

Review Article

Total thyroidectomy versus lobectomy for recurrence and complications of papillary thyroid microcarcinoma: a meta-analysis

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Received June 7, 2017; Accepted December 12, 2017; Epub January 15, 2018; Published January 30, 2018

Abstract: *Background:* Surgical extent (Total thyroidectomy VS lobectomy) in papillary thyroid microcarcinoma (PTMC) remains controversial. The objective of this meta-analysis is to summarize recurrence and complication of these two procedures in PTMC. *Methods:* Electronic databases, PubMed, Cochrane Library and Web of Science were searched up to May 1, 2017. This meta-analysis was performed by Review Manager Version 5.2. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) for recurrence and complications were calculated using random-effects models. And subgroup analysis were done to explore heterogeneity in extracted studies. *Results:* 15 eligible studies with a total of 21,223 patients were included. 13 trials (n=15,336 patients) evaluated the correlation between different surgery extent and recurrence rate, four (n=8,229 patients) analysed for complications. Meta-analysis of the pooled data revealed there is no significant difference in the recurrence rate between total thyroidectomy (TT) and lobectomy (LT) groups, (OR, 0.87; 95% CI, 0.60-1.27; $P=0.47$). TT group had a higher risk of complications (OR, 7.96; 95% CI, 1.06-59.4; $P=0.04$) mainly caused by transient hypoparathyroidism (OR, 13.16; 95% CI, 1.68-103.38; $P=0.01$) compared with the lobectomy group. No significant differences were observed between the two operative methods in terms of permanent hypoparathyroidism (OR, 5.26; 95% CI, 0.59-46.67; $P=0.14$) and recurrent laryngeal nerve injury (OR, 1.59; 95% CI, 0.41-6.20; $P=0.50$). *Conclusion:* This meta-analysis indicate, there is no significant difference in recurrence rate between total thyroidectomy and lobectomy surgical strategy, Lobectomy can also achieve comparable therapeutic effect and with low complications.

Keywords: Total thyroidectomy, lobectomy, recurrence, complications, papillary thyroid microcarcinoma, meta-analysis

Introduction

Thyroid cancer is the most common endocrine cancer and accounts for about 2% of all cancers [1]. As the most common type of thyroid cancer, papillary thyroid cancer (PTC) accounts for 85% to 90% of all thyroid cancer cases [2]. Over the past three decades, the incidence of thyroid cancer has risen worldwide [3]. Almost the entire change has been attributed to an increase in incidence of PTC [4]. Papillary thyroid microcarcinoma (PTMC) is a special subgroup of PTC, which defined as a tumor measuring ≤ 1 cm in the greatest dimension according to the World Health Organization [5]. The incidence of PTMC reached 30% of all PTC [6].

Loco-regional recurrence rates have been reported to be 2%-6%, and distant recurrence rates are 1%-2% [7].

Surgery is generally considered to be the fundamental management of these tumors [8], but there is no consensus on the extent of surgery (Total thyroidectomy VS Lobectomy) [1]. Some scholars advocate PTMC can not be considered early cancer, its biological behavior consistent with PTC, There is also the risk of extra-thyroidal invasion and distant metastases. total thyroidectomy may remove the entire primary tumor, and provide conditions for postoperative treatment. On the contrary, some research have suggested, PTMC has been overdiagnosis

and overtreatment [9]. Most PTMC follow a highly indolent course, they have been denoted as “low risk thyroid cancer” because of the low recurrence rate, low mortality rate and excellent prognosis [10]. Lobectomy can also achieve therapeutic effect, and preserve thyroid function, reduce surgical damage.

The definition of PTMC is based on tumor size, but there is no explicit understanding in invasive and metastatic capacity, unified criterion for diagnosis and treatment were not formed. There is much uncertainty about the benefits of these two surgical procedures. Objective of this analysis is to summarize available studies on total thyroidectomy and lobectomy, compare recurrence and complication of these two procedures in order to assist physicians and patients in selecting the most appropriate treatment for PTMC.

Materials and methods

Literature search

Followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, We searched PubMed, Cochrane Library and Web of Science up to May 1, 2017. The key words of the search were (“Papillary Thyroid Microcarcinoma” OR PTMC OR “Papillary Microcarcinoma of thyroid” OR “PMC of thyroid”) [Title/Abstract] AND (Thyroidectomy OR “Total thyroidectomy” OR “Non-total thyroidectomy” OR Lobectomy OR Hemithyroidectomy OR “Partial thyroidectomy” or “Less than total thyroidectomy” OR “Subtotal thyroidectomy” or “Near total thyroidectomy”) [Title/Abstract] AND (Recurrence OR Complication OR Complications OR “Transient hypoparathyroidism” OR “Permanent hypoparathyroidism” OR “Recurrent laryngeal nerve injury”) [Title/Abstract]. To broaden the search, specialty journals such as *Thyroid*, *The Journal of Clinical Endocrinology and Metabolism* were searched electronically, also related review articles and reference lists of selected studies were hand-searched to supplement electronic searches. The literatures were searched, screened and assessed by two authors (Liqin Dong and Xiaoping Wang) independently, disagreements were resolved by consensus of all the authors.

Inclusion criteria

Articles that satisfied the following criteria were included: (1) published case-control or cohort studies; (2) patients with PTMC were confirmed by histopathologic examinations; (3) Total thyroidectomy refer to bilateral resection including total, near-total, and subtotal and lobectomy means unilateral resection including lobectomy with or without isthmusectomy. (4) Studies provided sufficient recurrence or complication data. (5) when the population sources were recruitment by the same authors in different papers, we chose the most recent study with the larger sample size; Only studies published in English were included.

Exclusion criteria

Studies were excluded on the basis of: (1) reviews, comment, letters, case reports, editorials, animal studies or duplicated articles; (2) studies without control group or sufficient data of interest; and (3) The definition of total thyroidectomy and lobectomy not conformed to the inclusion criteria.

Data extraction

The data of all eligible articles were extracted by two authors (LQ Dong and XP Wang) independently, and the following information were collected: the first author, year of publication, study design, country or area, sample size, number of recurrent and complication events, follow-up time. when univariate and multivariate analysis were both provided in the study, multivariate analysis would be selected since it adjusted confounding factors and more convincing. Quality assessment of the included studies was performed according to The Newcastle-Ottawa Quality Assessment Scale (NOS) [11]. The score was from 0 to 9, LQ Dong and XP Wang assessed the study quality independently.

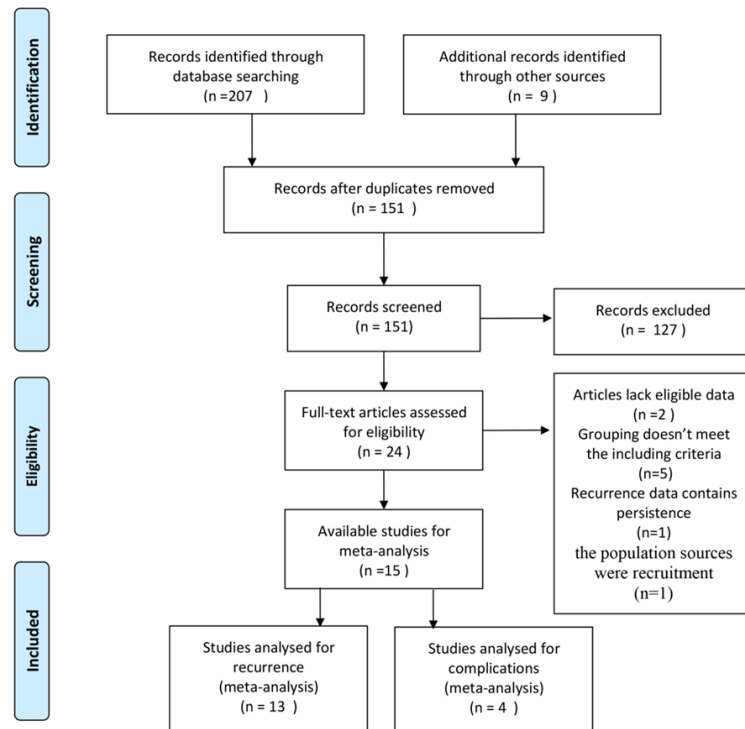
Statistical analyses

Meta-analysis was performed by Review Manager Version 5.2 software, The primary outcomes for analysis were the number of recurrent and complication events. Odds ratio (OR) and corresponding 95% confidence interval (CI) were used to evaluate pooled effects of different thyroidectomy on PTMC prognosis.



PRISMA 2009 Flow Diagram

Figure 1. Flow program of study selection.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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There are heterogeneity in extracted studies, these differences mainly come from patient selection, study design, intervention measures, disease situation and follow up time, etc. Cochrane Q test (X^2) and I-squared index (I^2) were used to measure the heterogeneity among the studies. P value < 0.1 for Q test or $I^2 \geq 50\%$ indicate significant heterogeneity, a random-effect models were selected to analyse the date. Otherwise, a fixed-effect model was applied if $I^2 < 50\%$ [12, 13].

Results

Search results and study characteristics

A total of 216 articles were retrieved according to the search strategy, 151 studies remained after excluding duplicate studies. After reading the full articles, 136 studies were excluded because they can not provide relevant statistical data or non-clinical studies. Finally 15 studies [14-28] matched the inclusion crite-

ria were included. Among the 15 literatures, thirteen [14-26] evaluated the the correlation between different surgery extent and recurrence of PTMC, and four [16, 19, 27, 28] analysed for complications. Study selection process is summarized in **Figure 1**. All eligible studies were published from 2006 to 2017, a total of 21,223 patients from Korea, China, Italy, the United States, France, Israel, Denmark, and Spain were included. The detailed information and quality scores of the studies are listed in **Table 1**.

Meta-analysis for recurrence

For recurrence, We included 13 studies with a total of 15,336 patients, of which 9586 (61%) were performed total thyroidectomy, and 5750 (39%) were treated with lobectomy. Ten of these studies showed no significant difference of the recurrence rate between two groups; The other three [16, 19, 26] indicated that recurrence risk was significantly less in TT group than in the LT group. A random-effect model was used with moderate heterogeneity ($I^2=48\%$, $P=0.03$). Meta-analysis of the pooled data revealed there is no significant difference in the recurrence rate between TT and LT groups, (OR, 0.87; 95% CI, 0.60-1.27; $P=0.47$) (**Figure 2**).

In addition, subgroup analysis was performed to compare recurrence according to area and publication year. There is no association between recurrence and operation method both in studies with Asian cases source (OR, 0.88; 95% CI, 0.58-1.33; $P=0.54$;) and in studies researched with non-Asian cases (OR, 0.82; 95% CI, 0.29-2.38; $P=0.72$;) (**Figure 3**). No significant difference between subgroups ($p=0.47$). Regarding the publication year, also no significant difference was observed both in studies published in recent three years (OR, 0.52; 95% CI, 0.23-1.20; $P=0.13$;) and in stud-

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Table 1. Characteristics of included studies in the meta-analysis

Study	Year	Design	Country or area	Recurrence rate (Events/Total)		Matching factors				Follow-up time (mean, month)	P value	Quality score
				Total thyroidectomy	Lobectomy	Age	Sex	Mean size	Multifocality			
Ardito [14]	2013	RS	Italy	20.74% (28/135)	0.00% (0/14)	NA	NA	NA	NA	64.8	NS	5
Cho [15]	2012	RS	Korea	3.06% (9/294)	3.43% (8/233)	NA	NA	NA	NA	48.2±24.6	NS	8
Donatini [16]	2016	RS	France	0.00% (0/251)	7.25% (5/69)	-	-	-	-	130.4	0.0004	8
Gershinsky [17]	2012	RS	Israel	9.81% (21/214)	10.13% (8/79)	-	-	-	+	86.4±81.6	0.806	8
Kim KJ [18]	2015	RS	Korea	2.37% (27/1140)	1.73% (9/521)	NA	NA	NA	NA	67.2±10.8	0.430	8
Kwon [19]	2017	RS	Korea	1.60% (11/688)	3.78% (26/688)	+	+	+	+	102	0.01	7
Londero [20]	2013	RS	Denmark	2.94% (1/34)	2.48% (3/121)	+	-	+	+	96-91.2	NS	7
Mantinan [21]	2012	PS	Spain	9.09% (7/77)	7.14% (1/14)	-	-	-	+	154.8±58.8	0.11	5
Pelizzo [22]	2006	RS	Italy	1.39% (5/359)	2.27% (1/44)	NA	NA	NA	NA	102	NS	5
Ross [23]	2009	RS	America	6.16% (29/471)	6.43% (9/140)	NA	NA	NA	NA	48	0.058	6
Kim SK [24]	2016	PS	Korea	1.65% (89/5387)	1.52% (50/3289)	NA	NA	NA	NA	64.6	0.640	7
Xue [25]	2017	RS	China	5.00% (2/40)	26.32% (15/57)	-	-	-	NA	127±4	0.007	8
Zheng [26]	2013	RS	China	6.45% (32/496)	4.57% (22/481)	NA	NA	NA	NA	93.6±14.4	0.05	6

Abbreviations: RS, retrospective study; PS, prospective study; NA, not available; "+" means statistically significant, "-" means no statistical differences; NS, no significance.

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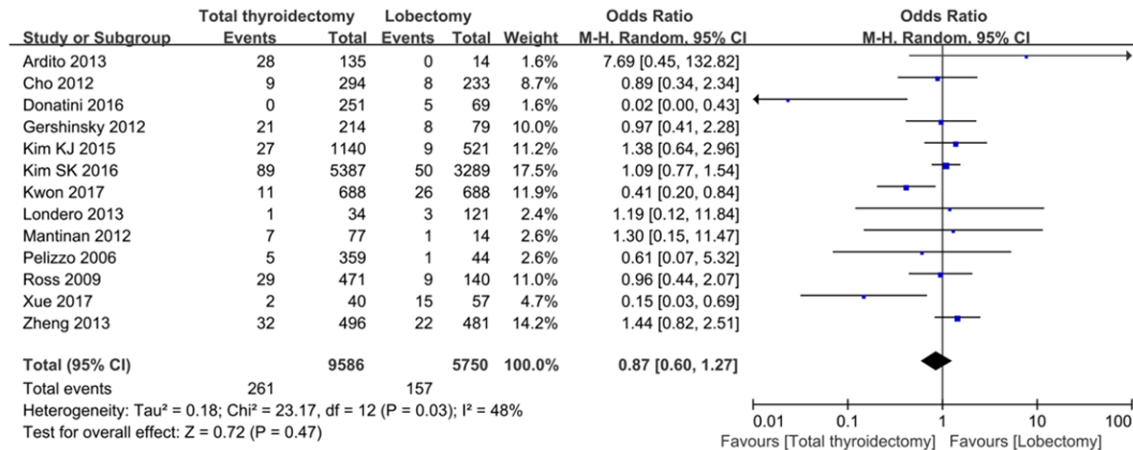


Figure 2. Forest plot of comparison between surgical extent (Total thyroidectomy VS lobectomy) and recurrence rate for PTMC patients.

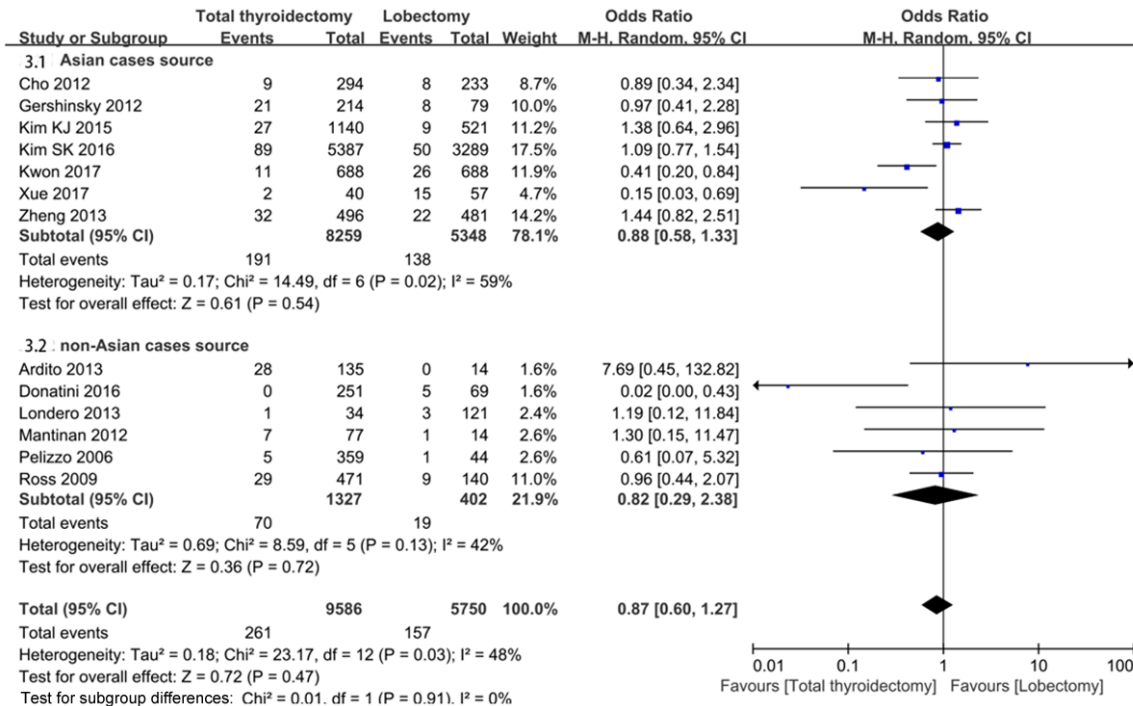


Figure 3. Subgroup analysis to compare recurrence rate according to area. 3.1, Recurrence rate for PTMC patients from Asian cases source; 3.2, Recurrence rate for PTMC patients from non-Asian cases source.

ies published three years ago (OR, 1.15; 95% CI, 0.81-1.64; $P=0.43$) (**Figure 4**). But heterogeneity in studies publication before 2014 was reduced. Subgroup difference: $P=0.47$ (**Table 2**).

Meta-analysis for complications

For complications, 8229 patients were included from 4 studies, of whom 6578 under went

total thyroidectomy and 1651 with lobectomy. Compared to lobectomy patients, TT patients had a higher risk of complications (**Figure 5**) and mainly attributed to transient hypoparathyroidism. No significant differences were observed between the two operative methods in terms of permanent hypoparathyroidism and recurrent laryngeal nerve injury (**Figure 6**). Random-effect model were used with signifi-

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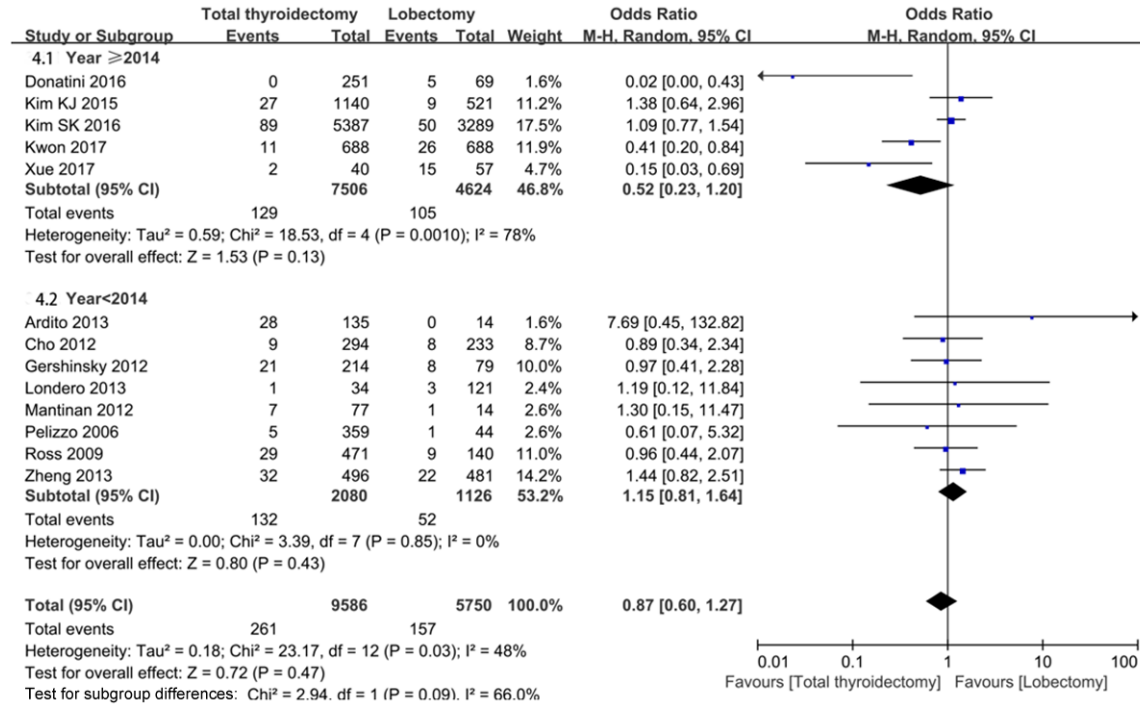


Figure 4. Subgroup analysis to compare recurrence rate according to publication year. 4.1, Recurrence rate for PTMC patients in studies published in recent three years. 4.2, Recurrence rate for PTMC patients in studies published before 2014.

Table 2. Outcomes of Meta-analysis Comparing total thyroidectomy Versus lobectomy

Outcomes	Studies (n)	Patients (n)	OR	95% CI	P value	Heterogeneity	
						I ² (%)	P value
Recurrence	13	15336	0.87	0.60-1.27	0.47	48	0.03
Studies from Asian	7	13607	0.88	0.58-1.33	0.54	59	0.02
Studies from non-Asian	6	1729	0.82	0.29-2.38	0.72	42	0.13
Studies in 2014-2017	5	12130	0.52	0.23-1.20	0.13	78	0.0010
Studies before 2014	8	3206	1.15	0.81-1.64	0.43	0	0.85
Complications	4	8229	7.96	1.06-59.4	0.04	96	< 0.00001
Transient hypoparathyroidism	4	8229	13.16	1.68-103.38	0.01	91	< 0.00001
Permanent hypoparathyroidism	4	8229	5.26	0.59-46.67	0.14	55	0.08
Recurrent laryngeal nerve injury	4	8229	1.59	0.41-6.20	0.50	79	0.003

Abbreviations: OR, odds ratios; CI, confidence interval.

cant heterogeneity, Results of the analyses are summarized in **Table 2**.

Publication bias

Begg's funnel plot and Peter's test were used to assess publication bias in the literatures, no obvious asymmetry was revealed according to the funnel plots (**Figure 7**). Moreover, the Peter's test score of $P=0.9355$, reflecting no significant publication bias in the analysis.

Discussion

A worldwide thyroid-cancer epidemiological research [29] described dramatic increase in incidence of thyroid cancer, but mortality rates have not changed substantially [30, 31]. The massive increase mainly caused by increased new diagnostic techniques and medical surveillance. A large number of asymptomatic, nonlethal microcarcinoma be detected [32]. For PTMC, disease-specific mortality rates have

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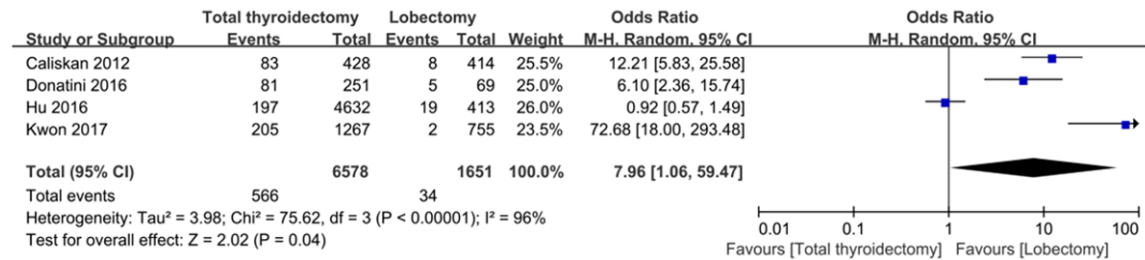


Figure 5. Forest plot for the relation between surgical extent (Total thyroidectomy VS lobectomy) and complications for PTMC patients.

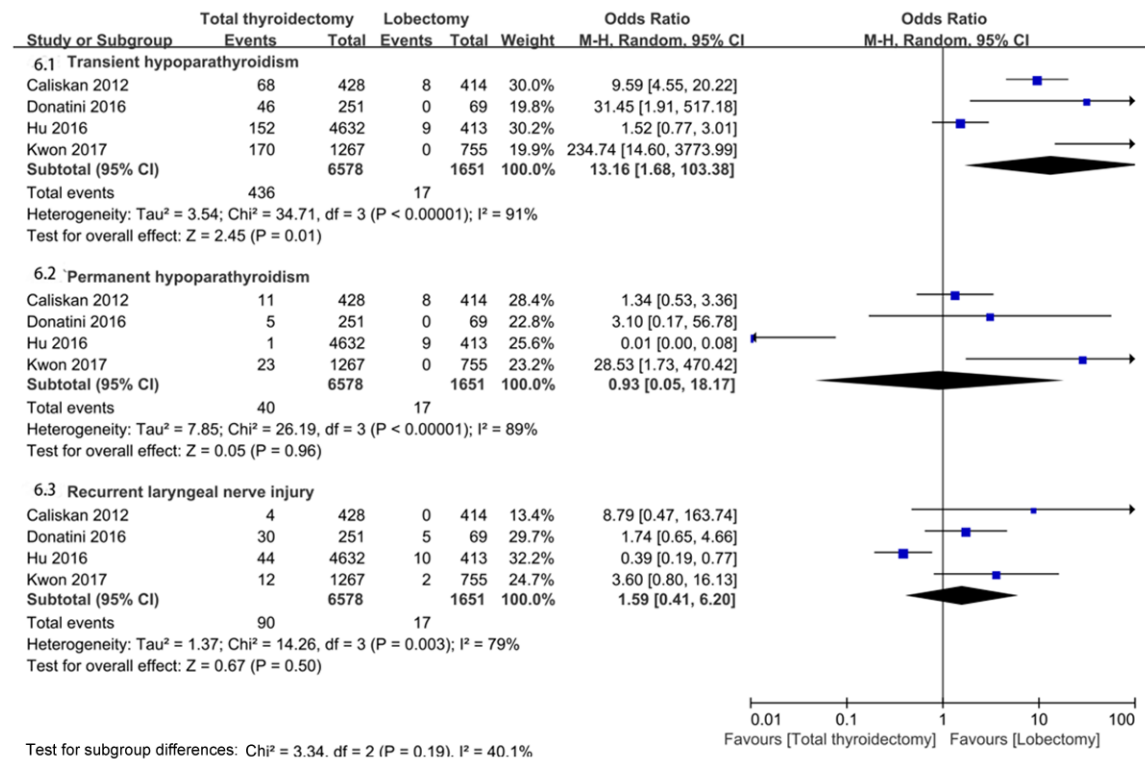


Figure 6. Subgroup analysis on comparison between surgical extent and transient hypoparathyroidism 6.1, permanent hypoparathyroidism 6.2, and recurrent laryngeal nerve injury 6.3.

been reported to be $< 1\%$, [7, 33]. The biological behavior of PTMC is not consistent, Some tumor onset occult, growth slow related to the indolent nature, patients can be long-term survival with tumors even asymptomatic lifetime. but no clinical features can reliably conclude that will not cause significant disease. There are some controversies about the treatment strategy and surgical extent of thyroid papillary carcinoma.

In this meta-analysis, 3 included studies [16, 19, 25] advocated total thyroidectomy as the

better approach to minimize recurrence rate. ATA and NCCN guidelines [4, 34] favored total or near total thyroidectomy for patients with tumors greater than 1 cm. But surgical extent is controversial for tumors smaller than 1 cm. Several researches support this approach. Ross [23] reported data analysis of 698 PTMC cases, The recurrence rate of patients undergoing total or near total thyroidectomy was significantly lower than that of patients undergoing lobectomy. Total thyroidectomy is often advocated because it may remove all the lesions as much as possible and provide condi-

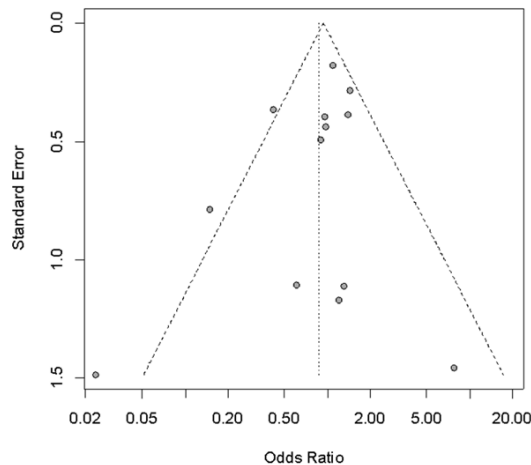


Figure 7. Funnel plot with pseudo 95% confidence limits of Total thyroidectomy versus lobectomy in terms of recurrence rate. Each circle represents a individual study.

tions for postoperative radioactive iodine (RAI) therapy [19]. In addition, the serum Tg levels can be used as a sensitive marker of recurrence after total thyroidectomy only [16].

Results from our meta-analysis indicate, for disease recurrence, there is no difference in extent of surgery, Lobectomy can also achieve comparable therapeutic effect and with low complications. There is no randomized controlled trials which demonstrates the benefit of surgical extent in prognosis of PTM. TS Wang *et al.* [16] included 29,512 patients with PTMC undergoing thyroid surgery from SEER database, this cohort study indicated many patients with PTMC may be over-treated, There were no significant differences in 5 and 10-year disease-specific survival (DSS) between partial and total thyroidectomy groups. Bilimoria KY *et al.* [35] identified 52,173 patients with PTC using the National Cancer Data Base (NCDB), 43,227 underwent total thyroidectomy and 8946 underwent lobectomy, this study demonstrate a survival benefit (HR 1.31, $p=0.009$) and lower recurrence rate (HR 1.15, $p=0.04$) for total thyroidectomy in tumors ≥ 1.0 cm compared with lobectomy. For tumors < 1 cm, there is no difference in recurrence and survival no matter extent of surgery. Another large observational study analyzed 22,724 patients who had undergone PTC surgery, for tumors smaller than 1 cm, multivariate analysis demonstrated no significant survival improvement based on surgical extent [36].

The limitation of this meta-analysis is that non-randomized surgical studies can not provide integrated individual characteristics (age, gender, tumor diameter, extrathyroid invasion, lesion pattern, multifocality, lymph node metastasis, distant metastasis, risk categories and etc.) according to surgical extent grouping, the use of which would have provided detailed data to perform subgroup analysis according to different baseline levels. We expect multiple-center, large-sample randomized controlled trials and long-term follow-up to improve the evidence-related evidence.

In conclusion, more aggressive surgical strategy can not bring prognosis benefit, In terms of recurrence rate, there was no significant difference in effect of two interventions (total thyroidectomy VS lobectomy). For low risk papillary microcarcinoma of thyroid, lobectomy and active surveillance could be a considerable primary surgical management, which achieve comparable therapeutic effect and reduce the complication (mainly transient complication). To achieve excellent prognosis with minimally injury, efficacy and potential harm of each therapies should be compared. According to each patient's specific circumstances to develop more individualized treatment approach.

Acknowledgements

This study was supported by Science and Technology Innovation Action Plan from Science and Technology Commission of Shanghai Municipality (17401933400), Research Subject from Shanghai Municipal Commission of Health and Family Planning (201640034). The sponsor had no influence on the design and implementation of the study.

Disclosure of conflict of interest

None.

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