

Review Article

Effect of different thyroidectomy in the treatment of differentiated thyroid carcinoma: a meta-analysis

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Abstract: Objectives: To explore the effect of different thyroidectomy in the treatment of differentiated thyroid carcinoma. Methods: We retrieved the relevant trials from several public databases, including PubMed, Medline, Springer, Elsevier Science Direct, Cochrane Library and Google scholar. Odds ratio (OR) and 95% confidence intervals (CI) of for the recurrence, complications, hypoparathyroidism and recurrent laryngeal nerve injury events were collected and calculated in a fixed-effects model (the Mantel-Haenszel method) or a random-effects model (the DerSimonian and Laird method) when appropriate. Results: A total of 9 separate studies consisting of 3343 patients (experimental group: 2201; control group: 1142) were included in this meta-analysis. The results of this meta-analysis showed that there were significant differences in the recurrence after operation (OR=0.21, 95% CI=0.12 to 0.39, $P<0.01$) and the rate of complications after operation (OR=2.77, 95% CI=1.75 to 4.41, $P<0.01$) between experimental group and placebo group, suggesting that the recurrence of patients after operation in experimental group may be lower than control group and the rate of postoperative complications of patients in experimental group may be higher than that of control group. The overall meta-analysis also showed that there were no significant differences in the hypoparathyroidism after operation (OR=1.79, 95% CI=0.56 to 5.69, $P=0.32$) and the recurrent laryngeal nerve injury after operation (OR=1.13, 95% CI=0.33 to 3.91, $P=0.85$) between the two groups, indicating that the rate of hypoparathyroidism and recurrent laryngeal nerve injury after operation of patients in experimental group may be equal to control group. Conclusions: Our results indicated that using total or near-total thyroidectomy in treatment of differentiated thyroid carcinoma may have lower recurrence but higher complications after operation.

Keywords: Differentiated thyroid carcinoma, thyroidectomy, meta-analysis

Introduction

Differentiated thyroid carcinoma is the most common endocrine malignancy with an excellent prognosis in the case at its early detection [1], it is the most common malignant endocrine tumor [2-4], which comprises 1% in all human tumors. Staging is difficult and treatment options are few for patients with progressive metastatic (or recurrent) differentiated thyroid carcinoma that either do not take up radioiodine or are unresponsive to continued radioiodine therapy [5]. The treatment-of-choice for differentiated thyroid carcinoma (DTC) is total thyroidectomy with subsequent radioiodine therapy [6]. Total thyroidectomy with dissection of the central compartment lymphatic nodes is a standard surgical procedure in differentiated thyroid carcinomas [7], it is the standard of care for differentiated thyroid cancer, but still there

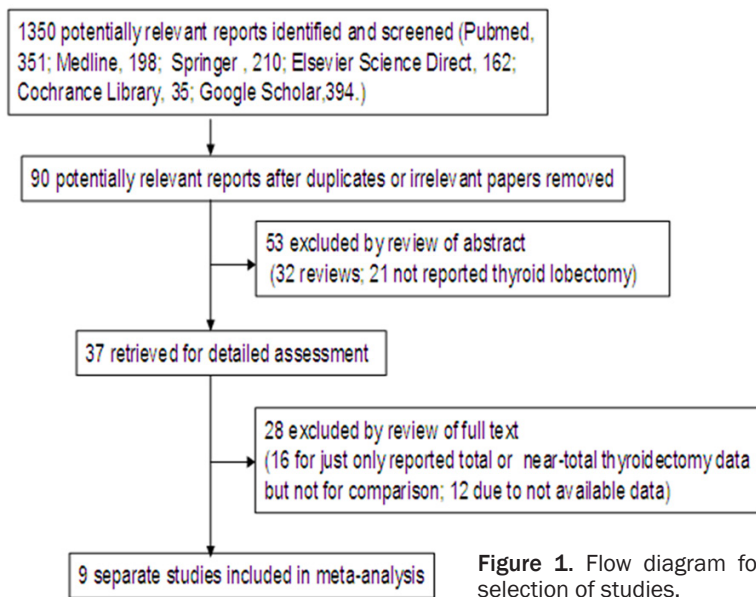
is no consensus about the role of routine use of prophylactic central lymph node dissection [8].

The effect of different thyroidectomy in the treatment of differentiated thyroid carcinoma for patients is controversial [9-13]. In order to achieve an integrative understanding of effect with gabapentin in treatment of postherpetic neuralgia, it is necessary to consider the findings as a whole, giving attention to methodological characteristics of the studies. Accordingly, we conducted a systematic review on published findings and used meta-analysis techniques to combine the results.

Material and methods

Source of material

We retrieved the relevant trials up to June 2016 from several public databases, mainly including



Evaluation of quality and extraction of data

We developed and extracted the data after we made training to all investigators. Data items included study details (e.g., the First author’s name, research year of study, year of study publication, location of participants, design of studies.), and characteristics of participants (e.g., age, gender and sample size). Two investigators extracted the data independently using the standard protocol, and the third investigator reviewed their results of studies. We contacted authors of incorporated studies to obtain further

PubMed, Medline, Springer, Elsevier Science Direct, Cochrane Library and Google scholar. The key words of “differentiated thyroid carcinoma”, “differentiated thyroid cancer”, “thyroidectomy”, “thyroid lobectomy”, “goiter”, “treatment”, “therapy”, “study” and “trial” were used for searching. Meanwhile, references from retrieved papers were checked for additional studies. We collected data from the all full-published English papers, not any meeting or conference abstract.

information for data items that needed clarification. Discrepancies were resolved by discussing within our research team or contracting with the original investigators via e-mail. We recorded the first author’s name, year of publication, sample size, country, age, duration of study follow up in experimental group vs. control group.

Assume that differences occur (Such as the included literature was not consistent with another investigator), a third investigator will make additional assessment. If the third investigator’ assessment was consistent with one of them, then the discussion should be made for the final decision of the included literatures.

Meta-analysis methods

Inclusion and exclusion standards of studies

The meta-analysis was performed in fixed or random effect models. Odds ratio (OR) and its 95% confidence interval (95% CI) were estimated with each study. The overall or pooled estimate of OR was obtained using Mantel-Haenszel method in the fixed effect model [14] or using DerSimonian and Laid method in the random effect model [15]. We assessed the within- and between-study variation or heterogeneity by testing Cochran’s Q-statistic [16]. We also quantified the effect of heterogeneity using $I^2=100\% \times (Q-df)/Q$ [17]. A significant Q-statistic ($P<0.10$) or I^2 -statistic ($I^2>50\%$) indicated heterogeneity across the studies, and then the random effects model was used for meta-analysis. Otherwise, the fixed effects model was used. We evaluated the publication bias using Egger’s linear regression test [18], which measures funnel plot asymmetry by the natural logarithm scale of the effect size. The meta-analysis was performed using the software of Review Manager 5.1 (Cochrane Collaboration, <http://ims.cochrane.org/revman>), and the pub-

The comparison between experimental group (Total or near-total thyroidectomy treatment) and control group (Thyroid lobectomy) were provided in papers, the study design was not limited, the effect size of recurrence, complications, hypoparathyroidism and recurrent laryngeal nerve injury was odds ratio (OR), sample size or range of age were not limited. We excluded the studies in which not described cancer recurrence events data with review or report, duplicated studies or records, and the studies in which did not compared experimental group vs. control group.

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

Study	Year of Publication	Country	Sample size	Male (%)	Age, years (mean \pm SD)	Duration of follow up, years
Perzik S.	1976	USA	345	NA	35	NA
Mazzaferrri EL, et al.	1981	USA	571	38.4	32.4 \pm 0.5	10
Grant CS, et al.	1988	USA	301	NA	NA	41
Arnold RE, et al.	1989	USA	65	NA	NA	30
Sand J, et al.	1996	Finland	178	NA	NA	12
Kebebew E, et al.	2000	USA	156	NA	NA	10
Ozbas S, et al.	2005	Turkey	750	NA	NA	5
Barczynski M, et al.	2010	Poland	381	8.7	46.5-48.2	5
Hurtado-Lopez LM, et al.	2011	Mexico	596	6.2	38.1-46.1	10

lication bias of the included studies were calculated using the STATA package v.11.0 (Stata Corporation, College Station, TX, USA). All the *P*-values were two-sided. The *P* value less than 0.05 was considered to be significant statistically, while the *P* value less than 0.1 was considered to be significant statistically in heterogeneity analysis.

Results

Characteristics of eligible studies

There were 1350 papers potentially relevant to the search terms (PubMed: 351; Medline: 198; Springer: 210; Elsevier Science Direct: 162; Cochrane Library: 35; Google Scholar: 394.) The study selection process is shown in **Figure 1**. There were 90 potentially relevant studies after removing duplicates or irrelevant studies. During the step of screening the abstracts, 53 of these articles were excluded (32 were review articles; 21 not reported the thyroid lobectomy). Then 37 studies were left for full publication review, 28 of which were excluded (16 only reported total or near-total thyroidectomy data but not for comparison; 12 provided no available data).

As is shown in **Table 1**, there were 9 studies [9-13, 19-22] in the meta-analysis, and the characteristics of included studies were presented. The included studies were published between 1976 and 2011. A total of 3343 patients (experimental group: 2201; control group: 1142) were considered in the meta-analysis. The studies' sample sizes were between 65 and 750, duration of follow up was between 5 and 41 years.

Overall effects of recurrence after operation

The summary of the meta-analysis for the recurrence after operation between experimental group and control group is shown in **Table 2** and **Figure 2**. A total of 7 separate studies consisting of 2248 patients (experimental group: 1405; control group: 843) been analyzed in the meta-analysis. Heterogeneities were found between studies ($Q_2=16.43$, $I^2=63.0\%$, $P<0.1$), so we used the random effects model to compare the recurrence after operation between this two groups. The overall meta-analysis showed that there were significant differences ($OR=0.21$, 95% $CI=0.12$ to 0.39 , $P<0.01$) between the two groups, suggesting that the recurrence of patients after operation in experimental group may be lower than control group.

Overall effects of complications after operation

The summary of the meta-analysis for the rate of complications after operation between experimental group and control group is shown in **Table 2** and **Figure 3**. A total of 5 separate studies consisting of 1125 patients (experimental group: 647; control group: 478) been analyzed in the meta-analysis. There were no heterogeneities were found between studies ($Q_2=4.47$, $I^2=10.0\%$, $P>0.1$), so we used the fixed effects model to compare the rate of complications after operation between this two groups. The overall meta-analysis showed that there were significant differences ($OR=2.77$, 95% $CI=1.75$ to 4.41 , $P<0.01$) between the two groups, suggesting that the rate of complications with patients after operation in experimental group may be higher than control group.

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Table 2. Pooled odds ratios for experimental group versus control group in meta-analyses

Overall effects	Sample size		No. of studies	Test of association			Test of heterogeneity			Model	Egger's test for publication bias	
	Case	Control		OR (95% CI)	Z	P value	Q	P value	I ² (%)		t	P value
Recurrence	1405	843	7	0.21 (0.12 to 0.39)	5.08	<0.01	16.43	0.01	63.0	Random	-2.73	0.04
Complications	647	478	5	2.77 (1.75 to 4.41)	4.32	<0.01	4.47	0.35	10.0	Fixed	-0.76	0.5
Hypoparathyroidism	1011	519	5	1.79 (0.56 to 5.69)	0.99	0.32	22.19	<0.01	82.0	Random	-0.001	0.99
Recurrent laryngeal nerve injury	1011	519	5	1.13 (0.33 to 3.91)	0.19	0.85	11.63	0.02	66.0	Random	-0.32	0.77

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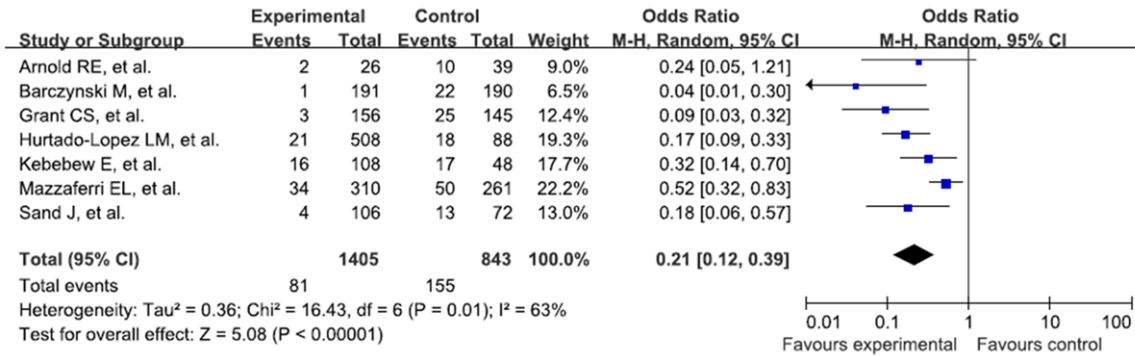


Figure 2. Forest plot of recurrence after operation with experimental group vs. control group.

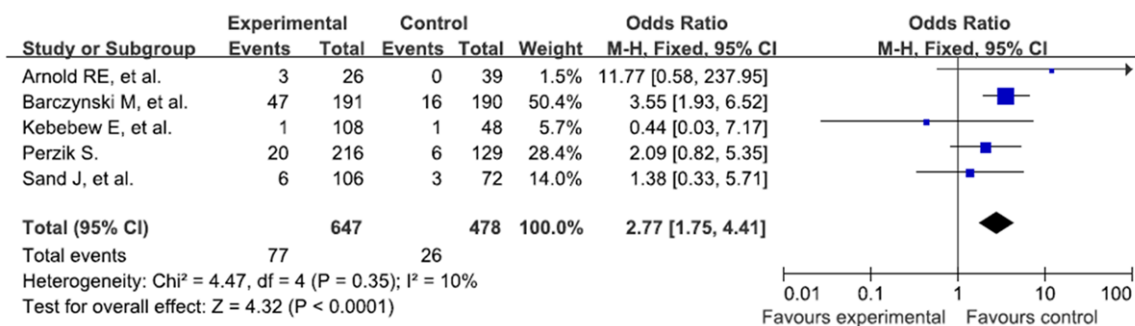


Figure 3. Forest plot of complications after operation with experimental group vs. control group.

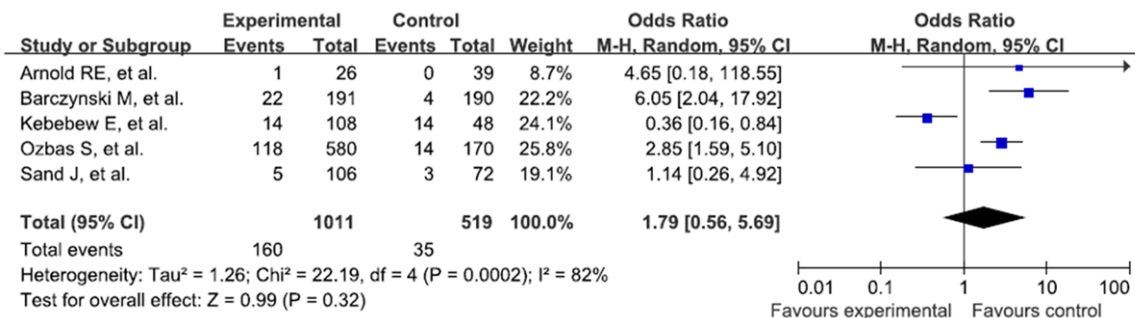


Figure 4. Forest plot of hypoparathyroidism after operation with experimental group vs. control group.

Overall effects of hypoparathyroidism after operation

The summary of the meta-analysis for the hypoparathyroidism after operation between experimental group and control group is shown in Table 2 and Figure 4. A total of 5 separate studies consisting of 1530 patients (experimental group: 1011; control group: 516) been analyzed in the meta-analysis. Heterogeneities were found between studies ($Q=22.19$, $I^2=82.0\%$, $P<0.1$), so we used the random effects model to compare the hypoparathyroidism after oper-

ation between this two groups. The overall meta-analysis showed that there was no significant difference ($OR=1.79$, $95\% CI=0.56$ to 5.69 , $P=0.32$) between the two groups, suggesting that the hypoparathyroidism of patients after operation in experimental group may be equal to control group.

Overall effects of recurrent laryngeal nerve injury after operation

The summary of the meta-analysis for the recurrent laryngeal nerve injury after operation

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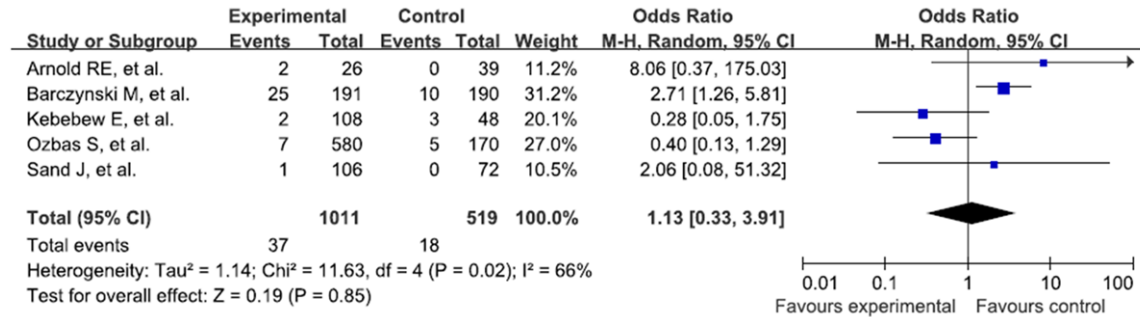


Figure 5. Forest plot of recurrent laryngeal nerve injury after operation with experimental group vs. control group.

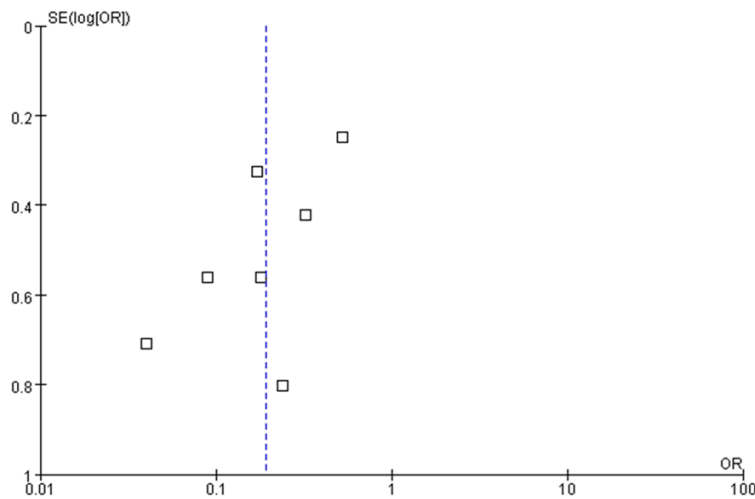


Figure 6. Funnel plot of recurrence after operation with experimental group vs. control group.

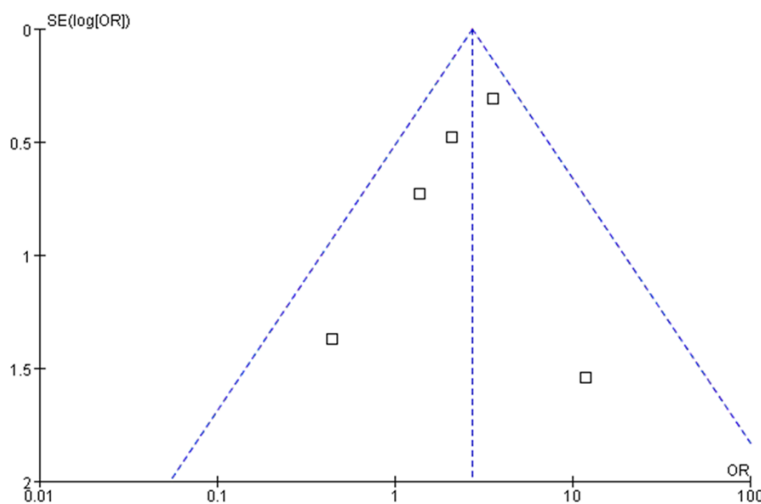


Figure 7. Funnel plot of complications after operation with experimental group vs. control group.

between experimental group and control group is shown in **Table 2** and **Figure 5**. A total of 5 separate studies consisting of 1530 patients (experimental group: 1011; control group: 516) been analyzed in the meta-analysis. Heterogeneities were found between studies ($Q=11.63$, $I^2=66.0\%$, $P<0.1$), so we used the random effects model to compare the recurrent laryngeal nerve injury after operation between this two groups. The overall meta-analysis showed that there was no significant difference ($OR=1.13$, $95\% CI = 0.33$ to 3.91 , $P=0.85$) between the two groups, suggesting that the recurrent laryngeal nerve injury of patients after operation in experimental group may be equal to control group.

Evaluation of publication bias analysis

The Egger's linear regression test (**Table 2**) showed that there were no publication bias existing in our study ($P>0.05$) except recurrence of the patients after operation which $P=0.04$ (**Figures 6-9**).

Discussion

Many studies [10-13, 19, 22] have reported the effect of

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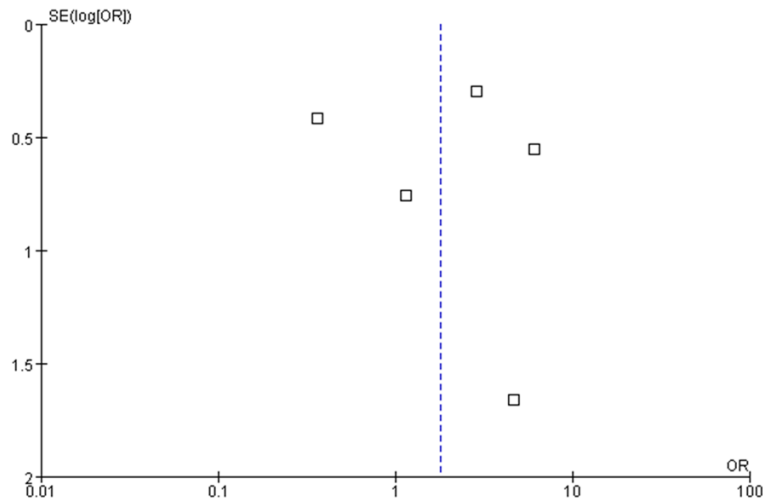


Figure 8. Funnel plot of hypoparathyroidism after operation with experimental group vs. control group.

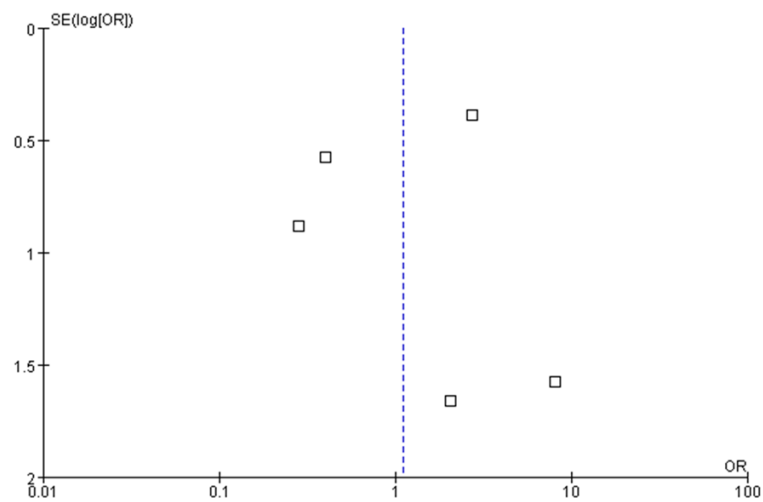


Figure 9. Funnel plot of recurrent laryngeal nerve injury after operation with experimental group vs. control group.

different thyroidectomy in the treatment of differentiated thyroid carcinoma for patients. However, these studies have shown mixed results due to small sample sizes or low statistical power. Thus, we combined 9 studies which including 3343 patients (experimental group: 2201; control group: 1142) were performed in the meta-analysis. The results of this meta-analysis showed that there were significant differences with the recurrence after operation ($OR=0.21$, $95\% CI=0.12$ to 0.39 , $P<0.01$) and the rate of complications after operation ($OR=2.77$, $95\% CI=1.75$ to 4.41 , $P<0.01$) between experimental group and placebo group, sug-

gesting that the recurrence of patients after operation in experimental group may be lower than control group and the rate of complications with patients after operation in experimental group may be higher than control group. The overall meta-analysis also showed that there were no significant differences with the hypoparathyroidism after operation ($OR=1.79$, $95\% CI=0.56$ to 5.69 , $P<0.01$) and the recurrent laryngeal nerve injury after operation ($OR=1.13$, $95\% CI=0.33$ to 3.91 , $P<0.01$) between the two groups, indicating that the rate of hypoparathyroidism and recurrent laryngeal nerve injury after operation of patients in experimental group may be equal to control group.

Patients with differentiated thyroid cancer who have a suspicious recurrent or persistent disease based on an elevated serum thyroglobulin (Tg) or Tg antibodies (TgAb) are usually referred for empiric radioiodine (^{131}I) administration to localize and treat the disease [23]. As for differentiated thyroid carcinoma, lymph nodes are the most common metastatic site for which the major treatment is ^{131}I therapy [2, 24, 25], but

the optimal dose and efficacy of ^{131}I treatment of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases are not well established [26]. Bone metastasis developing after differentiated thyroid carcinoma is common, and in most cases, this condition leads to osteolysis [27]. Elevated blood pressure levels that are associated with hypalgesia and hypothyroidism have major influences on the cardiovascular system [28].

Several limitations of this study should be discussed. First of all, significant between-study heterogeneities of the cancer recurrence, hypo-

parathyroidism and recurrent laryngeal nerve injury events were detected in the current meta-analysis, which may distort the meta-analysis. The degree of heterogeneity is one of the major concerns in meta-analysis for the validity [29], as non-homogeneous data are liable to result in misleading results. Secondly, causes of the sample size of some recruited studies were small (nine), there was still need for more and high-quality studies to test and verify the results of this meta-analysis. Therefore, we minimized the likelihood of bias by developing a detailed protocol before initiating the study, and performed a meticulous search for published studies and used explicit methods for study selection, data extraction and data analysis.

Our study indicated that using total or near-total thyroidectomy in treatment of differentiated thyroid carcinoma may have lower recurrence but higher complications after operation.

Disclosure of conflict of interest

None.

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