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Review

Local lymph node recurrence after central neck dissection in papillary thyroid cancers: A meta analysis

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ABSTRACT

Background: Prophylactic central neck dissection (CND) at the time of total thyroidectomy (TT) remains controversial in clinically node-negative (cN0) papillary thyroid carcinoma (PTC). This systematic review and meta-analysis was performed to compare the local recurrence between patients who underwent TT plus CND and those who underwent TT alone.
Methods: The publicly available literature published from January 1990 to October 2017 concerning TT plus prophylactic CND versus TT for PTC was retrieved by searching the national and international online databases. Meta-analysis was performed after the data extraction process.
Results: Twenty-five studies with comparison between TT + CND and TT alone were eligible and included in this meta-analysis. For both PTC and papillary thyroid microcarcinoma (PTMC), the overall recurrence in TT + CND group was significantly lower than that in TT alone group. The central compartment recurrence was significantly higher in TT alone group than TT + CND group (OR = 3.41, 95% Cl [2.00 ~ 5.80], $P < 0.00001$), while no significant difference of lateral compartment recurrence was observed between the two groups (OR = 1.19, 95%Cl [0.81 ~ 1.77], $P = 0.38$). We compared ipsilateral CND + TT with TT alone and found that the recurrence was not significantly different between the two groups (OR = 1.44, 95%Cl [0.74 ~ 2.81], $P = 0.28$). On the other hand, bilateral CND + TT showed significantly low recurrence (OR = 2.48, 95%Cl [1.75 ~ 3.53], $P < 0.00001$).
Conclusions: The addition of CND to TT resulted in a greater reduction in risk of local recurrence than TT alone, especially preventing central neck recurrences. Additionally, we discovered that bilateral CND in patients with PTC > 1 cm was necessary.

1. Introduction

While papillary thyroid carcinoma (PTC) accounts for more than 80% of thyroid cancer, the 10-year survival rate among PTC patients who receive appropriate treatment is > 90% [1]. The guidelines of the American Thyroid Association state that thyroid lobectomy alone is sufficient for patients with small (<1 cm diameter), low-risk, papillary carcinomas. Also the guidelines recommend total thyroidectomy (TT) is generally regarded as the procedure of choice for advanced primary tumors [2–4].

A prophylactic central neck dissection (CND) is defined as resection of level VI lymph nodes that appear normal on preoperative imaging and intraoperative exploration. Because prophylactic CND has potential benefits that can improve the accuracy of staging, decrease postoperative serum thyroglobulin levels, enable better selection of patients for radioiodine treatment, and decrease the recurrence in patients with clinically node negative (cN0) PTC, some surgeons suggested that prophylactic CND with TT should be performed in cN0 patients to reduce the locoregional recurrence, especially for tumor size > 1 cm [5,6]. Adversely, prophylactic CND carries a greater risk of postoperative complications, such as transient and permanent hypoparathyroidism and unintentional laryngeal nerve injury [7]. Due to the risk of complications following prophylactic CND, more limited (ipsilateral) CND has recently been proposed as an alternative safer treatment for patients with unilateral PTC [8–10]. An ipsilateral dissection involves the removal of central compartment lymph nodes only on the side of the primary tumor, and thus decreases the possibility of injury to the contralateral parathyroids and recurrent laryngeal nerve.

Previous meta-analyses have been performed, but have not compared the efficiency of bilateral and ipsilateral CND [7,11,12].

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Therefore, we conducted the analysis not only to cover local recurrence after central neck dissection, but also to evaluate the effectiveness of (bilateral or ipsilateral) CND +TT and TT alone for cN0 PTC with the current published literature.

2. Materials and methods

2.1. Search strategy

Two authors independently searched the literature published from January 1990 to October 2017 without language restrictions, by using PubMed, the Web of Knowledge, and the China Journal Net. The following keywords were used in all fields as search strategy:

- papillary thyroid carcinoma or papillary thyroid cancer;
- central neck dissection or central compartment neck dissection or central compartment lymph node dissection or central compartment node dissection.

The reference of previous meta-analyses was also backtracked. We cross-checked the reference list in the identified publications and independently extracted the data from each study with full text.

2.2. Study selection

The inclusion criteria of eligible studies were:

- retrospective or prospective studies;
- studies with more than 10 patients;
- patients with PTC and no lymph node metastasis according to preoperative imaging or inspection during surgery;
- studies having CND + TT group and TT alone group;
- available data about local recurrence;
- clear description in follow-up time and definitions of recurrence.

Studies were excluded as follows:

- therapeutic central neck dissection or CND combine with the lateral neck dissection were mixed in prophylactic CND + TT group or TT group;
- the full text of studies could not be accessed online or requested to authors.

2.3. Quality assessment and data extraction

The quality of retrospective and prospective studies was assessed according to the Newcastle-Ottawa Scale (NOS) [13]. This assessment of study quality was based on three parts to evaluate each case-control study or cohort study, including selection, comparability and exposure outcome condition. Studies with more than four stars would be regarded as relatively high quality studies. Correspondingly, the Jadad scoring system was used for the random clinical trials (RCTs) [14]. The scale consists of three items, such as randomization, blinding and description of the withdrawals and dropouts. Studies with a score of 3–5 were considered to be of high quality.

A standardized data form was used to extract all data we would evaluate. The information which we collected from each study includes the first authorship, the publication year, the type of study, sample size, the follow-up time, the characteristics of demographics, the number of patients in CND + TT group and TT alone group and the number of patients having LR (total, central compartment and lateral compartment).

2.4. Statistical analysis

Heterogeneity was assessed by χ^2 test and quantified with I^2 statistically. $P < 0.05$ and $I^2 > 50\%$ for heterogeneity would be considered significant difference. According to the result of heterogeneity analysis and type of studies, different method models would be chosen. A pooled odds ratio (OR) with 95% confidence interval (CI) by the random method (Mantel-Heanszel) model was used to estimate arms in studies included this review. In all the tests, a P value smaller than 0.05 was considered statistically significant. Begg's and Egger's tests [15,16] were used to estimate the publication bias. All the statistical analyses in this review were conducted using STATA software, version14.0.

3. Results

3.1. Eligible articles

The flow chart of literature filtration with reason was presented in Fig. 1. A total of 1051 publications were obtained from the initial search. Excluding the duplicates, unrelated topics, unoriginal studies, studies having no control group or TT alone group and studies combining lateral neck dissection, 37 full-text articles were assessed for eligibility. Finally, 25 studies [3,10,17–39] with comparison between TT + CND and TT alone were eligible and included in this meta-analysis.

3.2. Study characteristics and quality

The basic characteristics of included studies are showed in Table 1. Among 25 included studies, there were 22 retrospective case control studies, 2 prospective cohort studies and 1 randomized control trial (RCT). All the studies were published from 2000 to October 2017, 3 studies in the USA, 10 studies in Europe, 8 studies in Asia, 2 study in Australia, 1 study in Colombia and 1 study in Brazil. The study quality of 20 case control or cohort studies were judged on the basis of NOS and the scale distribution (0–10 stars) was from 5 to 8 stars, while the only RCT was judged by the Jadad scoring system (0-5 scores) and received 3 scores. All the included studies demonstrated a relatively high quality.

Among these 25 hospital-based studies, a total of 7052 cases were identified in this analysis, including 3413 cases in the TT + CND group and 3639 cases in the TT alone group. Recurrence of disease was determined clinically with cervical ultrasonographies or serum thyroglobulin (TG) levels.

Three [28,30,32] of the included studies set the subgroup analysis and divided the CND into ipsilateral CND and bilateral CND. The TT + CND group in four studies [21,23,29,39] was mixed with ipsilateral CND and bilateral CND. Eight studies [3,10,17,20,25,31,34,38] had a clear definition that CND was bilateral CND and defined the extent of lymph node dissection. Three studies [26,33,37] classified patients who underwent CND + TT group only received ipsilateral CND. Four [17,37–39] of 25 included studies described mean tumor size < 1 cm, while the others 16 studies included tumors more than 1 cm in size [10,18–23,25–27,29–34,36]. Besides, twenty-one studies compared extrathyroidal extension and multifocality between the two groups. The duration of follow-up ranged from 24.4 to 114 months.

3.3. Results of statistical analysis

The overall recurrence was reported in 25 studies. There was no significant heterogeneity between studies with $I^2 = 30.7\%$ and $P = 0.074$. The overall recurrence in TT + CND group was significantly lower than that in TT alone group (3.9% vs. 6.0% OR = 1.76, 95% CI [1.40 ~ 2.21], $P < 0.00001$, Fig. 2A). The publication bias confirmed

Table 1
Basic characteristics of included studies.

Author, Year	Country	No. of patients	Sex (male/female)	Mean tumor Size (mm)	Multifocality	Extrathyroidal extension	Mean age	Follow-up time (months)	Quality of score	Study design
Barczynski et al., 2012 [3]	Germany	640	CND+: 75/283 CND-: 60/222	–	234/640	83/640	52.7	TT: 128.8 TT + CND: 126.4	7/9	Retrospective
Moo et al., 2010 [10]	USA	81	CND+: 10/35 CND-: 4/32	CND+: 14.2 CND-: 20.4	48/81	24/81	CND+: 45.7 CND-: 49.2	37.2	5/9	Retrospective
Choi et al., 2008 [17]	Korea	101	CND+: 6/42 CND-: 11/42	5.84 ± 2.75	74/101	53/101	CND+: 52 CND-: 48	24.4	8/9	Retrospective
Calò et al., 2013 [18]	Italy	215	CND+: 8/38 CND-: 34/135	CND+: 16.17 CND-: 15.1	62/215	52/215	CND+: 47.15 ± 15.01 CND-: 52.3 ± 14	93	7/9	Retrospective
Calò et al., 2014 [19]	Italy	285	CND+: 12/53 CND-: 48/172	CND+: 17.27 ± 8.77 CND-: 16.13 ± 11.82	80/285	73/285	CND+: 46.36 CND-: 53.07	100	7/9	Retrospective
Conzo et al., 2014 [20]	Italy	752	CND+: 73/289 CND-: 78/312	CND+: 19 ± 16 CND-: 17 ± 11	98/752	–	CND+: 44.9 ± 9.9 CND-: 44.5 ± 10.9	114	8/9	Retrospective
Costa et al., 2009 [21]	Italy	244	CND+: 26/100 CND-: 24/94	CND+: 17 CND-: 15	105/244	85/244	–	TT: 64 TT + CND: 47	6/9	Retrospective
De Carvalho et al., 2015 [22]	Brazil	580	CND+: 87/15 CND-: 423/55	CND+: 14.8 CND-: 10.2	171/580	153/580	CND+: 41.2 CND-: 45.2	TT 67.4 TT + pCND 80.2	6/9	Retrospective
Dobrinja et al., 2017 [23]	Italy	186	CND+: 12/62 CND-: 29/83	CND+: 13 CND-: 11	–	–	CND+: 53 CND-: 57	TT 76 TT + pCND 37	6/9	Retrospective
Gemsenjäger et al., 2003 [24]	Switzerland	159	–	–	–	–	–	97.2	6/9	Retrospective
Hughes et al., 2010 [25]	USA	143	CND+: 17/61 CND-: 16/49	CND+: 19 CND-: 20	48/143	43/143	CND+: 46.8 CND-: 41.2	TT: 27.5 TT + CND: 19.1	6/9	Retrospective
Lang et al., 2012 [26]	China	185	CND+: 18/64 CND-: 22/81	CND+: 15 CND-: 10	58/185	37/185	CND+: 52 CND-: 50	TT: 27.1 TT + CND: 25.5	6/9	Retrospective
Lee et al., 2015 [27]	Korea	257	CND+: 30/123 CND-: 16/88	CND+: 17 ± 12 CND-: 16 ± 14	92/257	–	CND+: 52.3 CND-: 51.6	TT: 49.2 TT + CND: 55.2	8/9	Prospective randomized cohort
Perrino et al., 2009 [28]	Italy	251	53/198	–	48/110	–	46.5± 23.3	69.2	6/9	Retrospective
Popadich et al., 2011 [29]	Australia	606	CND+: 52/205 CND-: 81/266	CND+: 22.7 CND-: 22.3	273/606	156/606	CND+: 44 CND-: 48	TT: 50 TT + CND: 32	6/9	Retrospective
Raffaelli et al., 2012 [30]	Italy	186	39/149	15.9 ± 7.5	93/186	–	42.9 ± 11.5	25.1	8/9	Prospective cohort
Roh et al., 2007 [31]	Korea	155	CND+: 16/66 CND-: 9/64	CND+: 25 ± 14 CND-: 22 ± 17	28/155	67/155	CND+: 46.3 CND-: 48.5	TT 53 TT + pCND 51	6/9	Retrospective
Sadowski et al., 2009 [32]	USA	310	–	12.6	–	–	–	38.8	5/9	Retrospective
Sywak et al., 2006 [33]	Australia	447	–	CND+: 20 CND-: 23	–	–	CND+: 39.1 CND-: 42.6	TT: 70 TT + CND: 24.5	8/9	Retrospective
Viola et al., 2015 [34]	Italy	181	CND+: 25/68 CND-: 21/67	CND+: 16 ± 8 CND-: 16 ± 9	83/181	86/181	CND+: 45.7 CND-: 43.5	59.4	3	RCT
Wada et al., 2003 [35]	Japan	390	CND+: 25/210 CND-: 12/143	–	70/390	–	CND+: 48.3 CND-: 49.4	61.6	5/9	Retrospective
Zuniga et al., 2009 [36]	Colombia	266	23/243	–	69/266	97/266	41	82.8	6/9	Retrospective
Hyun et al., 2012 [37]	Korea	152	CND+: 9/56 CND-: 20/67	CND+: 6.8 ± 2.1 CND-: 7.3 ± 2.3	18/152	61/152	CND+: 46 CND-: 48	51.31	6/9	Retrospective
So et al., 2012 [38]	Korea	232	CND+: 98/21 CND-: 97/16	CND+: 6.2 ± 2.0 CND-: 6.2 ± 2.0	72/232	119/232	CND+: 49.18 CND-: 49.75	TT: 45.4 TT + CND: 44.7	6/9	Retrospective
Zhang et al., 2015 [39]	China	242	CND+: 26/108 CND-: 27/81	CND+: 7 CND-: 5	–	6/242	CND+: 48 CND-: 45	TT: 66 TT + CND: 61	6/9	Retrospective

CND: central neck dissection; RCT: random clinical trials; TT: total thyroidectomy.

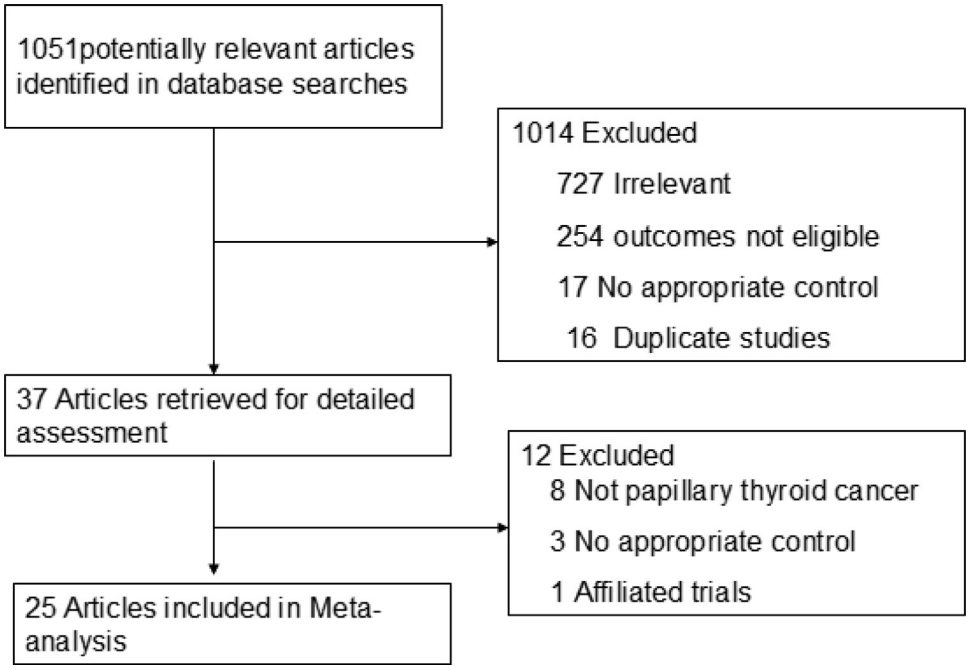

Fig. 1. Flowchart of the results of the literature search.

by the Begg's and Egger's tests did not appear significant (Pr > |z|= 0.907, $P > t = 0.571$, Fig. 2B and Fig. 2C). Similarly, for papillary thyroid microcarcinoma, the overall recurrence in TT + CND group was significantly lower than that in TT alone group (OR = 4.21, 95% CI [1.80∼9.83], $P = 0.001$, Fig. 2D).

Regarding central compartment recurrence, there were 13 relevant studies. The heterogeneity was not statistically significant with $I^2 = 29\%$ and $P = 0.153$. Compared with TT + CND group, the central compartment recurrence was significantly higher in TT alone group (2.57% vs. 0.81%, OR = 3.41, 95% CI [2.00 ∼ 5.80], $P < 0.00001$, Fig. 2E). No significant publication bias appeared (Pr > |z| = 0.246, $P > t = 0.559$).

Lateral compartment recurrence was mentioned in 12 studies. There was no significant heterogeneity with I 2 = 17.4% and $P = 0.264$. No significant difference of lateral compartment recurrence was observed between the two groups (2.49% vs. 2.43%, OR = 1.19, 95%CI [0.81 ∼ 1.77], $P = 0.38$, Fig. 2F). Publication bias is not significant (Pr >|z| = 0.913, $P > t = 0.595$).

Six of included studies reported patients who received TT versus ipsilateral CND + TT, and ten of included studies reported TT versus bilateral CND + TT. Compared with ipsilateral CND + TT group, there was no significant heterogeneity with I2 = 29.9% and $P = 0.21$. No significant difference of recurrence was observed between the two groups (8.4% vs. 4.3%, OR = 1.44, 95%CI [0.74v∼ 2.81], $P = 0.28$, Fig. 3A). Compared with bilateral CND + TT group, there was no significant heterogeneity with $I^2 = 30.7\%$ and $P = 0.163$. The recurrence was significantly higher in TT alone group than bilateral CND + TT group (7.8% vs. 3.3%, OR = 2.48, 95%CI [1.75 ∼ 3.53], $P < 0.00001$, Fig. 3B).

4. Discussion

PTC, as a common thyroid cancer, has the biological characteristic of metastasizing to the surrounding neck lymph nodes easily. Although therapeutic central node dissection has been proved efficient to improve the local recurrence in previous studies [40], the outcome of CND for cN0 PTC is still being debated, because previous studies did not weigh out benefit versus risk significantly. With original studies having larger sample-size and longer follow-up time published in the recent three years [23,34], we conducted a meta-analysis to evaluate the efficiency of CND + TT for cN0 PTC.

Our study was consistent with previous conclusions that TT + CND had a significant effect on reduction of local recurrence compared with TT alone. Additionally, central compartment lymph node recurrence in TT + CND group was significantly lower than those in TT alone group. This may illustrate that CND prevents central neck recurrences [41].

On the contrary, for patients with PTC, without clinical evidence of lateral lymph node metastasis, who underwent TT +CND, CND did not show any advantage of reducing the recurrence rate at the lateral site. We summarized the included studies and found most included studies with mean tumor size > 1 cm apart from four studies [17,37–39]. Moreover, the pooled extrathyroidal extension rate of 16 studies was 27.74%, the pooled multifocality rate of 20 studies was as high as 31.66%. These factors may affect the recurrence of lateral neck recurrence as previous studies demonstrated [42–45].

Because of the risk of complications following prophylactic CND, more limited (ipsilateral) CND has recently been proposed as an alternative safer treatment for patients with unilateral PTC [8–10]. We compared ipsilateral CND + TT with TT alone and found that the recurrence was not significantly different between the two groups. Nevertheless, bilateral CND + TT showed significantly low recurrence (OR = 2.48, 95%CI 1.75 ∼ 3.53, $P < 0.00001$, Fig. 3B). Two studies [17,38] indicated that bilateral CND + TT was not helpful in decreasing local recurrence in patients with tumor size ≤ 1 cm. Apart from both studies, other studies with mean tumor size > 1 cm demonstrated that bilateral CND + TT significantly reduces local recurrence (OR = 2.52, 95%CI 1.75 ∼ 3.62, $P < 0.00001$). According to previous studies [9,46,47], unilateral PTC with a maximal diameter greater than 1 cm is associated with a high rate of ipsilateral central neck lymph node metastasis. Moreover, ipsilateral central lymph node metastasis is a potential independent predictor of synchronous contralateral central lymph node metastasis. Besides, with the evidence of the former research [32,47,48], primary tumor size > 1 cm is a predictive factor of contralateral paratracheal lymph node metastasis in unilateral PTC. Therefore, routine bilateral CND in patients with PTC has the potential to clear metastatic disease.

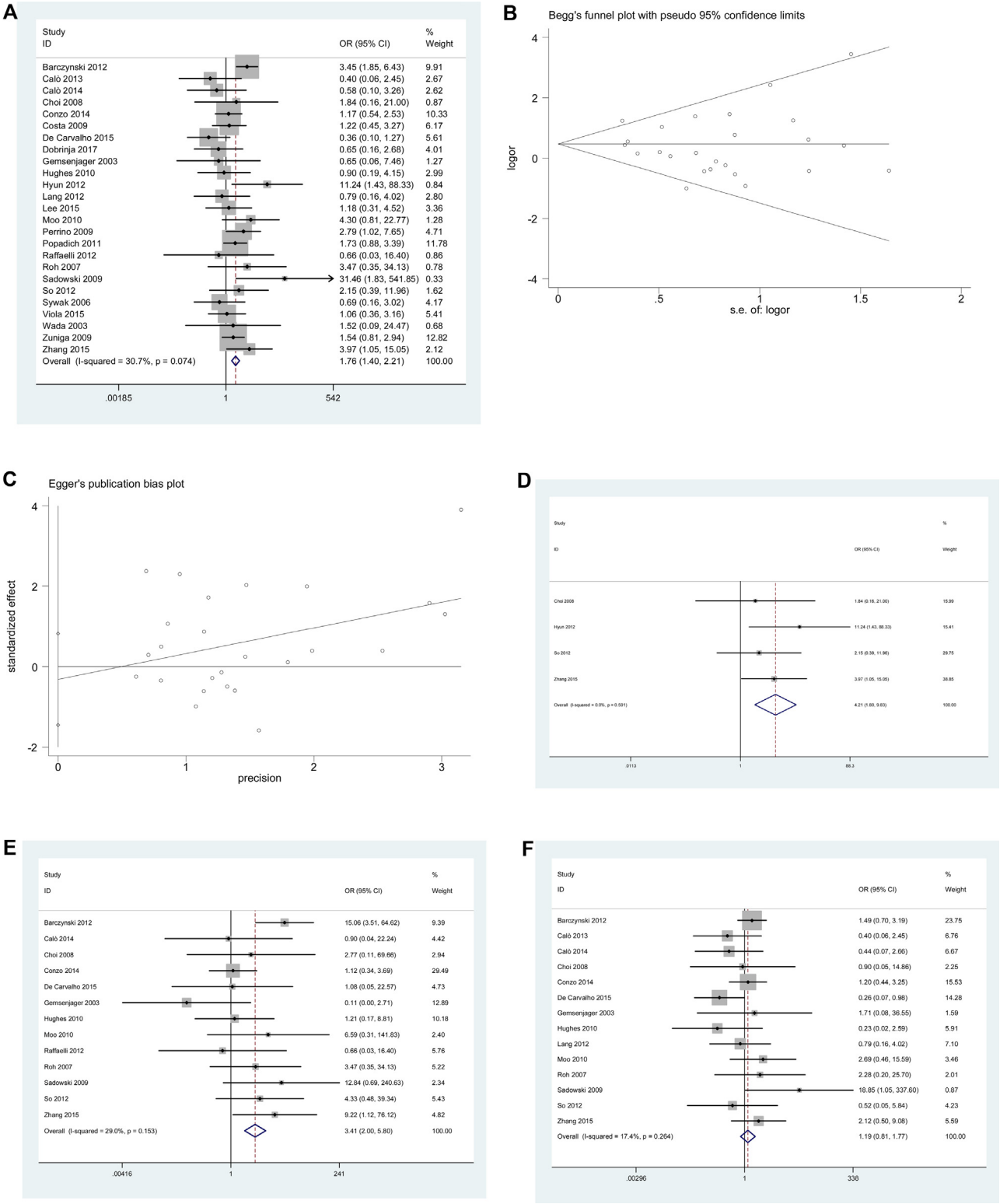

Fig. 2. Meta-analysis results for local recurrence between CND + TT and TT alone group. A. The total neck lymph node recurrence for PTC. B. Begg's funnel plot for visual assessment of no publication bias for overall recurrence. C. Egger's publication bias plot showed no publication bias for overall recurrence. D. The total neck lymph node recurrence for PTMC. E. The central lymph node recurrence for PTC. F. The lateral lymph node recurrence for PTC.

These findings suggest that contralateral as well as ipsilateral CND, performed during the initial thyroid operation, may be effective in the management of patients with unilateral PTC having a maximal diameter of greater than 1 cm and ipsilateral central lymph node metastasis.

There are several limitations in our meta-analysis. Firstly, the present study may have been limited by absence of high quality RCTs and bias is inevitable. Secondly, the decision to perform a CND may have been skewed by the surgeon's preference. Thirdly, the definitions of recurrence were not routinely defined in the

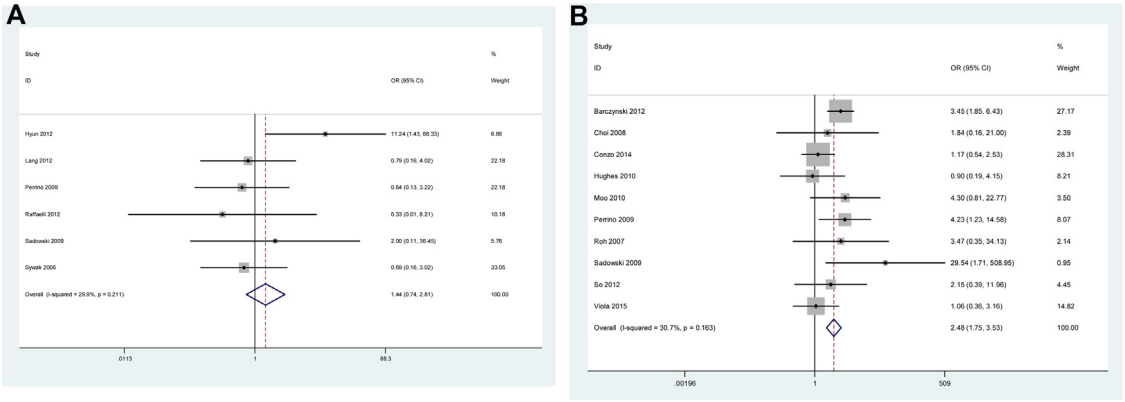

Fig. 3. Meta-analysis results for local recurrence between CND + TT and TT alone group. A. Ipsilateral CND + TT versus TT alone. B. Bilateral CND + TT versus TT alone.

studies. Fourthly, postoperative radioactive iodine administration is an important adjunct in the treatment of PTC, its use was not analyzed in our meta-analysis.

5. Conclusion

The addition of CND to TT resulted in a greater reduction in risk of local recurrence than TT alone, especially preventing central neck recurrences. Additionally, we found that bilateral CND in patients with PTC > 1 cm was necessary.

Disclosure of interest

The authors declare that they have no competing interest.

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