Original Article

A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy

Brief title: Prophylactic CND did not significantly lower LRR

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ABSTRACT

Background:

Prophylactic central neck dissection (pCND) at the time of total thyroidectomy (TT) remains controversial in clinically node- negative (cN0) papillary thyroid carcinoma (PTC). Despite occult central lymph node metastases being common, it is unclear if removing these metastases initially would reduce future locoregional recurrence (LRR). This systematic review and meta-analysis aimed at comparing the short-term LRR between patients who underwent TT+pCND and TT alone.

Methods:

A systematic review of the literature was performed to identify studies comparing LRR between patients with PTC who underwent TT+pCND (group A) and TT alone (group B). Inclusion criteria were: patients had to have cN0, each comparative group contained > 10 patients, the number of LRR and mean follow-up duration had to be available. The pooled incidence rate ratio (IRR) was used for calculating the LRR rate between the two groups. Other parameters evaluated included postoperative radioiodine (RAI) ablation, surgically-related complications and overall morbidity. Meta-analysis was performed using a fixed-effects model.

Results:

Fourteen studies matched the selection criteria. Of the 3331 patients, 1592 (47.8%) belonged to group A while 1739 (52.2%) to group B. Relative to group B, group A was significantly more likely to have postoperative RAI ablation (71.7% vs. 53.1%;OR=2.60; 95%CI=2.12 – 3.18), temporary hypocalcemia (26.0% vs. 10.8%;OR=2.56; 95%CI=2.04 – 3.21) and overall morbidity (33.2% vs. 17.7%;OR=2.12; 95%=1.75 – 2.57). When temporary hypocalcemia was excluded, overall morbidity became similar between the two groups (7.3% vs. 6.8%; OR=1.07;95%CI=0.78 – 1.47). Group A had significantly lower risk of LRR than group B (4.7% vs. 8.6%;IRR=0.65; 95%CI=0.48 – 0.86)

Conclusions:

Group A was more likely to have postoperative RAI ablation, temporary hypocalcemia and overall morbidity than B. Temporary hypocalcemia was the major surgical morbidity in pCND and when excluded, the overall morbidity appeared similar between the two groups. Although our meta-analysis would suggest that those who undergo TT+pCND may have a 35% reduction in risk of LRR than those who undergo TT alone in the short term (<5 years), it remains unclear how much of this risk reduction is related to increased use of RAI ablation and potential selection bias in some of the studies examined.

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid carcinoma with its age-adjusted incidence doubled in the last 25 years (1). Despite its good prognosis, locoregional recurrence (LRR) is common (2). With recognition of the step-wise progression of lymph node metastasis (LNM) from the central (level VI) to lateral compartment (levels II-V), some surgeons have advocated routine prophylactic central neck dissection (pCND) at the time of total thyroidectomy for PTC (3). Although there is general agreement that formal lymph node dissection should be performed in the setting of imageable, biopsy-proven or palpable nodal disease (cN1), it remains controversial in patients with no clinical evidence of nodal metastasis (cN0) (4). There is little evidence to suggest that patients with cN0 undergoing a total thyroidectomy (TT) and pCND (TT+pCND) would reduce risk of future LRR when compared to TT alone. Although the incidence of occult or microscopic LNM in patients with cN0 is relatively common, it is unclear whether removing these occult or microscopic LNM at the time of primary operation could prevent LRR (5,6). Analysis of short-term surrogates for recurrence (such as post-surgical thyroglobulin level) would suggest that pCND may improve short-term outcomes but this has not been fully resolved (4,7,8). Furthermore, patients undergoing pCND are at increased risk of temporary hypocalcemia (9-11).

One of the main reasons for the lack of evidence is that studies so far comparing TT+pCND and TT alone have not had the statistical power to detect a difference of LRR. A recent study estimated over 5000 patients would be required to have sufficient statistical power to demonstrate a 25% reduction in LRR with pCND in patients with cN0 (12). To our knowledge, 3 meta-analyses have compared the outcomes between TT+pCND and TT alone. Two were not strictly relevant because one included patients with benign disease while the other included patients who underwent therapeutic CND (9,10). Zetoune et al. pooled together 5 relevant studies and found similar overall LRR rate between TT+pCND and TT alone (2.02% vs. 3.92%;OR=1.05;95%CI=0.44 – 3.91) (11). However, this study did not account for the difference in follow-up duration between the two groups. With an increasing number of new publications on this controversial subject in recent years, we conducted a systematic review and meta-analysis to compare the risk of LRR between TT+pCND and TT alone by reviewing the current literature.

METHODS

This systematic review and meta-analysis was conducted in accordance with the PRISMA statement (13).

Search strategy

Studies comparing the rate of LRR between patients who underwent TT+pCND and TT alone were retrieved from the Scopus, Medline (PubMed) and Cochrane Library electronic databases on 30^{th} January 2013. We used the following free text search terms in "All fields"

#1: 'central neck dissection' OR 'level VI neck dissection' OR 'neck dissection'

#2: 'papillary thyroid carcinoma'

#3: #1 AND #2

There was no language restriction or methodological filters. The bibliographies of three previous meta-analyses were searched for other additional relevant references (9-11).

Study selection

All titles identified by the search strategy were independently screened by three authors (BHL, SHN, KPW). Search results were compared, and disagreements were resolved by consensus. Abstracts of potentially relevant titles were then reviewed for eligibility and full-length articles were selected for closer examination if there was a specific description on central neck dissection in patients with papillary thyroid carcinoma. The criteria for eligibility were: 1. any prospective or retrospective studies on patients with papillary thyroid carcinoma only; studies which analyzed differentiated thyroid carcinoma were considered if results of PTC were separately reported; 2. studies with two arms comparing LRR between TT+pCND and TT alone; 3. each study arm had to have > 10 patients; 4. patients in either arm had to be cN0 by preoperative imaging and intraoperative examination; patients with cN1 or distant metastasis (M1) were not included; 5. The number of LRR and the mean follow-up (in months) in each study arm had to be available. The reason for obtaining the mean follow-up period was because in order to work out the pooled incidence rate ratio (IRR) for TT+pCND and TT alone groups, we had to have first calculate the number of person-years in each respective arm. Studies which specifically reported the number of LRR and follow-up period in TT+pCND and TT alone as subgroups were included. Patients who underwent hemithyroidectomy with pCND or underwent simultaneous pCND and prophylactic lateral neck dissection were excluded. For studies which only provided the number of LRR without the mean follow-up duration or provided only the median and not the mean follow-up duration, the corresponding author of those studies was individually contacted for further information. Multiple reports of the same dataset were assessed and the most updated report of a study was included.

Data extraction

All data were extracted onto a standardized form. The primary data extracted from each article included: type or design of study, first authorship, country of origin, year of publication, patient demographics, preoperative nodal assessment, method of selection for pCND, tumor characteristics, number of patients who underwent TT+pCND or TT alone, extent of pCND (unilateral vs. bilateral), number of normal and metastatic central LNs harvested, mean follow-up period, radioiodine (RAI) ablation given or not, number of LRR, operating time, volume of blood loss and any surgically-related morbidities. LRR was defined as a recurrence occurring in the thyroid bed, central and / or lateral compartments. A patient found to have distant recurrence only (i.e. without concomitant LRR) was not counted as a LRR while a patient with concomitant LRR and distant recurrence was counted as a LRR. The percentage of recurrent laryngeal nerve (RLN) injury was calculated based on the number of patients. The overall morbidity rate was calculated by dividing the total number of patients who suffered ≥ 1 perioperative morbidity over the total number of patients. If a patient suffered from ≥ 2 morbidities, it was counted as one.

Statistical analysis

All the individual outcomes were integrated with the meta-analysis software Review Manager Software 5.0 (Cochrane Collaborative, Oxford, England). LRR was assessed by IRR according to person-year of follow up, and odds ratios (OR) were examined for the other surgical outcomes. All results were aggregated and analyzed using a fixed-effects model. A subgroup analysis of overall morbidity was performed excluding temporary postoperative hypocalcemia. Publication bias was estimated by Begg's rank correlation test and Egger's regression test (14,15). The meta-analyses in this study were conducted using R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria) and the metafor package (16).

RESULTS

Figure 1 shows the flowchart of studies retrieved and excluded. Of the 1822 titles initially identified from the database search, 41 full-length articles were assessed for inclusion, of which 27 were excluded and 14 studies were determined to be eligible and were included in this systematic review (7,17-29). Table 1 lists these 27 articles and the reason for their exclusion. No additional study was found from our search of the three bibliographies in previous meta-analyses (9-11). One study (8) was excluded as it analyzed a subset of study subjects that were later recruited in a multi-center cohort study (25).

Baseline characteristics

Table 2 shows a comparison of the baseline characteristics between the 14 eligible studies. There was no randomized trial. Thirteen studies were retrospective while one was prospective. Of the 3331 patients included, 1592 (47.8%) had TT + pCND (group A) while 1739 (52.2%) had TT only (group B). In terms of preoperative nodal assessment, ultrasonography (USG) was used as the standard imaging modality in all studies but only 2 studies specifically mentioned both bilateral central and lateral neck compartments were examined (25,27).

In terms of selection for pCND, 7 studies were based on individual surgeon's preference (7,18,22,24,25,27,28) while 4 studies did not specify their method of selection (17,19,23,26). Three studies used historical controls (TT alone) for comparison (20,21,29). Only 11 of 14 studies statistically compared age, gender ratio, tumor size, extrathyroidal extension and tumor multifocality between the two groups (7,17,18,21-26,28,29). Of these, 2 studies found age to be significantly older in group B (21,25) and 3 studies found tumor size to be significantly different (7,21,23). Two studies found tumor size to be significantly larger in group A (7,21) while one study found tumor size to be significantly smaller in group A (23). Three of 9 studies found the rate of extrathyroidal extension to be significantly higher in group A (7,22,24) and 2 of 9 studies found the rate of tumor multifocality to be significantly higher in group A (22,26). Bilateral pCND was performed in 8 studies (17,18,22-24,26,28,29) while the other 6 studies performed either unilateral or a combination of unilateral and bilateral pCND (7,19,20,21,25,27). Among the 8 studies reporting bilateral pCND,(17,18,22-24,26,28,29) the mean number of central lymph nodes harvested ranged between 5.6 to 9.6 while the one study reporting unilateral pCND harvested a median of 5 (7). The incidence of central LNM in group A ranged from 23.5% to

82.4% while in group B, it ranged from 0.9% to 9.7% with 9 of 14 studies did not report the incidence of central LNM in group B.

Surgical outcomes

Table 3 shows a comparison of outcomes between the two groups. Only 9 of the 14 studies reported whether RAI ablation was given after surgery (7,18,21-24,26,27,29). Their dose ranged from 2.78 to 5.55 GBq. One study empirically gave the same dose of RAI, irrespective of the extent of LNM (7). The mean frequency of postoperative RAI ablation in group A and B were 746/1041 (71.7%) and 498/937 (53.1%). Group A was significantly more likely to receive RAI ablation than group B (OR=2.60; 95%CI=2.12 – 3.18). This was expected because of the higher incidence of central LNM (or N1a) in group A leading to tumor group upstaging in patients aged > 45 years old (28). Only 1 of 14 studies compared operating time between the two groups and found group B to have a significantly shorter operating time than group A (28).

Figure 2 shows the forest plot for temporary hypocalcemia. Of the 14 studies, 11 studies compared temporary postoperative hypocalcemia between the two groups while 10 studies compared permanent postoperative hypocalcemia in the two groups. In 8 studies, permanent hypocalcemia was defined as persistent hypocalcemia and/or need for calcium supplements > 6 months (7,20,23-27,28) while two studies defined it as hypocalcemia > 12 months (18,29). If one assumed all studies utilized a similar definition for temporary and permanent hypocalcemia, the overall temporary hypocalcaemia rate in group A was significantly higher than that in B (336/1294 (26.0%) and 144/1330 (10.8%) respectively; OR=2.56, 95%CI= 2.04 – 3.21) while the overall permanent hypocalcaemia was also similar between the group A and B (25/1254 (2.0%) and 15/1257 (1.2%), respectively; OR=1.74, 95%CI= 0.87 – 3.50).

Similar to hypocalcemia, the definition for temporary and permanent RLN injury varied between studies. Routine perioperative DL was performed in 5 studies (7,25,26,28,29) and persistent impairment in vocal cord function > 6-month was defined as permanent RLN injury in 7 studies (19,23-27). The cumulative temporary RLN palsy was comparable between group A and B (42/1294 (3.2%) and 41/1330 (3.1%) respectively) (OR=1.02; 95%CI= 0.64 – 1.64). The cumulative permanent RLN palsy was also comparable between the group A and B (14/1197 (1.2%) and 21/1240 (1.7%), respectively) (OR=0.75; 95%CI= 0.37 – 1.55).

The rate of hematoma was reported in 8 studies. The cumulative hematoma rate was comparable between group A and B (8/842 (1.0%) and 7/975 (0.9%), respectively) (OR=1.33; 95%CI= 0.53 – 3.35). The wound infection / seroma rate was also similar between group A and B (3/842 (0.4%) and 7/975 (0.9%), respectively) (OR=0.78; 95%CI=0.28 – 2.07). Figure 3 shows the forest plot for overall morbidity. The overall morbidity rate ranged between 14.3% to 53.8% in group A while in group B, it ranged between 11.0% to 40.7%. The overall morbidity after thyroid surgery in group A was significantly higher than group B (430/1294 (33.2%) vs. 235/1330 (17.7%); OR=2.12, 95%CI=1.75 – 2.57). However, after excluding temporary hypocalcemia, the overall morbidity in group A was not significantly different from group B (94/1294 (7.3%) vs. 90/1330 (6.8%); OR=1.07; 95%CI=0.78 – 1.47). Figure 4 shows the forest plot for overall morbidity after excluding temporary hypocalcemia. The potential publication bias did not appear significant, as confirmed by the Begg analysis (Kendall's tau = -0.1636, p=0.5423) and the Egger regression test (z= -0.8921, p=0.4167).

LRR

Table 4 compares the LRR rate between the two groups. One study was excluded in the IRR calculation because the mean duration of follow-up was not available (19). Figure 5 shows the forest plot for LRR. The pooled mean follow-up in group A and B were 45.2 and 50.8 months, respectively while the pooled mean number of person-years in group A and B were 598.9 and 662.3, respectively. Group A had significantly lower LRR than group B (75/1592 (4.7%) vs. 149/1739 (8.6%); IRR=0.65; 95%CI=0.48 – 0.86). The potential publication bias was not significant, as confirmed by Begg analysis (Kendall's tau = -0.1677, *p*=0.4268) and the Egger regression test (z= 0.0984, *p*=0.9216).

DISCUSSION

To our knowledge, this is to date one the largest meta-analyses evaluating the impact of pCND on LRR in patients with clinically-nodal negative PTC or cN0. With significantly more patients being included than previous meta-analyses, our data suggested that those who undergo TT+pCND have a 35% reduction in risk of LRR than those who undergo TT alone. Although no significant publication bias was found in our meta-analysis as shown by the Begg's rank correlation test and Egger's regression test, it is worth nothing there was one particular large recent study which could have had a profound impact on the overall IRR (29). In fact, its number of person-years in group A and B were almost 2-3 times of that of the next largest study (25). Nevertheless, on the funnel plot (*data not shown*), this particular study was just on the margin of the funnel and therefore, it was not excluded from the final meta-analysis.

Despite this important positive finding, we remained cautious as there were a number of potential problems identified. Firstly, the mean follow-up period was relatively short with one study having a mean follow-up period of only 10 months. In fact, the overall mean follow-up duration for group A and B was only 45.2 and 50.8 months, respectively and so both groups had a mean follow-up of less than 5 years. Given the fact that PTC is a relatively slow-growing, indolent tumor, patients may not develop detectable LRR until many years after the initial operation. Therefore, a significant longer follow-up duration would be necessary to fully assess whether pCND could significantly reduce LRR at least in the medium to long term (12). Apart from this, 13 of 14 studies were retrospective analyses and so they were subjected to selection bias. Surgeon's preference or discretion was mentioned in 7 of 14 studies as their method of selecting pCND while 4 studies did not clearly describe their method of selection. Three studies actually used historical controls for outcome comparison (20,21,29). These selection biases were evident by the fact that only 1 of the 5 baseline characteristics (i.e. gender ratio) was consistently comparable in all studies. The other baseline characteristics such as age, tumor size, presence of extrathyroidal extension and tumor multifocality were not consistently comparable and since some of these could also potentially influence the risk of LRR, it was difficult to assess the real impact of pCND on LRR. Accounting for these factors in the multivariate analysis may help but not all these characteristics were readily available for analysis. Perhaps, the best way to resolve this would be to conduct a prospective randomized trial in the future. Although all studies did mention using USG as a method for preoperative nodal assessment, it was difficult to assess the quality and the comprehensiveness of the assessment. This issue was particularly relevant in the three studies where historical controls were analyzed because quality of imaging tended to change with time. Furthermore, it was unclear from these studies what USG criteria were used for deciding on fine needle aspiration or surgery.

In terms of other outcomes, similar to previous studies,(7,24,27) we found the rate of postoperative RAI ablation was significantly higher in group A than B (71.7% vs. 53.1%, respectively; OR=2.60; 95%CI=2.12 – 3.18). This was likely attributed to the higher incidence of central LNM in group A relative to B. However, it was interesting to note the incidence of central LNM varied widely from 23.5% to 82.4% between studies. Perhaps, this was also a reflection of the quality of preoperative USG assessment and might also have been a result of differences in the extent of the pCND and quality of the histological examination between studies (5,30,31). Also similar to previous meta-analyses,(9-11) we found the temporary hypocalcemia to be significantly higher in group A than B (26.0% vs. 10.8%, respectively; OR=2.56;95%CI=2.04 – 3.21). This would suggest that patients undergoing pCND during TT are at 2.6 times more likely to develop temporary hypocalcemia than TT alone. This was undoubtedly related to increased extent of surgical dissection leading to devascularization of parathyroid glands and / or inadvertent removal of parathyroid glands (7,17-27). However, it is worth noting that the rate of permanent hypocalcemia, temporary and permanent RLN injury, hematoma and wound infection/seroma were not dissimilar between the two groups. Also even though the overall morbidity was significantly higher in group A than B (OR=2.12;95%CI=1.75 – 2.57), when this analysis was repeated with temporary hypocalcemia excluded, the overall morbidity was similar between group A and B (OR=1.07;95%CI=0.78 – 1.47). This finding implied that the majority of morbidity arising from pCND was actually related to temporary hypocalcemia rather than other surgically-related complications.

Conclusion

The addition of pCND in TT resulted in greater likelihood of administrating postoperative RAI ablation, temporary hypocalcemia and overall morbidity. However, since temporary hypocalcemia accounted for the majority of overall morbidity in patients undergoing pCND, when temporary hypocalcemia was excluded from overall morbidity, it became similar between the two groups. Although our meta-analysis would suggest that those who undergo TT+pCND may have a 35% reduction in risk of LRR than those who undergo TT alone in the short term (<5 years), it remains unclear how much of this risk reduction is related to increased use of RAI ablation and potential selection bias in some of the studies examined.

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None

DISCLOSURE STATEMENT

All authors had nothing to disclose. No competing financial interests exist.

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Table 1. Articles which were excluded after reviewing the full-length text

First Author	Journal	Year, Country	Title	Main reason(s) for excluding from analysis
Henry (32)	Langenbeck's Archives of Surgery	1998, France	Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma.	The TT alone group had patients with benign thyroid disease.
Steinmuller (33)	Langenbeck's Archives of Surgery	1999, Germany	Complications associated with different surgical approaches to differentiated thyroid carcinoma.	Unable to separate some patients with follicular thyroid carcinoma and some who had therapeutic LND.
Wada (34)	Annals of Surgery	2003, Japan	Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection.	Unable to separate some patients who underwent therapeutic CND.
Gemsenjager (35)	Journal of the American College of Surgeons	2003, Switzerland	Lymph node surgery in papillary thyroid carcinoma.	Unable to separate patients with therapeutic LND and lobectomy.
Sywak (8)	Surgery	2006, Australia	Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer.	Data from this study were included into a later study (25).
Palestini (36)	Langenbeck's Archives of Surgery	2008, Italy	Is central neck dissection a safe procedure in the treatment of papillary thyroid cancer? Our experience.	Unable to exclude some patients with cN1. Also no follow-up and recurrence data were available.
Davidson	Laryngoscope	2008, USA	Papillary thyroid cancer: Controversies in the	Unable to separate patients who had nodal plucking, therapeutic

(37)			management of neck metastasis.	CND, LND or combination
Hu (38)	Chinese Journal of Cancer	2008, China	Application of central lymph node dissection to surgical operation for clinical stage N0 papillary thyroid carcinoma.	No follow-up or recurrence data were reported.
Sadowski (39)	Surgery	2009, USA	Routine bilateral central lymph node clearance for papillary thyroid cancer.	All patients who underwent CND had cN1.
Besic (40)	Annals of Surgical Oncology	2009, Slovenia	Extent of thyroidectomy and lymphadenectomy in 254 patients with papillary thyroid microcarcinoma: a single institution experience	Too few (i.e. <10) patients in the prophylactic arm.
Rosenbaum (41)	Archives of Otorhinolaryngology Head Neck Surgery	2009, USA	Central neck dissection for papillary thyroid cancer.	Unable to exclude patients with cN1.
Giles (42)	Surgery	2009, Turkey	The long term outcome of papillary thyroid carcinoma patients without primary central lymph node dissection: Expected improvement of routine dissection.	Only included patients who underwent TT without CND.
Bonnet (43)	Journal of Clinical and Endocrinology Metabolism	2009, France	Prophylactic lymph node dissection for papillary thyroid cancer less than 2cm: Implications for radioiodine treatment.	Prophylactic LND were included. Also no TT alone group was available for comparison.
Lim (44)	British Journal of Surgery	2009, Korea	Central lymph node metastases in unilateral papillary thyroid microcarcinoma.	No TT alone group was available for comparison.
Shen (45)	Surgery	2010, USA	Central neck lymph node dissection for papillary thyroid cancer: The reliability of surgeon judgment in predicting which patients	All patients had therapeutic CND.

			will benefit	
Chung (46)	Journal of the Korean Surgical Society	2010, Korea	Is central lymph node dissection mandatory in 2 cm or less sized papillary thyroid cancer?	All patients had lobectomy.
Shindo (47)	Archives of Otorhinolaryngology Head Neck Surgery	2010, USA	Total thyroidectomy with and without selective central compartment dissection	The TT alone group had benign thyroid disease.
Bozec (48)	European Archives of Otorhinolaryngology	2011, France	Clinical impact of cervical lymph node involvement and central neck dissection in patients with papillary thyroid carcinoma: a retrospective analysis of 368 cases	TT alone group was not available. Also some patients had therapeutic CND or LND.
Forest (49)	Annals of Surgery	2011, Australia	Central compartment dissection in thyroid papillary carcinoma	No TT alone group was available for comparison.
Mitra (50)	Journal of Laryngology & Otology	2011, UK	Effect of central compartment neck dissection on hypocalcaemia incidence after total thyroidectomy for carcinoma.	No follow-up or recurrence data reported.
Teixeira (6)	Surgery	2011, Brazil	The incidence of central neck micrometastatic disease in patients with papillary thyroid cancer staged preoperatively and intraoperatively as N0	No TT alone group for comparison.
Kutler (51)	Head and Neck	2012, USA	Routine central compartment lymph node dissection for patients with papillary thyroid carcinoma.	Unable to exclude patients who had hemithyroidectomy and CND. Also some therapeutic LND were included.
Hyun (52)	Annals of Surgical	2012, Korea	Impact of combined prophylactic unilateral central neck dissection and	All patients underwent

	Oncology		hemithyroidectomy in patients with papillary thyroid microcarcinoma	hemithyroidectomy.
Zhang (53)	Journal of Clinical Endocrinology and metabolism	2012, China	Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients	All patients underwent hemithyroidectomy.
Hartl (54)	Annals of Surgery	2012, France	Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma	All patients routinely underwent prophylactic CND and ipsilateral LND.
Yoo (55)	World Journal of Surgery	2012, USA	Level VI lymph node dissection does not decrease radioiodine uptake in patients undergoing radioiodine ablation for differentiated thyroid cancer	Unable to separate some patients who underwent therapeutic CND
Giordano (56)	Thyroid	2012, Italy	Complications of central neck dissection in patents with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature	No follow-up or recurrence data reported.

Abbreviations: TT = total thyroidectomy; cN1 = clinically involved lymph node metastases; LND = lateral neck dissection; CND = central neck dissection

Table 2. A summary and comparison of baseline characteristics between total thyroidectomy + prophylactic central neck dissection (group A) and total thyroidectomy alone (group B)

First Author (Country)	**No. of patients**		**Mean Age at operation (years)**	**Sex ratio (Male: Female)**	**Mean tumor size (mm)**	**ETE (%)**	**Multifocality (%)**	**No significant difference between A and B**	**No. of central LNs excised***		**Incidence of central LNM (%)**	
	A	**B**							**A**	**B**	**A**	**B**
Roh (Korea) (17)	40	73	A=na B=48.5	A=na B=9:64	A=na B=22	A=na B=30.1	A=na B=15.1	1,2,3,4,5	5.6	na	62.2	na
Choi (Korea) (18)	48	53	A=52 B=48	A=6:42 B=11:42	A=6.8 B=7.3	A=45.8 B=58.5	A=31.3 B=22.6	1,2,3,4,5	na	na	37.5	na
Bardet (France) (19)	36	161	na	na	na	na	na	na	na	na	23.5	na
Perrino (Italy) (20)	92	159	na	na	na	na	na	na	na	na	33 – 52	na
Costa (Italy) (21)	126	118	A=46 B=52	A=26:100 B=24:94	A=17 B=15	na	A=45.2 B=40.7	2,4,5	na	na	46.8	5.1
Zuniga (Columbia) (22)	136	130	A=42.9 B=41.5	A=10:126 B=13:117	na	A=44.8 B=27.3	A=38.2 B=13.1	1,2,3	na	na	82.4	na
Moo	45	36	A=45.7	A=10:35	A=14	A=24.4	A=55.6	1,2,4,5	8.8	1.7	33.3	na

(USA) (23)			B=49.2	B=4:32	B=20	B=36.1	B=63.9					
Hughes (USA) (24)	78	65	A=46.8 B=41.2	A=17:61 B=16:49	A=19 B=20	A=41.0 B=16.9	A=33.3 B=33.8	1,2,3,5	6.0	0.0	61.5	9.2
Popadich (Australia, USA & UK) (25)	259	347	A=44 B=48	A=52:207 B=81:266	A=23 B=22	A=27.8 B=24.2	A=48.3 B=42.7	2,3,4,5	6.8	0.35	49.0	0.9
So (Korea) (26)	119	113	A=49.2 B=49.8	A=21:98 B=16:97	A=6.6 B=6.2	A=51.3 B=51.3	A=37.8 B=23.9	1,2,3,4	na	na	37.0	na
Lang (China) (7)	82	103	A=52.0 B=50.0	A=18:64 B=22:81	A=15 B=10	A=26.8 B=14.6	A=36.6 B=27.2	1,2,5	5	0	54.9	4.9
Wang (USA) (27)	49	37	na	na	s	na	na	na	9	na	40.8	na
Raffaelli (Italy) (28)	124	62	A=42.7 B=43.2	A=24:100 B=13:49	A=12.9 B=12.1	na	A=51.6 B=46.8	1,2,3,5	9.6	1.5	35.5	9.7
Barczynski (Poland) (29)	358	282	na	A=75:283 B=60:222	na	A=13.1 B=12.8	A=37.7 B=35.1	1,2,4,5	6.7	na	na	na

Matching: 1 = age; 2 = sex ratio; 3 = tumor size; 4 = extrathyroidal extension; 5 = tumor multifocality

Abbreviations: s = significantly different (p-value < 0.05) between group A and B; ns = not significantly different between group A and B; na = not available or specified; LN = lymph node; LNM = lymph node metastasis; ETE = extrathyroidal extension

Table 3. A comparison of surgical outcomes between total thyroidectomy + prophylactic central neck dissection (group A) and total thyroidectomy alone (group B)

First author (years)	No. of postoperative RAI ablation (%)	No. of postoperative hypocalcemia (%)		No. of recurrent laryngeal nerve injury (%)		No. of hematoma formation (%)	No. of wound infection / seroma (%)	Total morbidity# (%)
		Temporary	Permanent	Temporary	Permanent			
Roh (2007) (17)	na	A=13 (32.5) B=7 (9.6)	na	A=0 (0.0) B=3 (4.1)	A=0 (0.0) B=2 (2.7)	A=1 (2.5) B=1 (1.4)	A=0 (0.0) B=0 (0.0)	A=14 (35.0) B=13 (17.8)
Choi (2008) (18)	A=48 (100) B=53 (100)	A=8 (16.7) B=6 (11.3)	A=0 (0.0) B=1 (1.9)	A=1 (2.1) B=0 (0.0)	na	A=0 (0.0) B=0 (0.0)	A=0 (0.0) B=0 (0.0)	A=9 (18.8) B=7 (13.2)
Bardet (2008) (19)	na	na	na	na	na	na	na	-
Perrino (2009) (20)	na	A=8 (8.7) B=11 (6.9)	A=3 (3.2) B=2 (1.3)	A=3 (3.3) B=5 (3.1)	A= 1 (1.1) B= 4 (2.5)	A=0 (0.0) B=0 (0.0)	A=0 (0.0) B=1 (0.6)	A=15 (16.3) B=23 (14.5)
Costa (2009) (21)	A=87 (69.0) B=62 (52.5)	na	na	na	na	na	na	-
Zuniga (2009) (22)	A=79 (58.1) B=55 (42.3)	na	na	na	na	na	na	-
Moo (2010) (23)	A=31 (68.9)	A=14 (31.1)	A=0 (0.0)	A=2 (4.4)	A=0 (0.0)	na	na	A=16 (35.6)

	B=26 (72.2)	B=2 (5.6)	B=2 (5.6)	B=0 (0.0)	B=0 (0.0)			B=4 (11.1)
Hughes (2010) (24)	A=72 (92.3) B=56 (86.2)	A=21 (26.9) B=5 (7.7)	A=2 (2.6) B= 0 (0.0)	A=0 (0.0) B=2 (3.1)	A=0 (0.0) B=na	A=1 (1.3) B=2 (3.1)	A=0 (0.0) B=1 (1.5)	A=24 (30.8) B=10 (15.4)
Popadich (2011) (25)	na	A=25 (9.7) B=14 (4.0)	A=2 (0.8) B=2 (0.6)	A=1 (0.4) B=8 (2.3)	A=1 (0.4) B=6 (1.7)	A=5 (1.9) B=3 (0.9)	A=3 (1.2) B=5 (1.4)	A=37 (14.3) B=38 (11.0)
So (2012) (26)	A=101 (84.9) B=92 (81.4)	A=49 (41.2) B=38 (33.6)	A=7 (5.9) B=2 (1.8)	A=4 (3.4) B=4 (3.5)	A=1 (0.8) B=2 (1.8)	A=1 (0.8) B=0 (0.0)	A=0 (0.0) B=0 (0.0)	A=64 (53.8)* B=46 (40.7)
Lang (2012) (7)	A=62 (75.6) B=63 (61.2)	A=15 (18.3) B=9 (8.7)	A=2 (2.4) B=1 (1.2)	A=3 (3.7) B=0 (0.0)	A=1 (1.2) B=1 (1.0)	A=0 (0.0) B=1 (1.0)	A=0 (0.0) B=0 (0.0)	A=21 (25.6) B=12 (11.7)
Wang (2012) (27)	A=35 (71.4) B=12 (32.4)	A=21 (42.9) B=4 (10.8)	A=0 (0.0) B=3 (8.3)	A=1 (2.0) B=1 (2.7)	na	na	na	A=22 (44.9) B=8 (21.6)
Raffaelli (Italy) (28)	na	A=53 (42.7) B=11 (17.7)	A=1 (0.8) B=0 (0.0)	A=1 (0.8) B=0 (0.0)	A=1 (0.8) B=0 (0.0)	A=0 (0.0) B=0 (0.0)	A=0 (0.0) B=0 (0.0)	A=56 (45.2) B=11 (17.7)
Barczynski (Poland) (29)	A=231 (64.5) B=79 (28.0)	A=109 (30.4) B=37 (13.1)	A=8 (2.2) B=2 (0.7)	A=26 (7.3) B=18 (6.4)	A=9 (2.5) B=6 (2.1)	na	na	A=152 (42.5) B=63 (22.3)

Abbreviations: na = not available or reported; RAI = radioactive iodine

#the sum of all complications; same patient with ≥2 complications was counted as one

*including 2 chyle leaks

Table 4. A comparison of locoregional recurrence rate between total thyroidectomy + prophylactic central neck dissection (group A) and total thyroidectomy alone (group B)

First author (year)	**Number of LRR (%)**		**Mean follow-up (months)**		**Number of person-years**		**Incidence rate ratio (95% confidence interval)**
	A	**B**	**A**	**B**	**A**	**B**	
Roh (2007) (17)	0 (0.0)	3 (4.1)	51	53	170	322	0.27 (0.01 – 5.25)
Choi (2008) (18)	1 (2.1)	2 (3.8)	24.4	24.4	98	108	0.55 (0.05 – 6.09)
Bardet (2008) (19)	4 (11.1)	6 (3.7)	na*	na*	-	-	-
Perrino (2009) (20)	5 (5.4)	22 (13.8)	69.2	69.2	531	917	0.39 (0.15 – 1.04)
Costa (2009) (21)	8 (6.3)	9 (7.6)	47	62	494	629	1.13 (0.44 – 2.94)
Zuniga (2009) (22)	19 (14.0)	26 (20.0)	73.44	95.52	832	1035	0.91 (0.50 – 1.64)
Moo (2010) (23)	2 (4.4)	6 (16.7)	37.2	37.2	140	112	0.27 (0.05 – 1.32)
Hughes (2010) (24)	2 (2.6)	2 (3.1)	19.1	27.5	124	149	1.20 (0.17 – 8.52)
Popadich (2011) (25)	13 (5.0)	29 (8.4)	32	50	691	1446	0.94 (0.49 – 1.81)

So (2012) (26)	2 (1.7)	4 (3.5)	44.7	45.4	443	428	0.48 (0.09 – 2.63)
Lang (2012) (7)	3 (3.7)	3 (2.9)	28.2	31.9	193	274	1.42 (0.29 – 7.04)
Wang (2012) (27)	0 (0.0)	0 (0.0)	10	10	41	31	0.76 (0.01 – 38.06)
Raffaelli (Italy) (28)	1 (0.8)	0 (0.0)	25.0	25.5	258	132	1.53 (0.06 – 37.56)
Barczynski (Poland) (29)	15 (5.8)	37 (13.1)	126.4	128.8	3771	3027	0.33 (0.18 – 0.59)
Overall	**75**	**149**	**45.2**	**50.8**	**598.9**	**662.3**	**0.65 (0.18 – 0.86)**

Abbreviations: LRR = locoregional recurrence; na = not available or reported

*only medians were provided and therefore IRR could not be calculated

LEGENDS

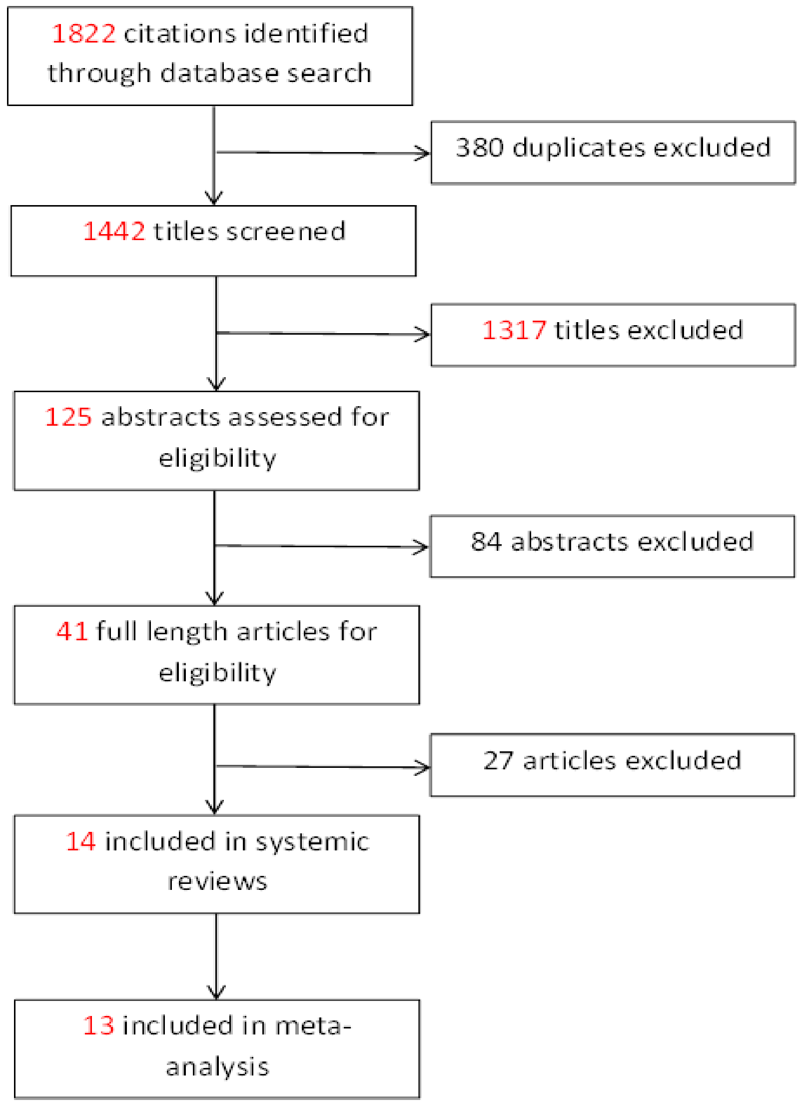

Figure 1. A flow diagram for study selection

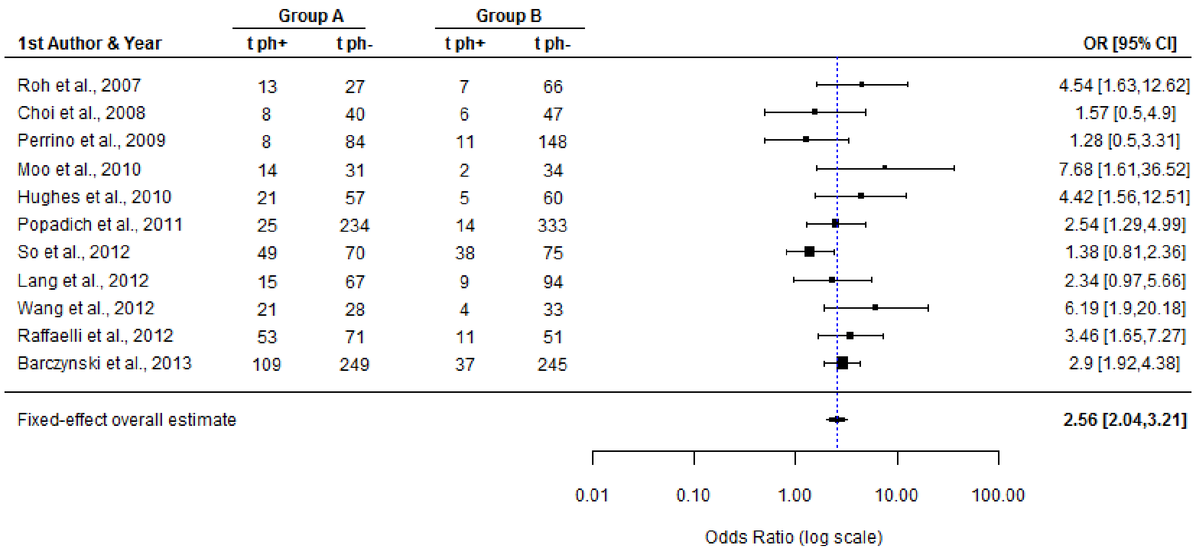

Figure 2. A forest plot for temporary hypocalcemia

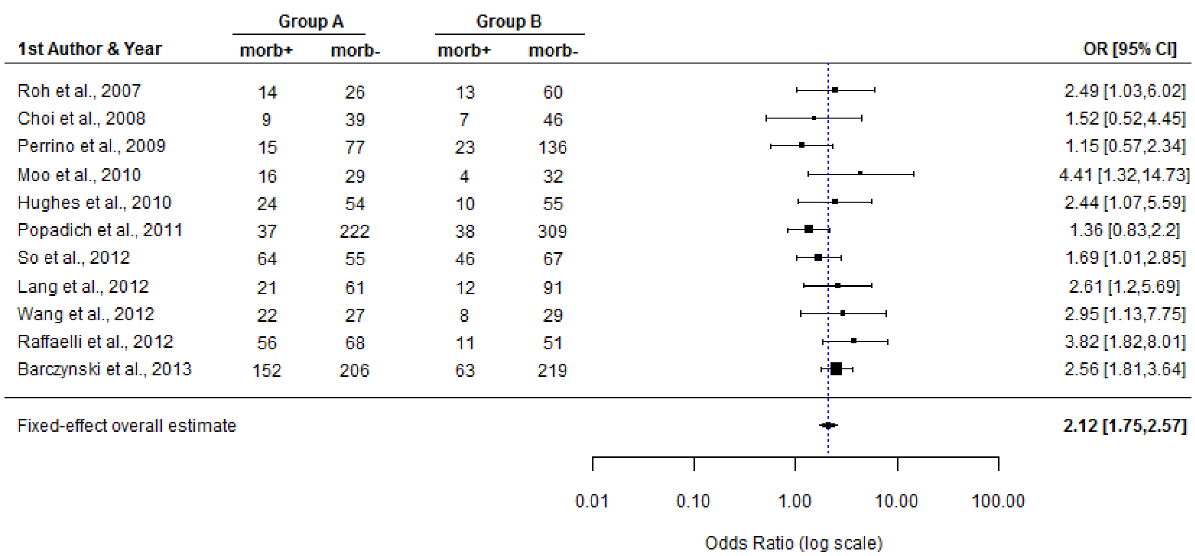

Figure 3. A forest plot for overall morbidity

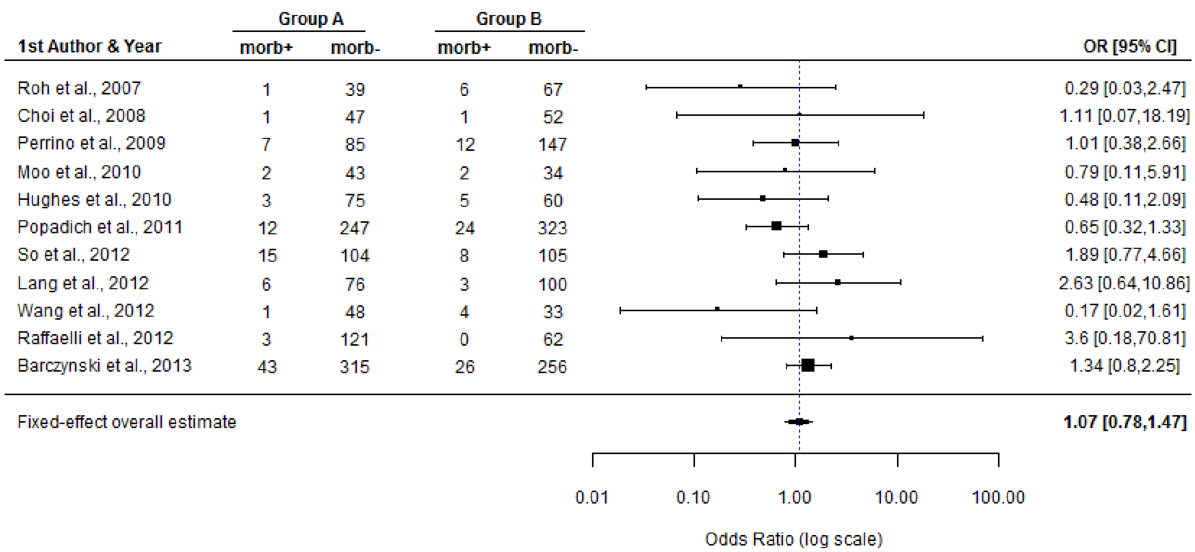

Figure 4. A forest plot for overall morbidity after excluding temporary hypocalcemia

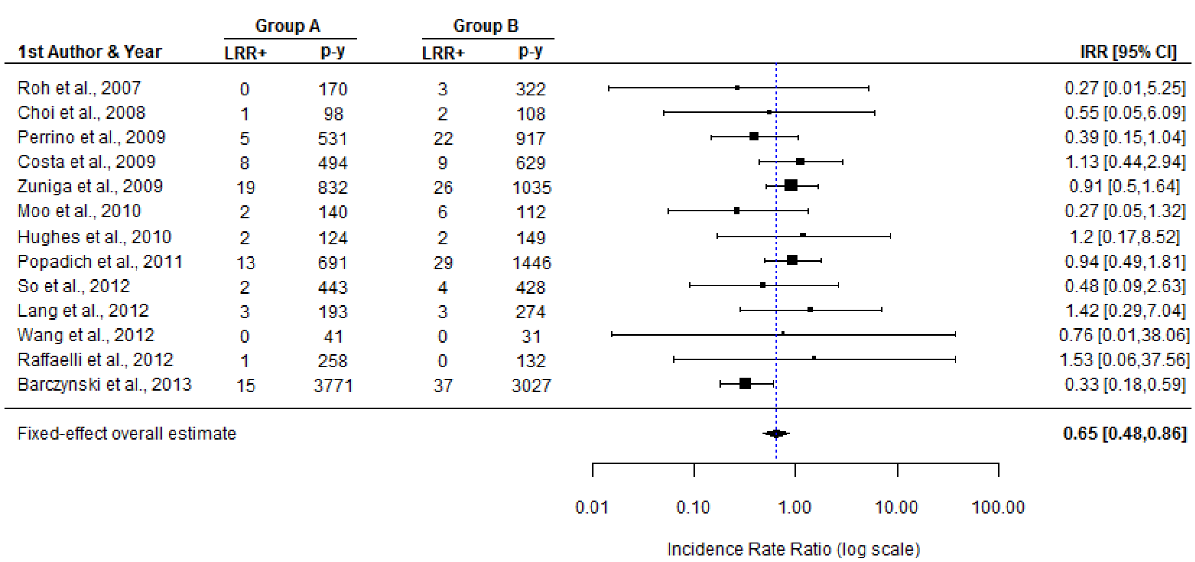

Figure 5. A forest plot for locoregional recurrence (LRR)