

1 **Original Article**

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

4 **Brief title: Prophylactic CND did not significantly lower LRR**

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1 **ABSTRACT**

2 **Background:**

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

9 **Methods:**

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

17 **Results:**

18 **Fourteen** studies matched the selection criteria. Of the **3331** patients, **1592 (47.8%)** belonged to  
19 group A while **1739 (52.2%)** to group B. Relative to group B, group A was significantly more  
20 likely to have postoperative RAI ablation (**71.7% vs. 53.1%;OR=2.60; 95%CI=2.12 – 3.18**),  
21 temporary hypocalcemia (**26.0% vs. 10.8%;OR=2.56; 95%CI=2.04 – 3.21**) and overall morbidity  
22 (**33.2% vs. 17.7%;OR=2.12; 95%=1.75 – 2.57**). When temporary hypocalcemia was excluded,  
23 overall morbidity became similar between the two groups (**7.3% vs. 6.8%;**  
24 **OR=1.07;95%CI=0.78 – 1.47**). Group A had significantly lower risk of LRR than group B (**4.7%**  
25 **vs. 8.6%;IRR=0.65; 95%CI=0.48 – 0.86**)

26 **Conclusions:**

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

8

## 1 INTRODUCTION

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

18 One of the main reasons for the lack of evidence is that studies so far comparing TT+pCND and  
19 TT alone have not had the statistical power to detect a difference of LRR. A recent study  
20 estimated over 5000 patients would be required to have sufficient statistical power to  
21 demonstrate a 25% reduction in LRR with pCND in patients with cN0 (12). To our knowledge, 3  
22 meta-analyses have compared the outcomes between TT+pCND and TT alone. Two were not  
23 strictly relevant because one included patients with benign disease while the other included  
24 patients who underwent therapeutic CND (9,10). Zetoune et al. pooled together 5 relevant studies  
25 and found similar overall LRR rate between TT+pCND and TT alone (2.02% vs.  
26 3.92%;OR=1.05;95%CI=0.44 – 3.91) (11). However, this study did not account for the  
27 difference in follow-up duration between the two groups. With an increasing number of new  
28 publications on this controversial subject **in recent years**, we conducted a systematic review and

- 1 meta-analysis to compare the risk of LRR between TT+pCND and TT alone by reviewing the
- 2 current literature.
- 3

## 1 **METHODS**

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

### 4 **Search strategy**

5 Studies comparing the rate of LRR between patients who underwent TT+pCND and TT alone  
6 were retrieved from the Scopus, Medline (PubMed) and Cochrane Library electronic databases  
7 on 30<sup>th</sup> January 2013. We used the following free text search terms in “All fields”

8 #1: ‘central neck dissection’ OR ‘level VI neck dissection’ OR ‘neck dissection’

9 #2: ‘papillary thyroid carcinoma’

10 #3: #1 AND #2

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

### 13 **Study selection**

14 All titles identified by the search strategy were independently screened by three authors (BHL,  
15 SHN, KPW). Search results were compared, and disagreements were resolved by consensus.

16 Abstracts of potentially relevant titles were then reviewed for eligibility and full-length articles  
17 were selected for closer examination if there was a specific description on central neck dissection  
18 in patients with papillary thyroid carcinoma. The criteria for eligibility were: 1. any prospective  
19 or retrospective studies on patients with papillary thyroid carcinoma only; studies which  
20 analyzed differentiated thyroid carcinoma were considered if results of PTC were separately  
21 reported; 2. studies with two arms comparing LRR between TT+pCND and TT alone; 3. each  
22 study arm had to have > 10 patients; 4. patients in either arm had to be cN0 by preoperative  
23 imaging and intraoperative examination; patients with cN1 or distant metastasis (M1) were not  
24 included; 5. The number of LRR and the mean follow-up (in months) in each study arm had to  
25 be available. The reason for obtaining the mean follow-up period was because in order to work  
26 out the pooled incidence rate ratio (IRR) for TT+pCND and TT alone groups, we had to have  
27 first calculate the number of person-years in each respective arm. Studies which specifically  
28 reported the number of LRR and follow-up period in TT+pCND and TT alone as subgroups were  
29 included. Patients who underwent hemithyroidectomy with pCND or underwent simultaneous  
30 pCND and prophylactic lateral neck dissection were excluded. For studies which only provided

1 the number of LRR without the mean follow-up duration or provided only the median and not  
2 the mean follow-up duration, the corresponding author of those studies was individually  
3 contacted for further information. Multiple reports of the same dataset were assessed and the  
4 most updated report of a study was included.

#### 5 **Data extraction**

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

#### 19 **Statistical analysis**

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

28

29

## 1 RESULTS

2 Figure 1 shows the flowchart of studies retrieved and excluded. Of the 1822 titles initially  
3 identified from the database search, 41 full-length articles were assessed for inclusion, of which  
4 27 were excluded and 14 studies were determined to be eligible and were included in this  
5 systematic review (7,17-29). Table 1 lists these 27 articles and the reason for their exclusion. No  
6 additional study was found from our search of the three bibliographies in previous meta-analyses  
7 (9-11). One study (8) was excluded as it analyzed a subset of study subjects that were later  
8 recruited in a multi-center cohort study (25).

### 9 Baseline characteristics

10 Table 2 shows a comparison of the baseline characteristics between the 14 eligible studies. There  
11 was no randomized trial. Thirteen studies were retrospective while one was prospective. Of the  
12 3331 patients included, 1592 (47.8%) had TT + pCND (group A) while 1739 (52.2%) had TT  
13 only (group B). In terms of preoperative nodal assessment, ultrasonography (USG) was used as  
14 the standard imaging modality in all studies but only 2 studies specifically mentioned both  
15 bilateral central and lateral neck compartments were examined (25,27).

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

1 82.4% while in group B, it ranged from 0.9% to 9.7% with 9 of 14 studies did not report the  
2 incidence of central LNM in group B.

### 3 **Surgical outcomes**

4 Table 3 shows a comparison of outcomes between the two groups. Only 9 of the 14 studies  
5 reported whether RAI ablation was given after surgery (7,18,21-24,26,27,29). Their dose ranged  
6 from 2.78 to 5.55 GBq. One study empirically gave the same dose of RAI, irrespective of the  
7 extent of LNM (7). The mean frequency of postoperative RAI ablation in group A and B were  
8 746/1041 (71.7%) and 498/937 (53.1%). Group A was significantly more likely to receive RAI  
9 ablation than group B (OR=2.60; 95%CI=2.12 – 3.18). This was expected because of the higher  
10 incidence of central LNM (or N1a) in group A leading to tumor group upstaging in patients aged  
11 > 45 years old (28). Only 1 of 14 studies compared operating time between the two groups and  
12 found group B to have a significantly shorter operating time than group A (28).

13 Figure 2 shows the forest plot for temporary hypocalcemia. Of the 14 studies, 11 studies  
14 compared temporary postoperative hypocalcemia between the two groups while 10 studies  
15 compared permanent postoperative hypocalcemia in the two groups. In 8 studies, permanent  
16 hypocalcemia was defined as persistent hypocalcemia and/or need for calcium supplements > 6  
17 months (7,20,23-27,28) while two studies defined it as hypocalcemia > 12 months (18,29). If one  
18 assumed all studies utilized a similar definition for temporary and permanent hypocalcemia, the  
19 overall temporary hypocalcaemia rate in group A was significantly higher than that in B  
20 (336/1294 (26.0%) and 144/1330 (10.8%) respectively; OR=2.56, 95%CI= 2.04 – 3.21) while  
21 the overall permanent hypocalcaemia was also similar between the group A and B (25/1254  
22 (2.0%) and 15/1257 (1.2%), respectively; OR=1.74, 95%CI= 0.87 – 3.50).

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

1 The rate of hematoma was reported in 8 studies. The cumulative hematoma rate was comparable  
2 between group A and B (8/842 (1.0%) and 7/975 (0.9%), respectively) (OR=1.33; 95%CI=  
3 0.53 – 3.35). The wound infection / seroma rate was also similar between group A and B (3/842  
4 (0.4%) and 7/975 (0.9%), respectively) (OR=0.78; 95%CI=0.28 – 2.07). Figure 3 shows the  
5 forest plot for overall morbidity. The overall morbidity rate ranged between 14.3% to 53.8% in  
6 group A while in group B, it ranged between 11.0% to 40.7%. The overall morbidity after  
7 thyroid surgery in group A was significantly higher than group B (430/1294 (33.2%) vs.  
8 235/1330 (17.7%); OR=2.12, 95%CI=1.75 – 2.57). However, after excluding temporary  
9 hypocalcemia, the overall morbidity in group A was not significantly different from group B  
10 (94/1294 (7.3%) vs. 90/1330 (6.8%); OR=1.07; 95%CI=0.78 – 1.47). Figure 4 shows the forest  
11 plot for overall morbidity after excluding temporary hypocalcemia. The potential publication  
12 bias did not appear significant, as confirmed by the Begg analysis (Kendall's tau = -0.1636,  
13 p=0.5423) and the Egger regression test (z= -0.8921, p=0.4167).

#### 14 **LRR**

15 Table 4 compares the LRR rate between the two groups. One study was excluded in the IRR  
16 calculation because the mean duration of follow-up was not available (19). Figure 5 shows the  
17 forest plot for LRR. The pooled mean follow-up in group A and B were 45.2 and 50.8 months,  
18 respectively while the pooled mean number of person-years in group A and B were 598.9 and  
19 662.3, respectively. Group A had significantly lower LRR than group B (75/1592 (4.7%) vs.  
20 149/1739 (8.6%); IRR=0.65; 95%CI=0.48 – 0.86). The potential publication bias was not  
21 significant, as confirmed by Begg analysis (Kendall's tau = -0.1677, p=0.4268) and the Egger  
22 regression test (z= 0.0984, p=0.9216).

23

24

## 1 DISCUSSION

2 To our knowledge, this is to date one the largest meta-analyses evaluating the impact of pCND  
3 on LRR in patients with clinically-nodal negative PTC or cN0. With significantly more patients  
4 being included than previous meta-analyses, our data suggested that those who undergo  
5 TT+pCND have a 35% reduction in risk of LRR than those who undergo TT alone. Although no  
6 significant publication bias was found in our meta-analysis as shown by the Begg's rank  
7 correlation test and Egger's regression test, it is worth noting there was one particular large  
8 recent study which could have had a profound impact on the overall IRR (29). In fact, its number  
9 of person-years in group A and B were almost 2-3 times of that of the next largest study (25).  
10 Nevertheless, on the funnel plot (*data not shown*), this particular study was just on the margin of  
11 the funnel and therefore, it was not excluded from the final meta-analysis.

12 Despite this important positive finding, we remained cautious as there were a number of  
13 potential problems identified. Firstly, the mean follow-up period was relatively short with one  
14 study having a mean follow-up period of only 10 months. In fact, the overall mean follow-up  
15 duration for group A and B was only 45.2 and 50.8 months, respectively and so both groups had  
16 a mean follow-up of less than 5 years. Given the fact that PTC is a relatively slow-growing,  
17 indolent tumor, patients may not develop detectable LRR until many years after the initial  
18 operation. Therefore, a significant longer follow-up duration would be necessary to fully assess  
19 whether pCND could significantly reduce LRR at least in the medium to long term (12). Apart  
20 from this, 13 of 14 studies were retrospective analyses and so they were subjected to selection  
21 bias. Surgeon's preference or discretion was mentioned in 7 of 14 studies as their method of  
22 selecting pCND while 4 studies did not clearly describe their method of selection. Three studies  
23 actually used historical controls for outcome comparison (20,21,29). These selection biases were  
24 evident by the fact that only 1 of the 5 baseline characteristics (i.e. gender ratio) was consistently  
25 comparable in all studies. The other baseline characteristics such as age, tumor size, presence of  
26 extrathyroidal extension and tumor multifocality were not consistently comparable and since  
27 some of these could also potentially influence the risk of LRR, it was difficult to assess the real  
28 impact of pCND on LRR. Accounting for these factors in the multivariate analysis may help but  
29 not all these characteristics were readily available for analysis. Perhaps, the best way to resolve

1 this would be to conduct a prospective randomized trial in the future. Although all studies did  
2 mention using USG as a method for preoperative nodal assessment, it was difficult to assess the  
3 quality and the comprehensiveness of the assessment. This issue was particularly relevant in the  
4 **three** studies where historical controls were analyzed because quality of imaging tended to  
5 change with time. Furthermore, it was unclear from these studies what USG criteria were used  
6 for deciding on fine needle aspiration or surgery.

7 In terms of other outcomes, similar to previous studies,(7,24,27) we found the rate of  
8 postoperative RAI ablation was significantly higher in group A than B (**71.7% vs. 53.1%**,  
9 respectively; **OR=2.60; 95%CI=2.12 – 3.18**). This was likely attributed to the higher incidence of  
10 central LNM in group A relative to B. However, it was interesting to note the incidence of  
11 central LNM varied widely from 23.5% to 82.4% between studies. Perhaps, this was also a  
12 reflection of the quality of preoperative USG assessment and might also have been a result of  
13 differences in the extent of the pCND and quality of the histological examination between  
14 studies (5,30,31). Also similar to previous meta-analyses,(9-11) we found the temporary  
15 hypocalcemia to be significantly higher in group A than B (**26.0% vs. 10.8%**, respectively;  
16 **OR=2.56;95%CI=2.04 – 3.21**). This would suggest that patients undergoing pCND during TT  
17 **are at 2.6 times** more likely to develop temporary hypocalcemia than TT alone. This was  
18 undoubtedly related to increased extent of surgical dissection leading to devascularization of  
19 parathyroid glands and / or inadvertent removal of parathyroid glands (7,17-27). However, it is  
20 worth noting that the rate of permanent hypocalcemia, temporary and permanent RLN injury,  
21 hematoma and wound infection/seroma were not dissimilar between the two groups. Also even  
22 though the overall morbidity was significantly higher in group A than B  
23 (**OR=2.12;95%CI=1.75 – 2.57**), when this analysis was repeated with temporary hypocalcemia  
24 excluded, the overall morbidity was similar between group A and B (**OR=1.07;95%CI=0.78 –**  
25 **1.47**). This finding implied that the majority of morbidity arising from pCND was actually  
26 related to temporary hypocalcemia rather than other surgically-related complications.

## 27 **Conclusion**

28 The addition of pCND in TT resulted in greater likelihood of administering postoperative RAI  
29 ablation, temporary hypocalcemia and overall morbidity. However, since temporary

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

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3 **DISCLOSURE STATEMENT**

4 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

<b>First Author</b>	<b>Journal</b>	<b>Year, Country</b>	<b>Title</b>	<b>Main reason(s) for excluding from analysis</b>
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.
Basic (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 patients 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  $\geq 2$  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)
<b>Overall</b>	<b>75</b>	<b>149</b>	<b>45.2</b>	<b>50.8</b>	<b>598.9</b>	<b>662.3</b>	<b>0.65 (0.18 – 0.86)</b>

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

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

## LEGENDS

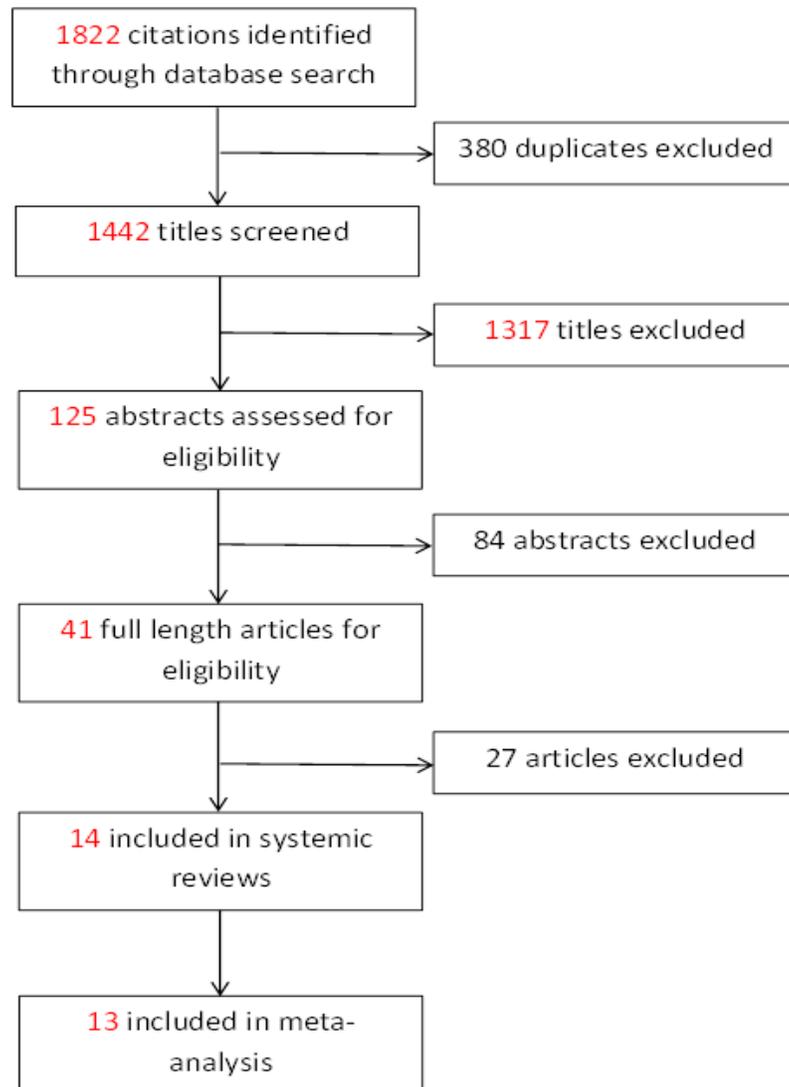


Figure 1. A flow diagram for study selection

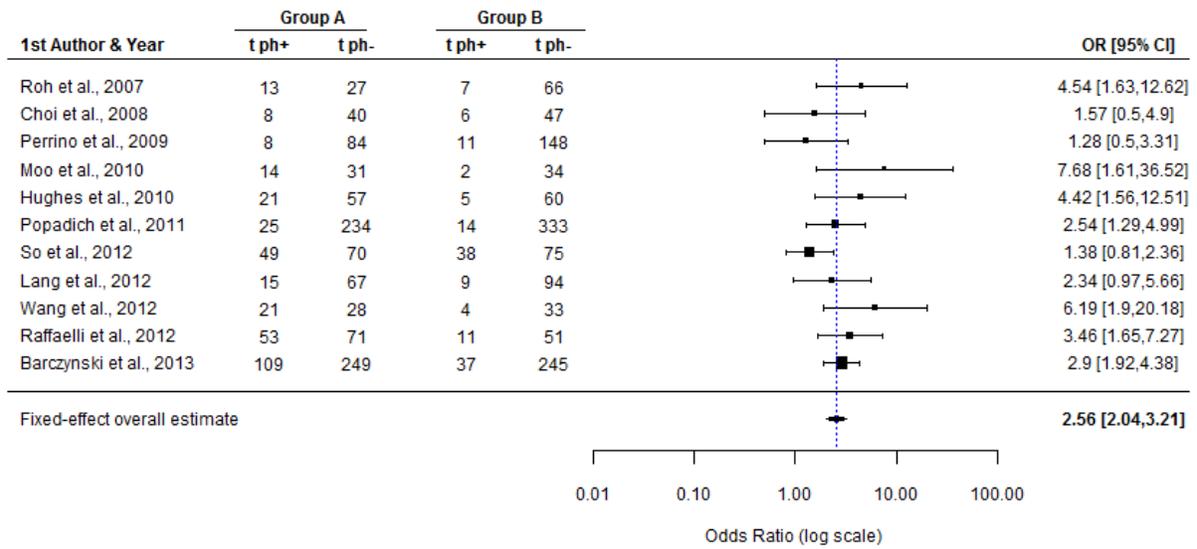


Figure 2. A forest plot for temporary hypocalcemia

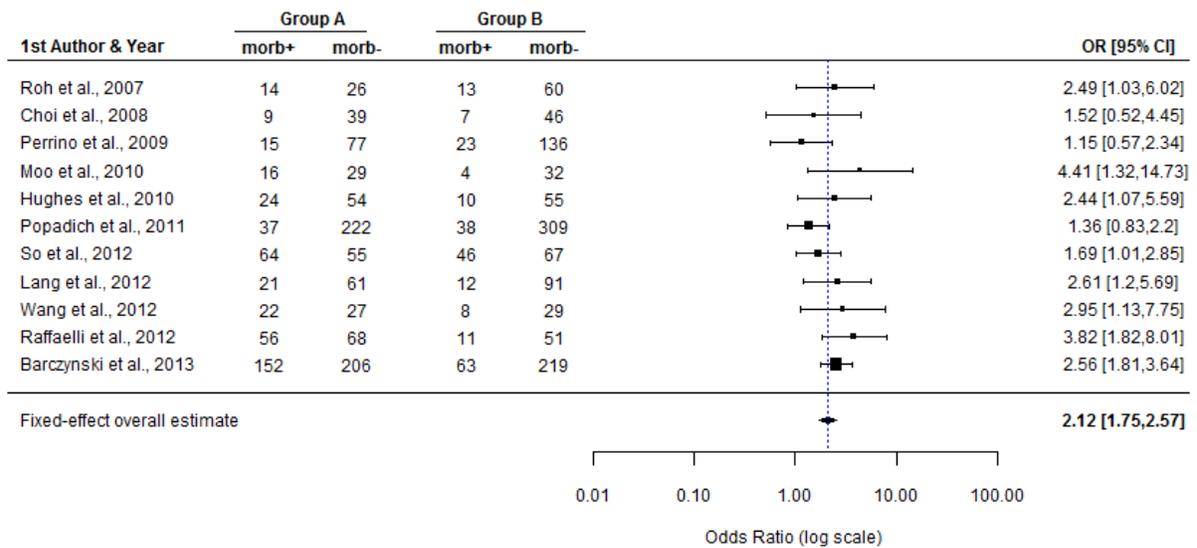


Figure 3. A forest plot for overall morbidity

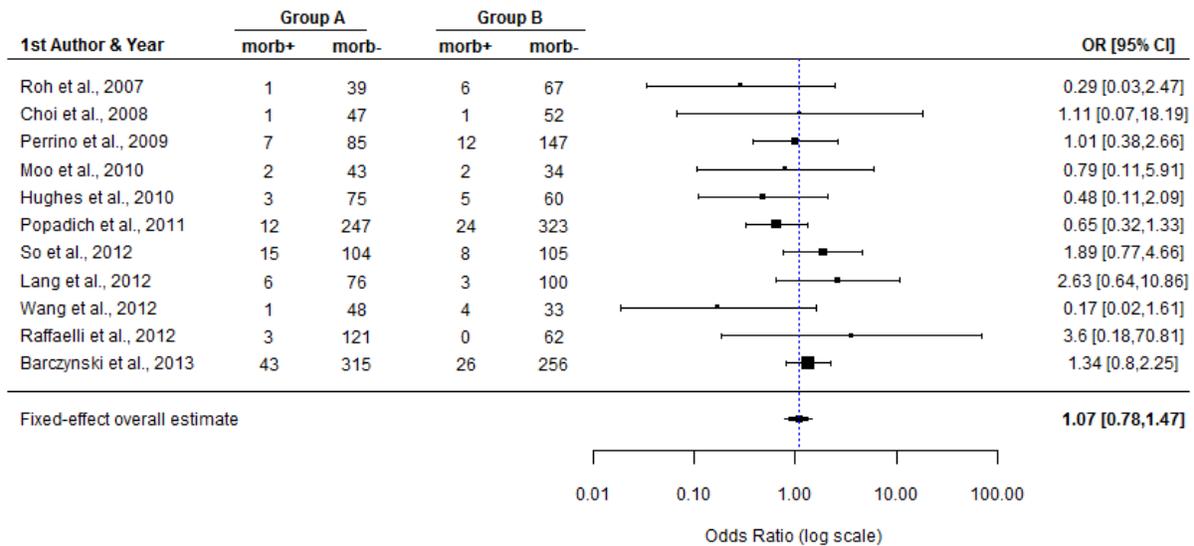


Figure 4. A forest plot for overall morbidity after excluding temporary hypocalcemia

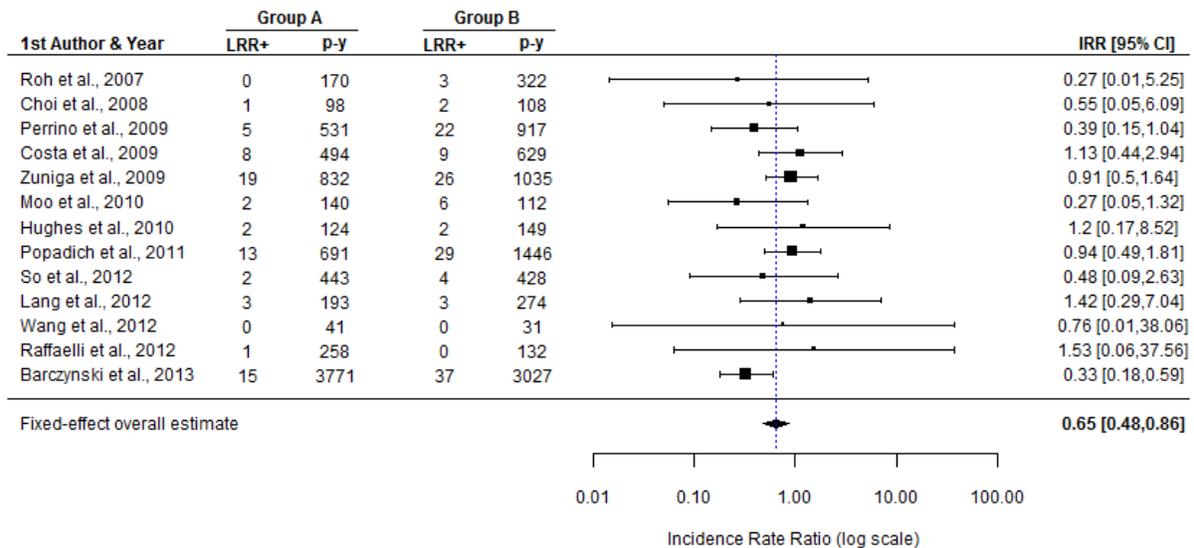


Figure 5. A forest plot for locoregional recurrence (LRR)