that TT + pCND was not associated with LRR in the long term. Stratifying the analysis by study design did not affect the estimates (Figure 2a). The effect size was not statistically significant for RCTs (OR = 0.61, p = 0.28) or non-experimental studies (OR = 0.82, p = 0.4). However, substantial heterogeneity was observed between studies ($I^2$ = 67.4% and 51.6%, for experiments and non-experimental study designs, respectively).

Two outliers were identified [29], [32] based on sensitivity analysis (Appendix 2). Results did not change when these two studies were omitted (Figure 2b), although no heterogeneity was observed between the included studies after omission ($I^2 = 0$ for experimental and non-experimental study designs). The pooled OR for experimental and non-experimental study designs after the omission of outliers were 1.18 (p = 0.66) and 1.01 (p = 0.94), respectively.

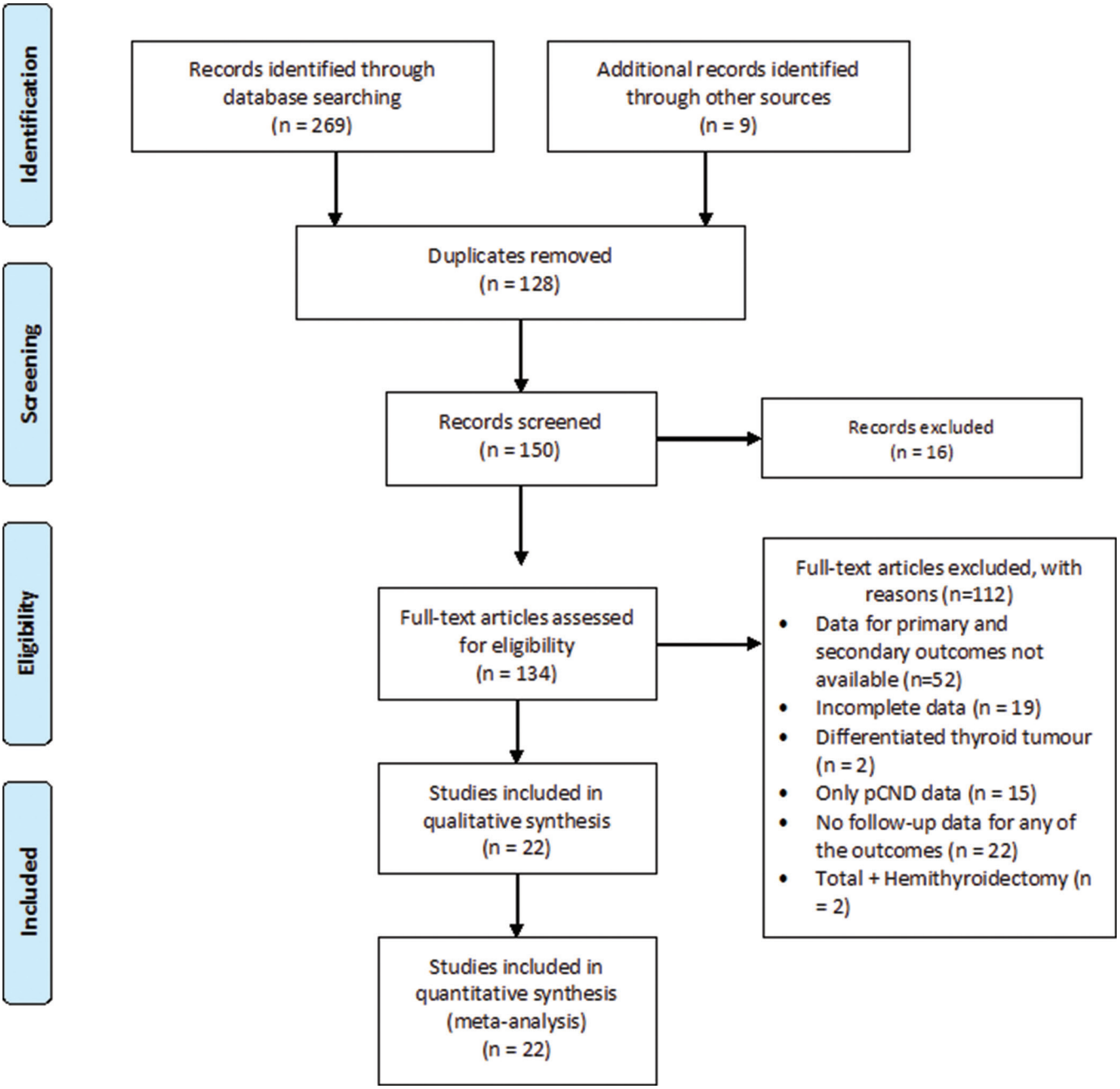


*Figure 1: PRISMA flow chart for study selection*

The Funnel plot (Appendix 3) was symmetric, and publication bias was not statistically significant when Egger's test was used (p = 0.41). No studies were added using the trim-and-fill method after excluding the two outliers (Appendix 4), and the results were robust to the leave-one-out sensitivity analysis (Appendix 2).

### *Secondary outcomes*

Fourteen studies (10 non-experimental and 4 RCTs) provided data regarding the use of RAI (Figure 3a). Stratifying the analysis by study design showed some interesting results. The pooled estimate from RCTs indicated that the use of post-operative RAI therapy was lower in patients who underwent pCND (OR = 0.44, 95% CI [0.23–0.86], p = 0.02). However, results from studies with a non-experimental design showed that the use of RAI was not significantly different between groups (OR = 1.07, 95% CI [0.64–1.78], p = 0.8). One study [32] was identified as an outlier and excluded from further analysis (Appendix 5).

After exclusion (Figure 3b), the pooled OR was statistically significant (OR = 1.34, 95% CI [1.05–1.72], p = 0.02) and indicated a higher use of RAI therapy in patients who underwent pCND, which is opposite to the observed pooled effect size in the RCTs. The results in either design were not robust to the leave-one-out sensitivity analysis. The removal of one of two of the included nine studies with non-experimental design resulted in non-statistically significant effect size

**Table 1: Characteristics of the included studies and patients**

| Author | Data | Design | Country | Total sample | TT+pCND | TT | Age C/E | Male C/E | Mean tumor size C/E | Follow-up time | Extent of dissection |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ahn *et al.* [13] | 2020 | RCT | Korea | 101 | 51 | 50 | 51.8/53.6 | 22/25.5 | 1/1.1 cm | 46.6±9.1 | Ipsilateral, bilateral |
| Lin *et al.* [14] | 2017 | Retrospective cohort | China | 167 | 105 | 62 | <45 years (53.2%/57.1%) | 19.4/25.7 | 1.17/0.97 cm | 29.9±5.2 | NA |
| De Carvalho *et al.* [15] | 2015 | Retrospective cohort | USA | 152 | 102 | 478 | 45.2/41.2 | 11.5/14.3 | 10.2/14.8 mm | 67.4/80.2 | Ipsilateral, bilateral |
| Dobrinja *et al.* [16] | 2017 | Retrospective cohort | Italy | 186 | 74 | 112 | 57/53 | 25.9/16.2 | 11/13 cm | 37/76 (median) | Ipsilateral, bilateral |
| Gambardella *et al.* [17] | 2019 | Retrospective cohort | Italy | 371 | 187 | 184 | 152/32 (65+/75+) 146/41 (65+/75+) | 25/28.3 | 17.9 mm | 6 months | Bilateral |
| Giordano *et al.* [18] | 2017 | Retrospective cohort | Italy | 610 | 405 | 205 | <45 (39.7%) | 22.10% | NA | 113 months | Ipsilateral, bilateral |
| Harera *et al.* [19] | 2020 | RCT | Egypt | 70 | 40 | 30 | <40 (66.7%/62.5%) | 23.7%/27.5% | Range (1–2.5/2–4 cm) | 60 months | Ipsilateral, bilateral |
| Harries *et al.* [20] | 2020 | Retrospective cohort | USA | 152 | 49 | 103 | <55 (65.1%/73.5%) | 38.8%/44.7% | 1–4 cm (96.7%) | 65 months | Ipsilateral, bilateral |
| Korkmaz *et al.* [21] | 2016 | Retrospective cohort | Turkey | 302 | 162 | 140 | 49.6/42.3 | 14.2%/11.1% | Median (8/10) | Median 34/35 | Ipsilateral, bilateral |
| Kwan *et al.* [22] | 2015 | Retrospective cohort | China | 105 | 54 | 51 | 50/51 | 13%/29% | NA | Median 48/59 | Ipsilateral, bilateral |
| Lee *et al.* [23] | 2015 | Prospective Cohort Study | Korea | 257 | 153 | 104 | 51.6/52.3 | 1:5.5/1:4.1 | 1.6/1.7 cm | 49.2/55.2 | Ipsilateral, bilateral |
| Said *et al.* [24] | 2016 | Retrospective cohort | USA | 864 | 34 | 830 | 46.4/40 | 14.6/29.4 | 1.9/2.7 | 7.9 years | Not defined |
| Pelizzo *et al.* [25] | 2015 | Case–control | Italy | 263 | 149 | 114 | 50/48.5 | 17.5%/16.8% | 1.5/1.5 cm | 22/15 months | Ipsilateral, bilateral |
| Sippel *et al.* [26] | 2020 | RCT | USA | 61 | 31 | 30 | 46.1/50.1 | 23%/25% | 2.45/1.91 cm | 12 months | Unilateral |
| Selberherr *et al.* [27] | 2016 | Retrospective cohort | Austria | 349 | 112 | 237 | 54/46 | 19.4%/33.9% | NA | 6 months | Ipsilateral, bilateral |
| Shuai *et al.* [28] | 2021 | Retrospective cohort | China | 429 | 352 | 77 | 46.81/46.48 | 20.8%/23.3% | 0.89/1.03 cm | 53 months | Bilateral |
| Sieda *et al.* [29] | 2020 | RCT | Egypt | 197 | 84 | 113 | 42.4/46 | 58.4%/56.6% | 14.37/16 | 24 months | Ipsilateral, bilateral |
| Simescu *et al.* [30] | 2019 | Retrospective cohort | Romania | 84 | 33 | 51 | >45 (58.82%/66.67%) | 29.41%/24.24% | NA | 60 months | Not defined |
| Viola *et al.* [31] | 2015 | RCT | Italy | 181 | 93 | 88 | 43.5/45.7 | 23.9%/26.9% | 1.6/1.6 cm | 60 months | Ipsilateral, bilateral |
| Yazici *et al.* [32] | 2020 | Case–control | Turkey | 358 | 258 | 100 | 41.2/42.5 | 27%/25.2% | 1.7/1.9 cm | 60 months | Unilateral |
| Yoo *et al.* [33] | 2019 | Retrospective cohort | Korea | 270 | 135 | 135 | 48.24/49.39 | 15.5%/14% | 8.97/8.01 | 90.1/92.19 months | Not defined |
| Zhang *et al.* [34] | 2015 | Retrospective cohort | China | 242 | 134 | 108 | 48/45 | 25%/19.4% | 0.5/0.7 cm | 66/61 months | Ipsilateral, bilateral |

C: Control (TT); E: Experimental (TT+pCND); TT: Total thyroidectomy; pCND: Prophylactic central neck dissection.

(Appendix 6). The same was observed when one of two of the included RCTs was removed (Appendix 7). No studies were added when the trim and fill methods were used to detect publication bias (Appendix 8), and Egger's test was not statistically significant (p = 0.1).

Sixteen studies provided data regarding the incidence of postoperative hypoparathyroidism (Figure 4a and b). The rates of transient (OR = 1.81, 95% CI [1.36–2.41], p < 0.001) and permanent (OR = 2.56, 95% CI [1.72–3.8], p < 0.001) hypoparathyroidism were significantly higher in patients who underwent pCND than patients who underwent only TT. Stratifying the analysis by study design did not affect the results, although the pooled estimate for transient hyperparathyroidism was not statistically

**Table 2: Outcomes of the included studies**

| Study | Year | LRR (C/L) | | | | RAI (n) | | tHPT | | pHPT | | tLNI | | pLNI | | Included outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | E | nE | C | nC | E | C | E | C | E | C | E | C | E | C | |
| Ahn *et al.* | 2020 | 0 (0/0) | 51 | 0 (0/0) | 50 | 11 | 11 | 7 | 13 | 0 | 0 | 5 | 3 | 0 | 0 | 1,4:8 |
| Lin *et al.* | 2017 | 6 | 105 | 4 | 62 | 87 | 46 | 21 | 8 | 15 | 2 | NA | NA | 4 | 0 | 4568 |
| De Carvalho *et al.* | 2015 | 4 (0/4) | 102 | 7 (2/4) | 478 | 58 | 212 | 47 | 154 | 12 | 11 | 12 | 29 | 6 | 7 | 12345678 |
| Dobrinja *et al.* | 2017 | 4 | 74 | 4 | 112 | 43 | 55 | 11 | 9 | 6 | 1 | 7 | 3 | 3 | 1 | 145678 |
| Gambardella *et al.* | 2019 | 16 (8/8) | 187 | 17 (10/7) | 184 | NA | NA | 40 | 21 | 4 | 1 | 12 | 3 | 1 | 0 | 12345678 |
| Giordano *et al.* | 2017 | 20 | 405 | 12 | 205 | NA | NA | NA | NA | 3 | 1 | NA | NA | 36 | 9 | 168 |
| Harera *et al.* | 2020 | 14 | 40 | 8 | 30 | NA | NA | 7 | 3 | NA | NA | 5 | 2 | NA | NA | 157 |
| Harries *et al.* | 2020 | 7 (3/4) | 49 | 9 (2/7) | 103 | 38 | 73 | NA | NA | NA | NA | NA | NA | NA | NA | 1234 |
| Korkmaz *et al.* | 2016 | 0 (0/0) | 162 | 0 (0/0) | 140 | 139 | 104 | 22 | 17 | 6 | 5 | NA | NA | 2 | 0 | 1234568 |
| Kwan *et al.* | 2015 | 0 (0/0) | 54 | 0 (0/0) | 51 | NA | NA | 11 | 9 | 2 | 1 | 2 | 5 | 0 | 1 | 1235678 |
| Lee *et al.* | 2015 | 5 | 153 | 4 | 104 | 112 | 74 | 56 | 21 | 5 | 2 | 5 | 2 | 2 | 0 | 145678 |
| Said *et al.* | 2016 | 1 (0/1) | 34 | 23 (9/18) | 830 | 4 | 52 | NA | NA | NA | NA | NA | NA | NA | NA | 1234 |
| Pelizzo *et al.* | 2015 | 0 | 149 | 1 | 114 | 120 | 92 | 75 | 25 | 2 | 2 | 11 | 3 | 2 | 1 | 145678 |
| Sippel *et al.* | 2020 | 0 (0/0) | 30 | 0 (0/0) | 30 | 17 | 22 | 7 | 10 | NA | NA | 3 | 4 | NA | NA | 123457 |
| Selberherr *et al.* | 2016 | NA | 112 | NA | 237 | NA | NA | 25 | 50 | 2 | 2 | 16 | 22 | 1 | 4 | 5678 |
| Shuai *et al.* | 2021 | 4 | 352 | 0 | 77 | | | | | | | | | | | 1 |
| Sieda *et al.* | 2020 | 8 | 84 | 43 | 113 | 16 | 42 | | | | | | | | | 14 |
| Simescu *et al.* | 2019 | NA | 33 | NA | 51 | NA | NA | 10 | 5 | 1 | 0 | 1 | 1 | 0 | 0 | 5678 |
| Voila | 2015 | 7 | 93 | 7 | 88 | 3 | 15 | NA | NA | 18 | 7 | 7 | 4 | NA | NA | 1467 |
| Yazici *et al.* | 2020 | 7 | 258 | 19 | 100 | 146 | 91 | 69 | 10 | 3 | 2 | 16 | 5 | 1 | 1 | 145678 |
| Yoo *et al.* | 2019 | 4 | 135 | 2 | 135 | 110 | 119 | 75 | 58 | 5 | 3 | 1 | 4 | 0 | 0 | 145678 |
| Zhang *et al.* | 2015 | 3 (1/3) | 134 | 9 (7/5) | 108 | | | 40 | 10 | 2 | 0 | 2 | 1 | 1 | 1 | 1235678 |

nE: Sample size for the pCND + TT group; nC: Sample size for the TT group; E: Event in the pCND + TT group; C: Event in the TT group. 1: Locoregional recurrence (overall); 2: recurrence (central compartment); 3: recurrence (lateral compartment); 4: RAI; 5: tHPT; 6: pHPT; 7: tLNI; 8: pLNI. Numbers between parentheses represent the incidence of central and lateral locoregional recurrence, respectively. RAI: Radioiodine ablation; tHPT: Transient hypoparathyroidism; pHPT: Permanent hypoparathyroidism; tLNI: Transient laryngeal nerve injury; pLNI: Permanent laryngeal nerve injury; NA: Not applicable.

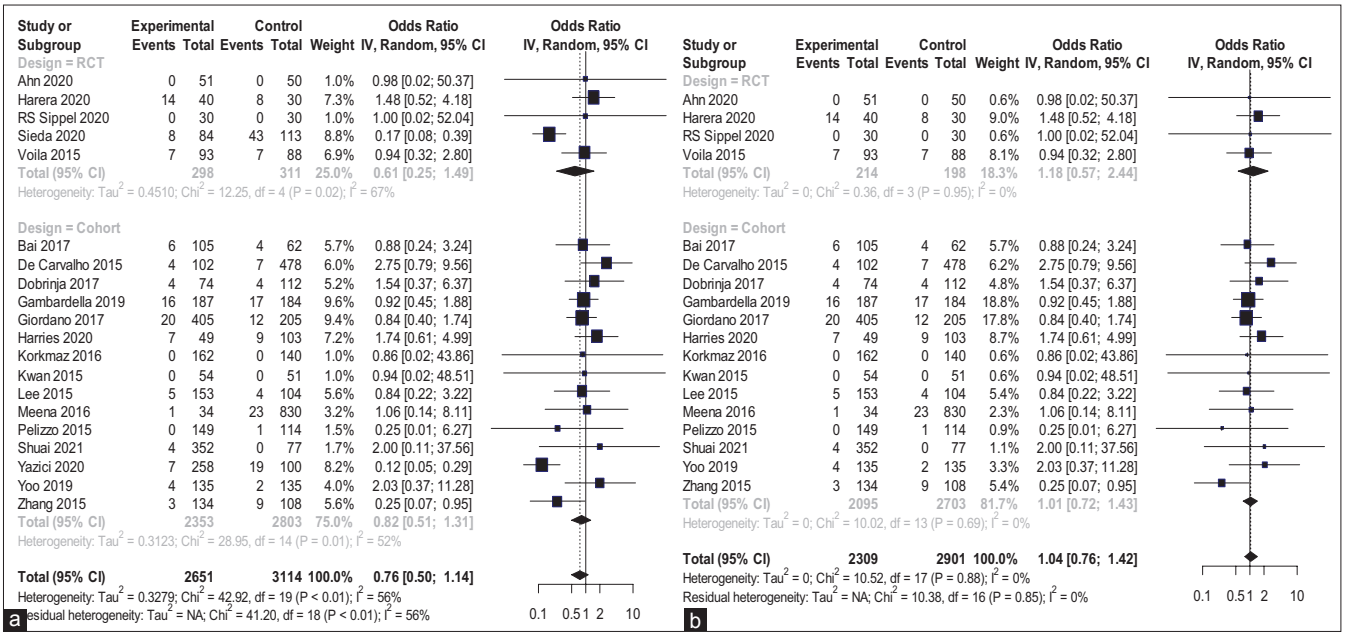


*Figure 2: Pooled estimates (OR) for LRR (a) all studies included (b) outliers excluded*

significant (OR = 0.71, 95% CI [0.32–1.57], p = 0.4). No outliers were detected, and no studies were added to either outcome when the trim and fill method was used (Appendix 9). No heterogeneity was observed between studies that assessed permanent hypothyroidism ($I^2$ = 0) and less than substantial heterogeneity was observed between experimental ($I^2$ = 23%) and non-experimental ($I^2$ = 44%) studies that assessed transient hypothyroidism. However, none of the included studies alone was identified as a possible source for the observed heterogeneity.

The summary OR for transient laryngeal nerve injury in RCTs and non-experimental studies were 1.46 (95% CI 0.69–3.06, p = 0.32) and 1.76 (95% CI 1.19–2.6, p < 0.001), with the latter suggesting a higher rate of LNI in patients who underwent pCND. Only one RCT reported the incidence of permanent LNI. (Figure 5a and b). Analysis of studies with a non-experimental study design showed that the pooled odds of permanent LNI were also higher in patients who underwent pCND (OR = 2.14, 95% CI 1.3–3.52, p < 0.001). Results were robust to the leave-one-out sensitivity analysis. Minimal heterogeneity was observed between studies for transient and permanent LNI. Funnel plots were symmetric around the calculated summary measures suggesting the absence of publication bias (Appendix 10).

## Discussion

We evaluated the LRR in 22 studies comprising the sum of 5765 patients (3114 in TT + pCND and 2651 in TT). TT+ pCND group exhibited 110 (4.1%) events of locoregional recurrence, and TT group patients showed 169 (5.4%) events of LRR. These results support the

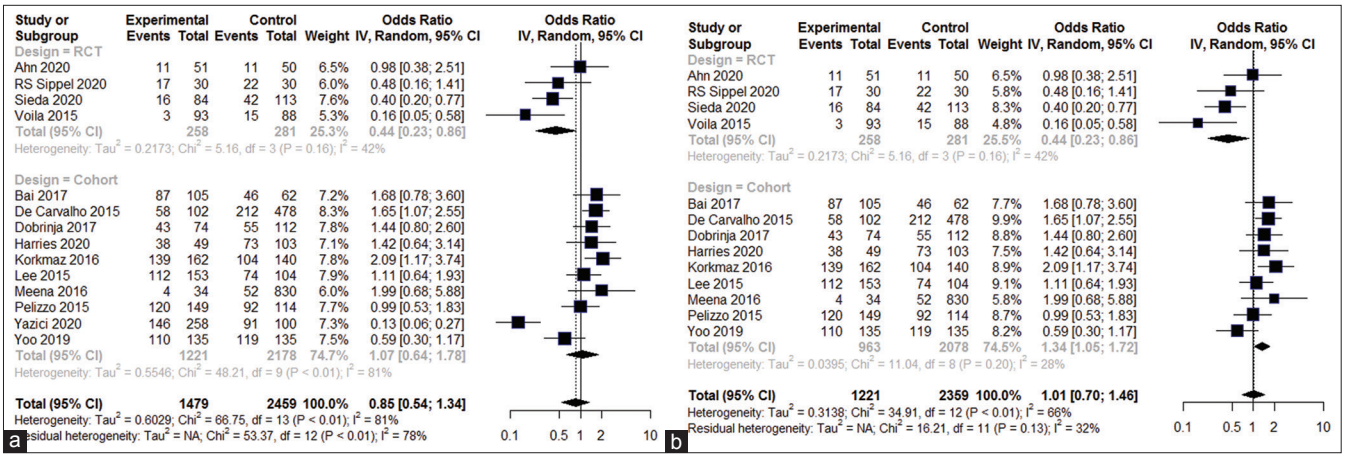


*Figure 3: Pooled OR for postoperative use of RAI. (a) All studies. (b) One outlier excluded OR > 1 indicates higher incidence in the TT + pCND group*

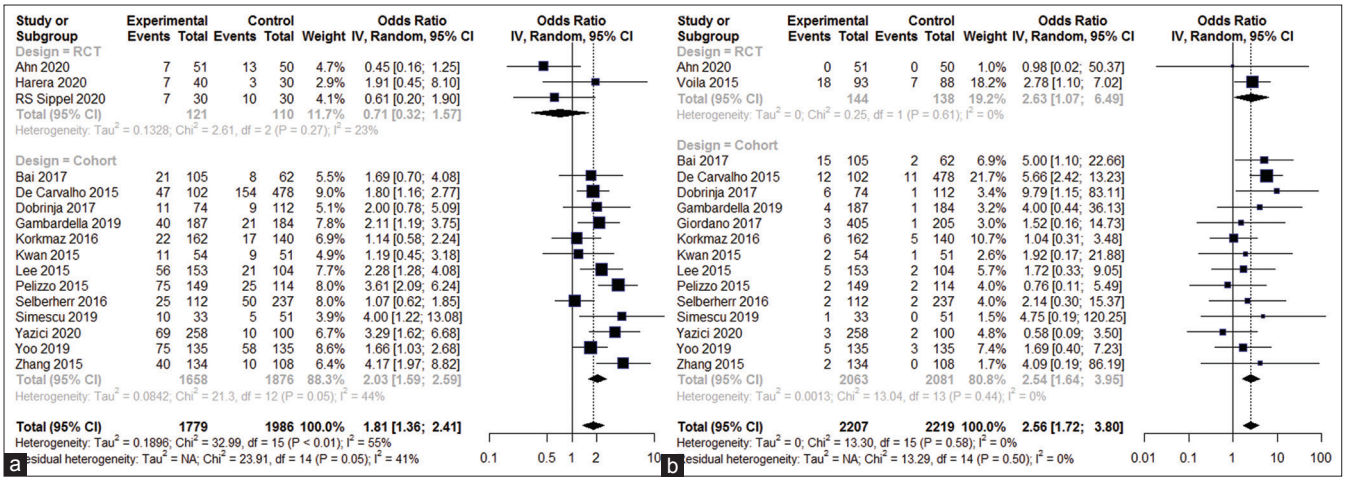


*Figure 4: Pooled OR for postoperative (a) transient and (b) permanent hypoparathyroidism OR >1 indicates higher incidence in the TT + pCND group*

low rate of LRR after TT, irrespective of pCND. The meta-analysis outcomes suggest that the rates of LRR were not significantly different between patients who underwent TT alone or those who underwent TT + pCND. The results were similar irrespective of the study design.

The current meta-analysis supports the accumulating evidence regarding the lack of efficacy of pCND in PTC patients with no preoperative lymph node metastasis (N0). Moreover, the current meta-analysis included the summary estimate from five RCTs (OR = 0.61, 95% CI [0.25–1.49]). Four of the included RCTs did not show a beneficial effect for pCND, and only one showed a favorable effect for TT + pCND. However, the recurrence rate was higher compared to what was reported in the literature [29]. The summary OR from studies with a non-experimental design showed a similar result with a summary OR of 1.01 (95% CI 0.72–1.43).

Two outliers were identified in the current meta-analysis [29], [32]. These studies had an unexpectedly higher recurrence rate in the control group (19% and 38%, respectively), although an event rate of 10% is expected at seven years [29], [32]. In the current meta-analysis, the pooled estimate (%) for the incidence of LRR in the TT and TT + pCND groups was 3% (after excluding these outliers), which is much lower than the observed % in the two studies. Furthermore, one of these two studies was a case–control study with one endocrine surgeon performing all the operations in the case group [32]. However, it must be noted that three of the included RCTs recruited 50 patients or less per arm, and two of them had a follow-up of 12 and 24 months, respectively. Thus, these two studies may have been underpowered to detect a statistically significant difference in locoregional recurrence rate.

The controversial topic in the treatment of papillary thyroid malignancy is the administration of pCND. The beneficial pCND is recommended for patients with cN1 PTC [35], [36]. However, many authors have suggested that TT should be considered the operation of choice in the treatment of low-risk clinically node-negative DTC patients with cancers larger than 10 mm in diameter. Furthermore, there is agreement on routine central lymph node dissection indications in high-risk patients, defined as male patients over the age of 45, T > 3 cm, and BRAF positive [37], [38], [39]. Previous meta-analyses have reported the advantages of TT + pCND compared to the TT group in terms of a decrease in the

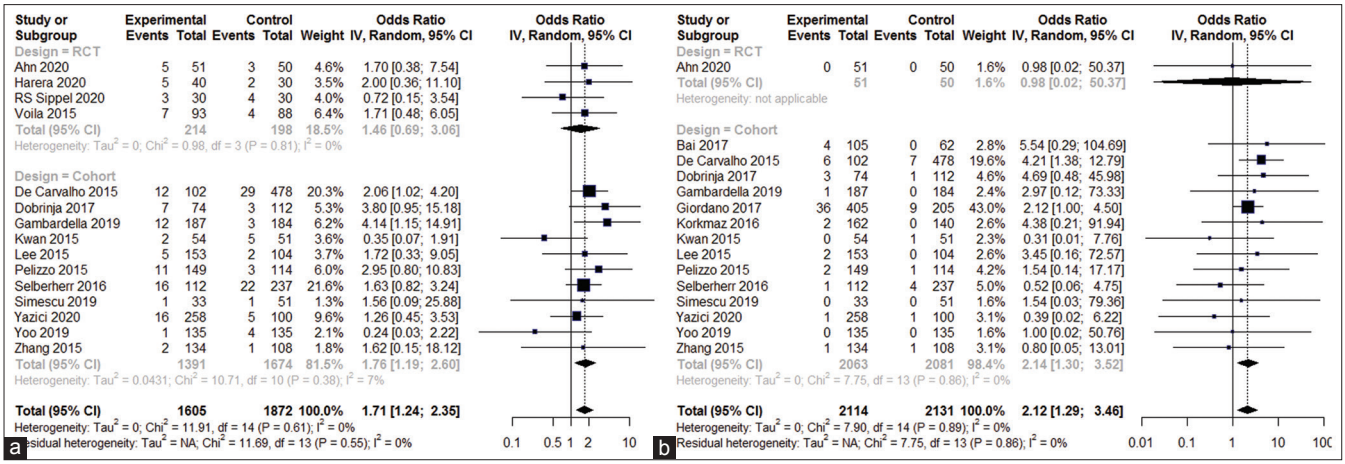


*Figure 5: Pooled OR for postoperative (a) transient (b) permanent laryngeal nerve injury OR > 1 indicates a higher incidence in the TT + pCND group*

postoperative Tg, an increase in the tumor stage, and decreasing the LRR. However, it is still unclear whether prolonged TT helps diminish the LRR. The possible advantage of reducing postoperative RAI therapy must be weighed against postoperative complications such as hypoparathyroidism and laryngeal nerve injury in patients undergoing pCND.

According to the ATA guidelines published in 2015 [40], less than 2% and 8% of low-risk and intermediate-risk patients, respectively, had structural disease recurrence after 5–10 years following thyroid surgery without RAI ablation therapy. Since the majority of the data included in the current analysis were published after 2015, it is expected that the clinical outcomes associated with recurrence would be superior to those observed in previous reports, which may reduce the benefit of pCND. In the current meta-analysis, fourteen studies reported the use of postoperative RAI. Moreover, all but one of the included trials recruited patients after 2015 [31].

The meta-analysis outcomes indicated that TT+pCND has no additional benefit over only TT, which contradicts the results of past meta-analyses. Zetoune and his colleagues reported in their meta-analysis that pCND does not greatly decrease LRR. In contrast, another meta-analysis conducted by Lang *et al.* showed that pCND could result in a 35% reduction in the risk of LRR [7], [41]. Previous studies reported a positive association between pCND and the higher risk of post-surgery complications, including transient and permanent hypoparathyroidism and unintentional recurrent laryngeal nerve injury [42]. Although several other meta-analyses showed similar results regarding the beneficial effect of pCND, most of the primary studies included in these meta-analyses were identical [8], [43]. Thus, they can be considered replicates rather than complementary studies.

There are also other possible explanations for the contradictory results. The change in guidelines after 2015 may be a possible explanation. However, there are other possible explanations. Our meta-analysis only included a more homogenous population (patients with only PTC), while previous meta-analyses included patients with PTC in addition to other types of differentiated thyroid tumors. Our analysis only included papers published after 2015 to take into account the ATA 2015 guidelines. Previous analyses may have also been influenced by the large sample size of some individual studies without reporting important measures such as publication bias and sensitivity analysis to ensure the robustness of the results. Our meta-analysis is also the first to include RCTs. We also used the OR to pool the analysis results, which is more appropriate for case-control studies. Even if such a beneficial effect existed, the absolute risk reduction would be equivalent to ~1% based on both groups' observed event rates. Thus, the benefit of pCND must be weighed against the possible postoperative complications.

The non-significant results for RCTs may also be attributed to the small number of RCTs included. The direction of the effect was similar for transient and permanent complications and LRR. The small number of events and relatively shorter follow-up time may have contributed to the wide confidence intervals and, consequently, the non-statistically significant summary measures. Regarding postoperative complications, our results align with two meta-analyses published in 2017, both of which showed that the incidence of LNI and hypoparathyroidism were higher in patients who underwent pCND [6], [8].

### *Limitations*

Another limitation of the current meta-analysis is the lack of statistical power for many individual trials. Another limitation is the lack of events for LRR in many trials, which results in wide CI, which can bias the final estimate for LRR. We also used the unadjusted estimates rather than the adjusted estimates for consistency due to the lack of a standardized protocol for obtaining the adjusted estimates across studies. Thus, demographic characteristics were not balanced between the two cohorts, which could impact the frequency of recurrence. Only one of the included studies used propensity matching for the primary outcome of LRR. However, we used the pooled data for all patients.

Nonetheless, many of the included cohort studies and RCTs were sufficient and still showed a lack of benefit for PTC + pCND. Analysis showed that a sample size of 5840 patients is required for a randomized controlled trial to achieve at least 80% statistical power to detect a 25% reduction in the recurrence risks at 7 years, assuming a recurrence risk of 10% [7]. Unfortunately, none of the included studies reached such sample size or follow-up time.

The data regarding LNR and CNR was also unavailable in all of the studies, and the separate results for bilateral and ipsilateral pCND. The follow-up period was also variable across studies. Hence, a subsequent period would be an important factor in analyzing LRR and recognizing actual recurrence and chronic illness.

Moreover, the recurrences were not regularly characterized in the examinations. Those distinctions in monitoring likewise affected the meaning of recurrence and observing the exact time of relapse. The majority of the included studies were retrospective, with the technique being left to the surgeon.

## Conclusion

The meta-analysis and the systematic review suggest that pCND was not associated with lower odds

of LRR in patients with PTC. On the contrary, results showed that tHPT, pHPT, and recurrent laryngeal nerve injury were higher in patients undergoing TT + PCND. Sufficiently powered multicenter controlled trials are needed to provide conclusive evidence regarding the efficacy and safety of pCND in PTC patients. TT + pCND should not be routinely recommended except in high-risk patients due to the lack of benefit and lower safety profile than TT only. However, the current evidence is limited, and we need more evidence from multicenter, prospective, randomized, controlled clinical trials to clarify further the true role of PCND in PTC patients with cN0.

## Ethics Approval

The corresponding institutional review board approved all studies. Approval was not required for the current secondary data analysis. Informed consent was obtained from patients in all included studies.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Supplementary Data

## Appendix 1: PICOS format

- P: Patients undergoing total thyroidectomy for non-metastatic N0-N1 papillary thyroid tumor
- I: Prophylactic unilateral or bilateral central neck dissection
- C: Patients undergoing only total thyroidectomy
- O: Locoregional recurrence, the need for radioiodine ablation, hypoparathyroidism (transient or permanent), laryngeal nerve injury (transient or permanent).

## Appendix 2

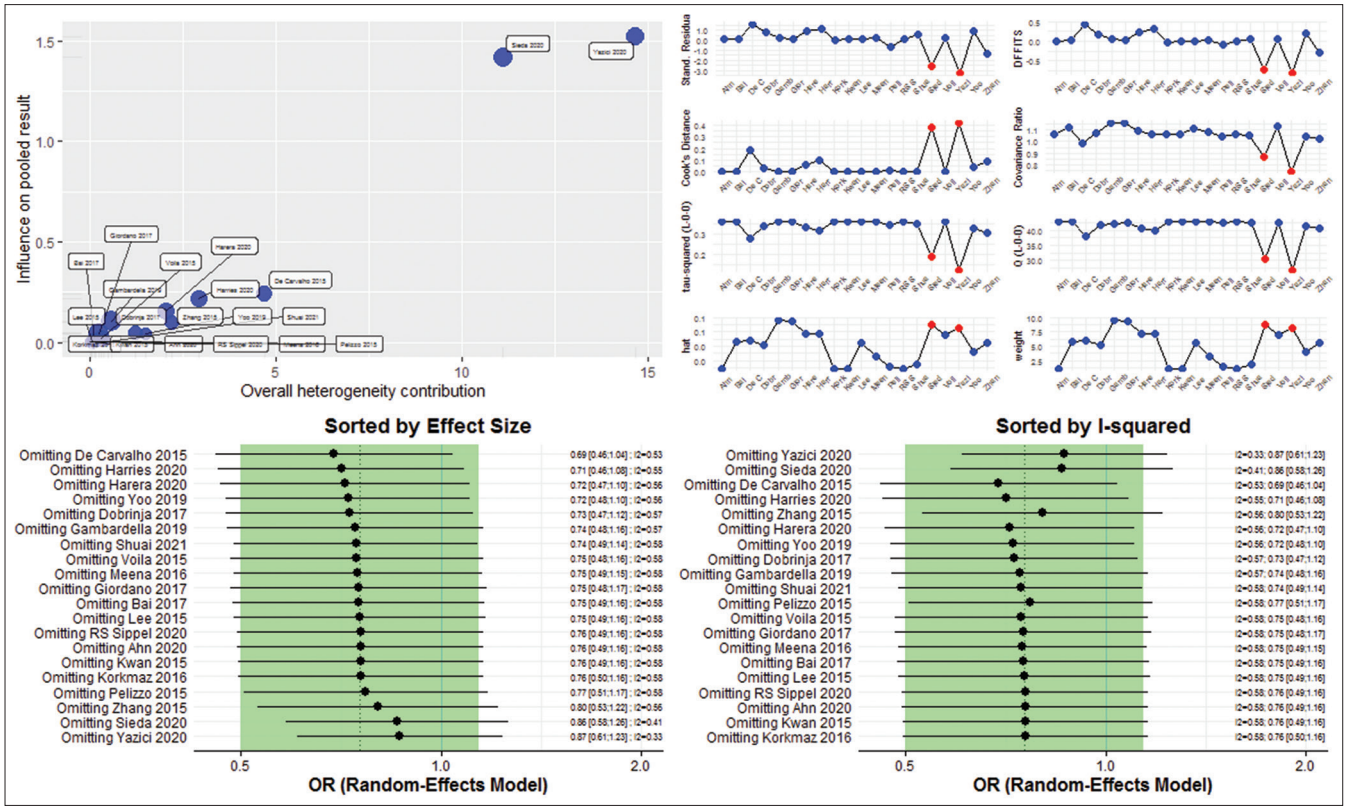


*Figure S1: Sensitivity analysis for locoregional recurrence*

# Appendix 3

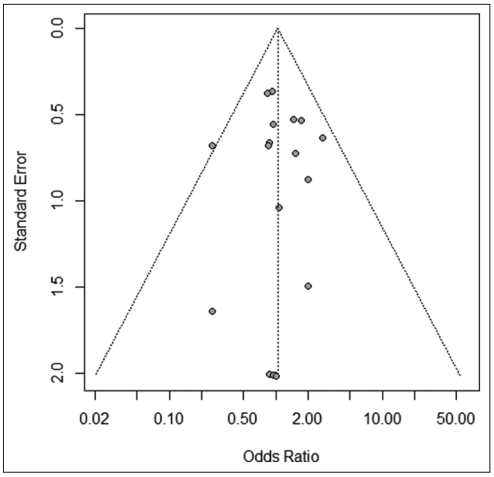


*Figure S2: Funnel plot for locoregional recurrence*

# Appendix 4

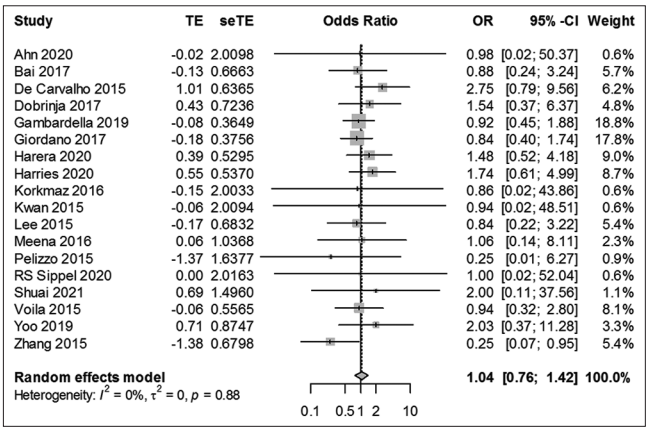


*Figure S3: Pooled OR for the association between pCND and LRR after using the trim and fill method. The trim and Fill method was used after excluding outliers*

# Appendix 5

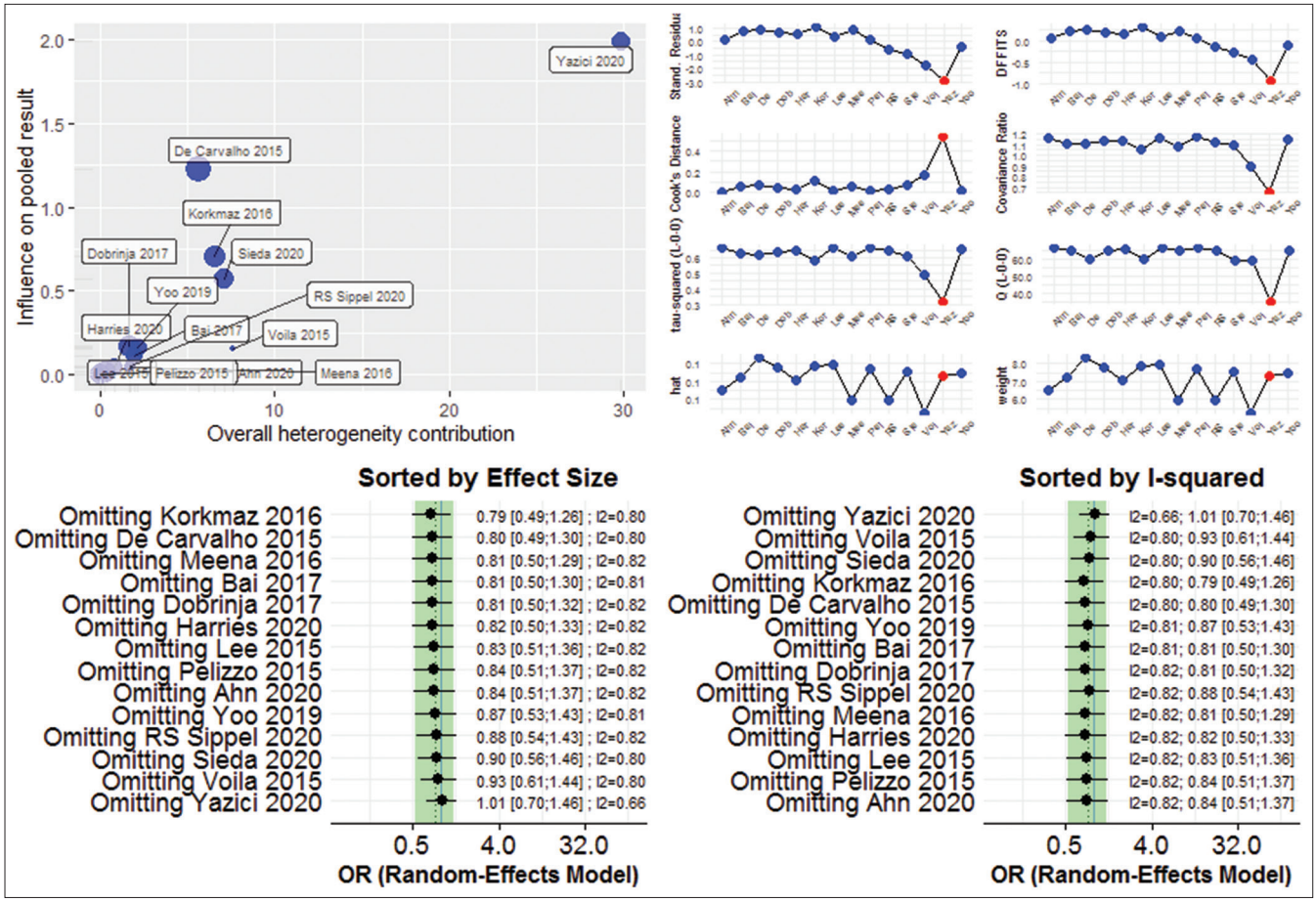


*Figure S4: Sensitivity analysis for the use of RAI in all studies*

# Appendix 6

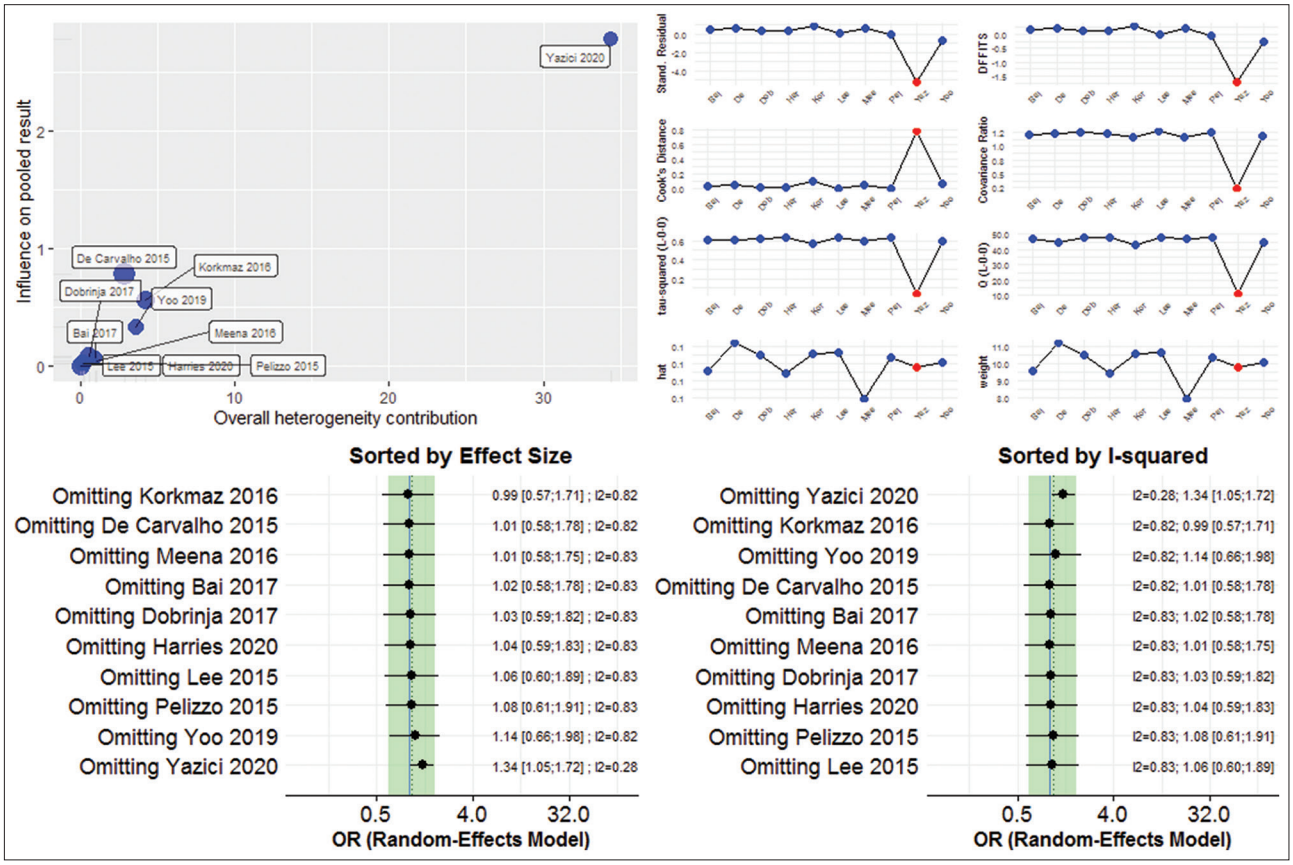


*Figure S5: Sensitivity analysis for the use of RAI in studies with a non-experimental design*

# Appendix 7

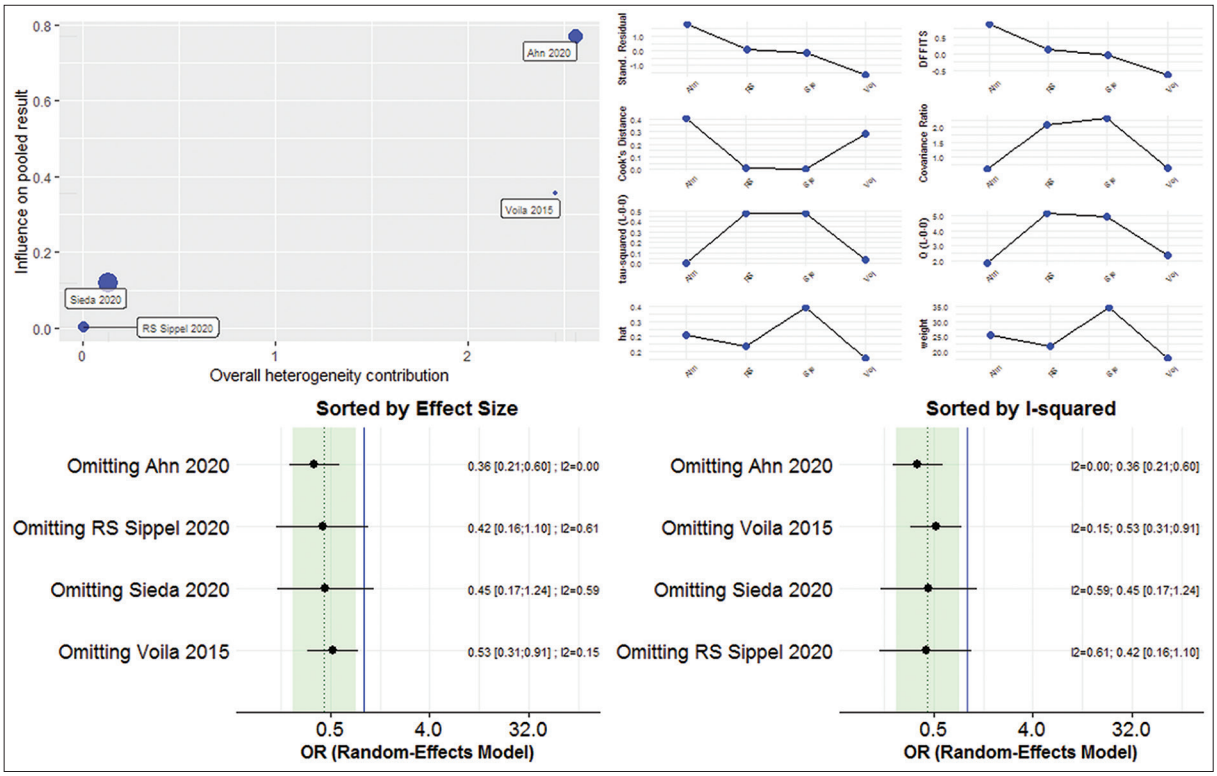


*Figure S6: Sensitivity analysis for the use of RAI in studies with an experimental design*

## Appendix 8

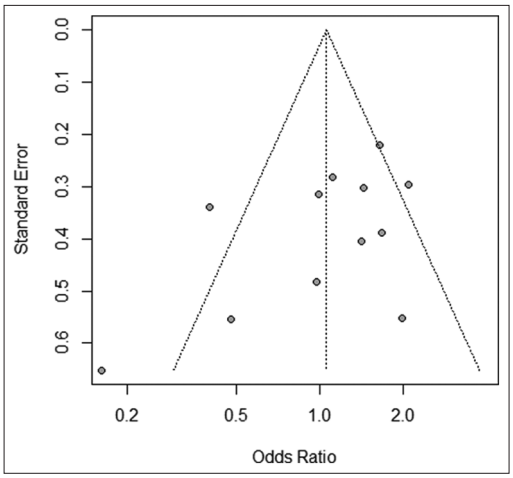


*Figure S7: Funnel plot for post-operative use of RAI therapy*

## Appendix 9

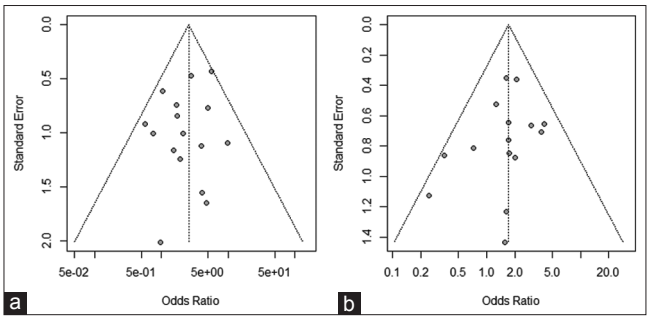


*Figure S8: Funnel plot for (a) transient and (b) permanent hypoparathyroidism*

## Appendix 10

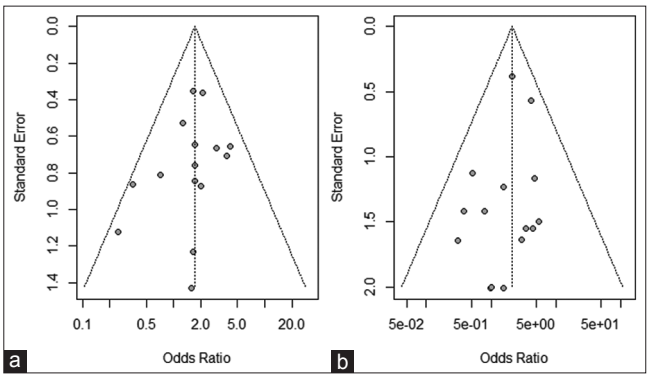


*Figure S9: Funnel plot for (a) transient and (b) permanent laryngeal nerve injury*