

Robotic thyroidectomy versus conventional open thyroidectomy for differentiated thyroid cancer: meta-analysis

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Abstract

Objective: To conduct a meta-analysis to compare the short-term outcomes of robotic thyroidectomy and conventional open thyroidectomy for differentiated thyroid cancer.

Methods: Medline, Embase, Science Citation Index Expanded and the Cochrane Library databases were searched for relevant literature. The evaluated endpoints were intra-operative and post-operative outcomes.

Results: Twelve eligible, non-randomised comparative studies involving 2513 patients were included, with 923 patients in the robotic thyroidectomy group and 1590 patients in the conventional open thyroidectomy group. Meta-analysis results revealed that robotic thyroidectomy was associated with significantly longer operative time and a lower number of retrieved central lymph nodes, as compared with conventional open thyroidectomy. No significant differences were found between robotic thyroidectomy and conventional open thyroidectomy in terms of post-operative outcomes.

Conclusion: Robotic thyroidectomy appears to be a feasible and safe surgical procedure for patients with differentiated thyroid cancer. However, more high-quality randomised clinical trials should be undertaken to confirm these findings.

Key words: Robotics; Thyroidectomy; Thyroid Neoplasms; Meta-Analysis

Introduction

Differentiated thyroid carcinoma is a common malignancy of the thyroid; it is prevalent worldwide but is more common in women.^{1,2} Conventional open thyroidectomy is an effective cure for thyroid cancer; however, it leaves a long conspicuous scar on the anterior of the neck.³ Recent developments in endoscopic thyroidectomy have improved the aesthetic outcome, as no scar is left on the neck.^{4,5} However, endoscopic thyroidectomy is associated with limitations, including a narrow working space on the neck, two-dimensional operative visualisation and inadequate endoscopic instrumentation.^{6–8} Robotic thyroidectomy performed using the da Vinci[®] S surgical robotic system overcomes these limitations by providing hand-tremor filtration technology, a three-dimensional operative view, and multi-articulated and fine instrumentation.^{6,9,10}

Recently, a few studies have reported the applicability of robotic thyroidectomy for thyroid cancer.^{7,11,12} However, the general application of robotic thyroidectomy for malignant thyroid tumours continues to be debated.^{13,14} This is partly because of the small sample size of the studies conducted, which assessed

patients within a single institution, and a lack of definitive evidence about recurrence and survival rates.

To date, three published meta-analyses have reported on the feasibility and safety of robotic thyroidectomy compared to that of conventional open thyroidectomy.^{15–17} However, these meta-analyses included patients with benign and malignant thyroid diseases. No meta-analysis has systematically reviewed the differences between robotic thyroidectomy and conventional open thyroidectomy for differentiated thyroid cancer patients only. Furthermore, since those meta-analysis studies were published, several new studies with greater numbers of participants have been published.^{14,18–20} Thus, a systematic and comprehensive analysis of the published data on robotic thyroidectomy and conventional open thyroidectomy for differentiated thyroid cancer was undertaken to compare the peri-operative outcomes.

Materials and methods

Systematic literature search

In order to compare robotic thyroidectomy with conventional open thyroidectomy for differentiated

thyroid cancer, the databases Medline, Embase, Science Citation Index Expanded and the Cochrane Central Register of Controlled Trials in the Cochrane Library were systematically searched for relevant articles published between January 2003 and May 2014. The following Medical Subject Headings and key words (and the combinations of these headings) were used: 'robotics', 'da Vinci surgical system', 'robotic assisted thyroidectomy', 'robotic thyroidectomy', 'conventional thyroidectomy', 'open thyroidectomy', 'thyroid neoplasms' and 'differentiated thyroid cancer'. Only human studies published in English language with full text descriptions were considered for inclusion. Reference lists from retrieved articles were also examined to identify further relevant studies. The final inclusion of articles was determined by consensus from two reviewers; when this failed, a third author adjudicated.

Inclusion criteria

All included studies fulfilled the following criteria: (1) they compared the outcomes of robotic thyroidectomy with those of conventional open thyroidectomy in differentiated thyroid cancer patients; (2) they clearly documented the operative techniques as 'robotic' or 'conventional open'; and (3) they reported at least one of the outcomes mentioned below. When similar studies were published by the same institution or authors, either the one of higher quality or the most recent publication was included in the analysis.

Exclusion criteria

The following publications were excluded from the analysis: (1) abstracts, case reports, letters, editorials, expert opinions and reviews; (2) studies with no clearly reported outcomes of interest; (3) studies with no control groups; and (4) studies evaluating patients with benign thyroid lesions.

Outcomes measured

Intra-operative and post-operative outcomes were evaluated to compare robotic thyroidectomy and conventional open thyroidectomy. Intra-operative outcomes included operative time and number of retrieved central lymph nodes. Post-operative outcomes included post-operative hospital stay, transient recurrent laryngeal nerve (RLN) palsy, permanent RLN palsy, transient hypocalcaemia, permanent hypocalcaemia, chyle leakage, post-operative suppressed serum thyroglobulin levels and post-operative thyroid stimulating hormone (TSH)-stimulated serum thyroglobulin levels.

Data extraction and quality assessment

Two researchers independently extracted data using standardised forms. Data extracted from each study included patient characteristics, operative details, and post-operative outcomes. The quality of the studies was assessed using the Newcastle–Ottawa Scale,²¹ with some modifications. Specifically, three factors

were examined: patient selection, comparability of the two groups (robotic thyroidectomy and conventional open thyroidectomy) and assessment of outcome. Studies awarded six or more stars were considered as higher quality.²²

Statistical analysis

The meta-analysis was performed using Review Manager software, version 5.0 (Cochrane Collaboration, Oxford, UK). Categorical variables were analysed in terms of odds ratios and corresponding 95 per cent confidence intervals (CIs). Continuous variables were analysed using weighted mean differences and corresponding 95 per cent CIs. The pooled effect was calculated using either a fixed-effects or random-effects model based on heterogeneity. Heterogeneity was measured using the chi-square test and I^2 statistic, with a p value of <0.1 considered significant.²³ If the I^2 statistic was over 50 per cent, the random-effects analysis was performed. Subgroups were used for the sensitivity analysis. Funnel plots were created to evaluate the potential publication bias.

Results

Study characteristics

The search strategy initially identified 176 potentially relevant clinical studies. Twenty-seven articles were selected for further assessment following application of the study criteria. Of these, five studies were published without comparison,^{12,13,24–26} five studies reported benign and malignant tumour cases,^{7,27–30} one study only investigated benign tumour cases,³¹ and two studies included other operations;^{32,33} these studies were excluded from the analysis. In addition, four studies were published by the same institute and had overlapping patient populations,^{18,34–36} only the higher quality studies^{18,35} were included.

A total of 12 studies published between 2010 and 2014 that matched the inclusion criteria were included in this study.^{14,18–20,35,37–43} All 12 studies were non-randomised, controlled trials. A flow chart demonstrating the process of article selection is shown in [Figure 1](#).

The general characteristics of studies included in the meta-analysis are summarised in [Table I](#). The quality assessment results for these 12 studies are presented in [Table II](#).

The 12 studies involved 2513 patients: 923 patients in the robotic thyroidectomy group and 1590 patients in the conventional open thyroidectomy group. In terms of surgical approaches, eight studies were performed using a gasless transaxillary approach,^{14,19,20,37–39,41,42} three studies were performed using a bilateral axillo-breast approach,^{18,40,43} and one study was performed using a gasless unilateral axillo-breast or axillary approach.³⁵ One study focused on robotic modified radical neck dissection for papillary thyroid carcinoma with lateral neck metastasis.¹⁹ Two studies reported on patients with papillary thyroid cancer and follicular thyroid cancer.^{20,39}

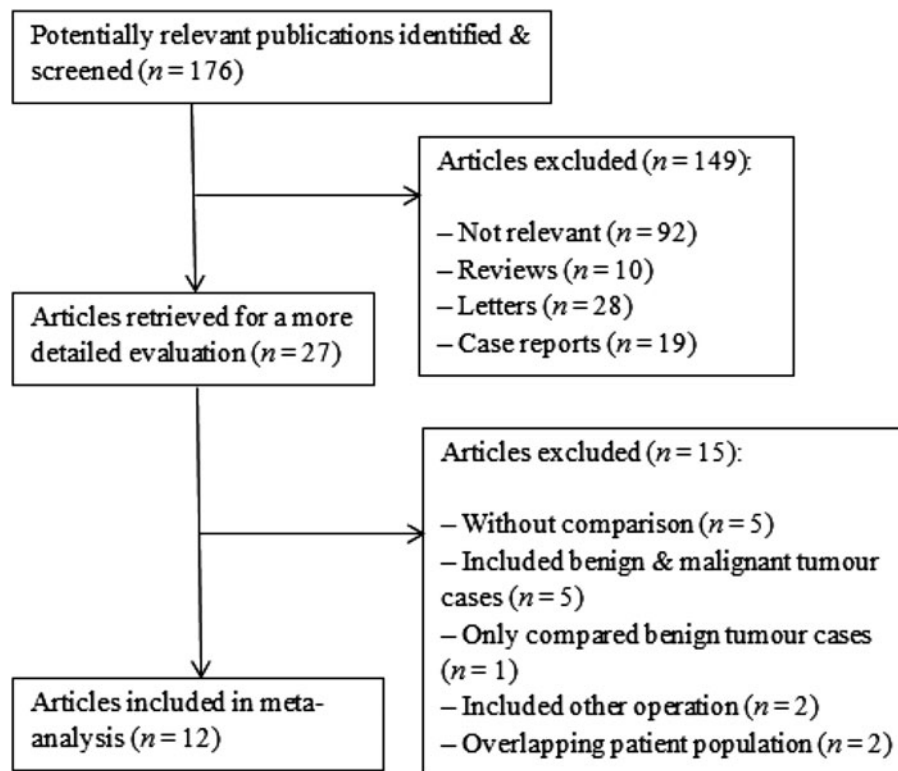


FIG. 1

Flow chart showing the process of article identification and selection.

The patients in the other studies had only papillary thyroid cancer. Eleven studies were performed in Korea^{14,18,19,35,37–43} and one study was carried out in the USA.²⁰

Meta-analysis results

The results of the meta-analysis are summarised in Table III.

Intra-operative outcomes. The operative time was reported in six studies.^{19,20,35,37,40,42} The pooled data revealed that the operative time was significantly longer in the robotic thyroidectomy group than the conventional open thyroidectomy group (weighted mean difference = 53.59, 95 per cent CI = 14.67–92.51, $p = 0.007$), although there was significant heterogeneity between the studies ($I^2 = 99$ per cent) (Figure 2a). The number of retrieved central lymph nodes, reported in five studies,^{14,19,38,39,42} was found to be significantly lower in the robotic thyroidectomy group than in the conventional open thyroidectomy group (weighted mean difference = -0.81 , 95 per cent CI = -1.32 to -0.29 , $p = 0.002$) (Figure 2b).

Post-operative outcomes. With respect to complications, eight studies reported transient RLN palsy,^{18–20,35,37–40} but analysis of the pooled data showed that the two groups (robotic thyroidectomy and conventional open thyroidectomy) did not differ significantly (odds ratio = 1.69, 95 per cent CI = 0.92–3.11, $p = 0.09$)

(Figure 3a). Analysis of the pooled data from the six studies that reported permanent RLN palsy^{19,35,37,38,40,42} again revealed no significant difference between the two groups (odds ratio = 9.84, 95 per cent CI = 0.51–191.70, $p = 0.13$) (Figure 3b). Nine studies reported transient hypocalcaemia,^{18–20,35,37–41} which also did not differ significantly between the two groups (odds ratio = 1.08, 95 per cent CI = 0.87–1.34, $p = 0.49$) (Figure 3c). The pooled data on permanent hypocalcaemia, provided in eight studies,^{18,19,35,37,38,40–42} also revealed no significant difference between the two groups (odds ratio = 1.00, 95 per cent CI = 0.38–2.65, $p = 0.99$) (Figure 3d). No significant differences were seen between the two groups regarding chyle leakage (odds ratio = 1.42, 95 per cent CI = 0.57–3.53, $p = 0.45$) (Figure 3e) or post-operative hospital stay (weighted mean difference = -0.26 , 95 per cent CI = -0.61 – 0.09 , $p = 0.14$) (Figure 3f).

With regard to oncological outcomes, there was no statistically significant difference in either post-operative suppressed serum thyroglobulin levels (weighted mean difference = 0.07, 95 per cent CI = -0.06 – 0.20 , $p = 0.30$) (Figure 4a) or in post-operative TSH-stimulated serum thyroglobulin levels (weighted mean difference = 3.05, 95 per cent CI = -3.17 – 9.27 , $p = 0.34$) (Figure 4b). Three studies reported no tumour recurrences in either the robotic thyroidectomy or conventional open thyroidectomy groups during 12-months' follow up.^{19,35,37} However, significant heterogeneity among the studies was observed for post-operative hospital stay

TABLE I
CHARACTERISTICS OF INCLUDED STUDIES

Study	Year	Country	Study type	Group	Pts (n)	Age ± SD (years)	Male/female (n)	Matching factors*	RT surgical approach
Lee <i>et al.</i> ³⁹	2010	Korea	Prospective	RT	41	39.0 ± 7.0	3/38	1–10	Gasless transaxillary
Lee <i>et al.</i> ⁴³	2011	Korea	Retrospective, matched	COT	43	37.7 ± 6.5	3/40	1–5, 7	Gasless bilateral axillo-breast
				RT	108	43.7 ± 7.4	17/91		
Kim <i>et al.</i> ⁴⁰	2011	Korea	Retrospective	COT	108	43.8 ± 8.8	17/91	–	Gasless bilateral axillo-breast
				RT	69	41.3 ± 7.8	6/63		
Lee <i>et al.</i> ³⁸	2012	Korea	Retrospective	COT	138	51.8 ± 8.9	34/104	3, 4, 7–9	Gasless transaxillary
				RT	192	41.9 ± 9.2	13/179		
Kang <i>et al.</i> ³⁷	2012	Korea	Retrospective	COT	266	48.7 ± 10.8	53/213	2, 4, 5, 8	Gasless transaxillary
				RT	56	35.8 ± 9.1	10/46		
Yi <i>et al.</i> ⁴¹	2013	Korea	Retrospective	COT	109	46.1 ± 13.0	26/83	3–5, 8, 9	Gasless transaxillary
				RT	98	42.15 ± 8.17	–		
Lee <i>et al.</i> ¹⁹	2013	Korea	Prospective	COT	423	51.82 ± 10.53	–	1, 4, 5, 7–10	Gasless transaxillary
				RT	62	40.2 ± 11.8	5/57		
Ryu <i>et al.</i> ⁴²	2013	Korea	Retrospective	COT	66	45.1 ± 12.8	12/54	2, 5, 8, 9	Gasless transaxillary
				RT	45	39.0 ± 7.8	3/42		
Noureddine <i>et al.</i> ²⁰	2013	USA	Retrospective	COT	45	48.9 ± 10.3	9/36	2, 3, 6	Gasless transaxillary
				RT	24	45.4 ± 10.1	4/20		
Lee <i>et al.</i> ¹⁴	2014	Korea	Prospective	COT	35	52.6 ± 12.4	14/21	3–5, 7–9	Gasless transaxillary
				RT	43	39.8 ± 10.2	–		
Kim <i>et al.</i> ¹⁸	2014	Korea	Retrospective	COT	51	48.3 ± 10.6	–	1–4, 6, 7, 10	Gasless bilateral axillo-breast
				RT	123	39.8 ± 9.3	20/103		
Tae <i>et al.</i> ³⁵	2014	Korea	Retrospective	COT	123	38.9 ± 10.1	16/107	3–9	Gasless unilateral axillo-breast or axillary
				RT	62	40.5 ± 69.6	1/61		
				COT	183	51.4 ± 11.3	42/141		

*1 = age, 2 = gender, 3 = tumour size, 4 = multiplicity, 5 = bilateralism, 6 = type of thyroidectomy, 7 = extrathyroidal extension, 8 = tumour classification, 9 = node classification, 10 = tumour–node–metastasis stage. Pts = patients; SD = standard deviation; RT = robotic thyroidectomy; COT = conventional open thyroidectomy

(I² = 88 per cent) and post-operative TSH-stimulated serum thyroglobulin levels (I² = 95 per cent). None of the included studies reported the long-term survival outcome.

Publication bias

A funnel plot of the studies reporting transient RLN palsy is shown in Figure 5. There was no evidence of

publication bias. None of the study findings lay outside the limits of 95 per cent CIs.

Sensitivity and subgroup analysis

Sensitivity analyses were conducted by removing individual studies from the data set. These exclusions did not change the overall results of the analyses. Subgroup analyses were undertaken by including only the higher

TABLE II
QUALITY ASSESSMENT RESULTS*

Study	Quality category (number of stars awarded)			
	Patient selection	Group (RT & COT) comparability [†]	Outcome assessment	Total [‡]
Lee <i>et al.</i> ³⁹	3	3	1	7
Lee <i>et al.</i> ⁴³	2	3	1	6
Kim <i>et al.</i> ⁴⁰	3	1	1	5
Lee <i>et al.</i> ³⁸	3	0	2	5
Kang <i>et al.</i> ³⁷	3	0	2	5
Yi <i>et al.</i> ⁴¹	3	2	2	7
Lee <i>et al.</i> ¹⁹	3	3	2	8
Ryu <i>et al.</i> ⁴²	3	1	2	6
Noureddine <i>et al.</i> ²⁰	3	1	2	6
Lee <i>et al.</i> ¹⁴	3	2	2	7
Kim <i>et al.</i> ¹⁸	3	2	1	6
Tae <i>et al.</i> ³⁵	3	0	2	5

*Quality was assessed using the Newcastle–Ottawa Scale,²¹ with some modifications. [†]Comparability variables include age, tumour size, multiplicity, bilateralism, extrathyroidal extension, type of thyroidectomy and tumour–node–metastasis stage. [‡]Studies awarded six or more stars were considered higher quality.²² RT = robotic thyroidectomy; COT = conventional open thyroidectomy

TABLE III
META-ANALYSIS RESULTS OF INTEREST

Outcome of interest	Studies (n)	Pts (n)	OR/WMD	95% CI	p	I ² (%)
Intra-operative outcomes						
– Operative time (min)	6	894	53.59 (WMD)	14.67 to 92.51	0.007	99
– Number of retrieved central lymph nodes	5	854	–0.81 (WMD)	–1.32 to –0.29	0.002	20
Post-op outcomes						
– Post-op hospital stay (days)	8	1712	–0.26 (WMD)	–0.61 to 0.09	0.14	88
– Transient RLN palsy	8	1592	1.69 (OR)	0.92 to 3.11	0.09	0
– Permanent RLN palsy	6	1293	9.84 (OR)	0.51 to 191.70	0.13	–
– Transient hypocalcaemia	9	2113	1.08 (OR)	0.87 to 1.34	0.49	27
– Permanent hypocalcaemia	8	2060	1.00 (OR)	0.38 to 2.65	0.99	37
– Chyle leakage	5	1479	1.42 (OR)	0.57 to 3.53	0.45	0
Oncological outcomes						
– Post-op suppressed serum thyroglobulin levels (ng/ml)	4	559	0.07 (WMD)	–0.06 to 0.20	0.30	0
– Post-op TSH-stimulated serum thyroglobulin levels (ng/ml)	2	461	3.05 (WMD)	–3.17 to 9.27	0.34	95

Pts = patients; OR = odds ratio; WMD = weighted mean difference; CI = confidence interval; post-op = post-operative; RLN = recurrent laryngeal nerve; TSH = thyroid stimulating hormone

quality studies. Analysis of the higher quality studies showed results that were similar to those of all studies together, except for the cumulative number of retrieved central lymph nodes. The cumulative numbers of retrieved central lymph nodes were comparable between groups (weighted mean difference = –0.48, 95 per cent CI = –1.23–0.27, *p* = 0.21). The results of the sensitivity analyses are summarised in Table IV.

Discussion

Recently, with the improvement of endoscopic apparatus and accumulation of surgical skills, robotic thyroid surgery has gradually been applied to thyroid cancer. However, there seems to be a lack of consensus

regarding oncological safety and surgical completeness.^{44,45} To the best of our knowledge, this is the first meta-analysis to compare robotic thyroidectomy with conventional open thyroidectomy for patients with differentiated thyroid cancer.

The results of this meta-analysis showed that operative time was significantly longer in the robotic thyroidectomy group as compared to the conventional open thyroidectomy group, which can be explained by the extra time needed to prepare the working space and robotic docking.^{7,46,47} This result is consistent with previous studies.^{15–17} We believe that robotic thyroidectomy operative time may decrease with accumulation of the surgeon’s experiences and skills.

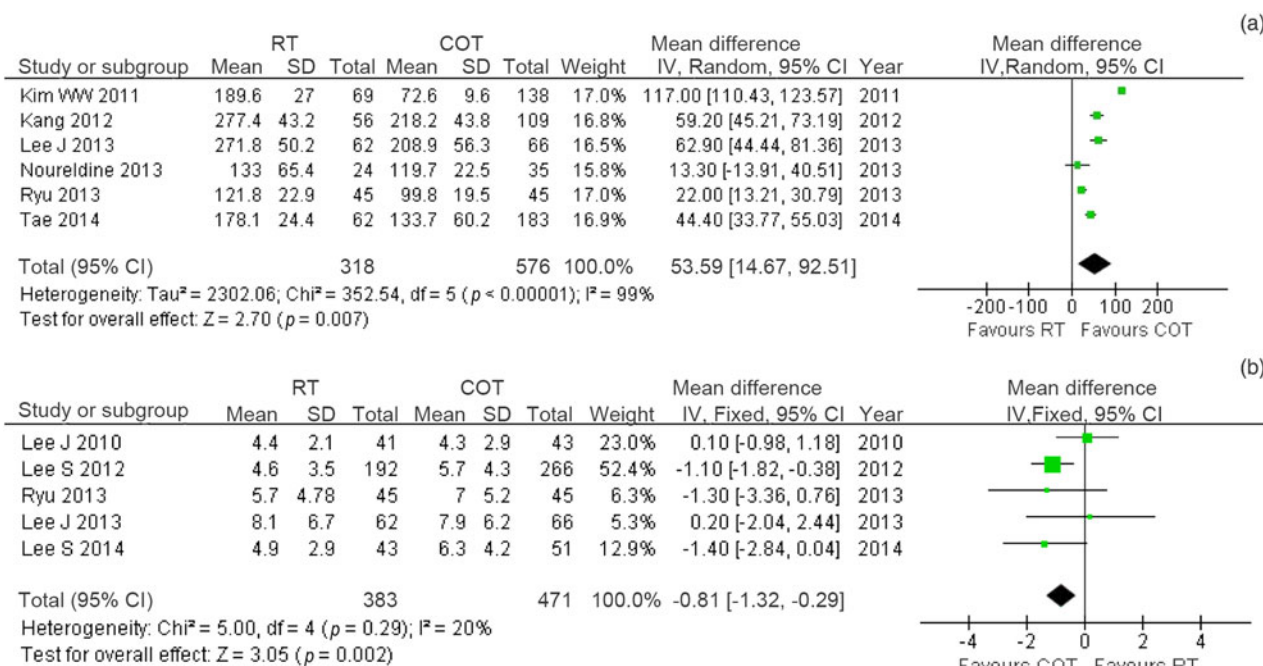


FIG. 2

Forest plots displaying (a) operative time and (b) number of retrieved central lymph nodes, comparing robotic thyroidectomy with conventional open thyroidectomy. RT = robotic thyroidectomy; COT = conventional open thyroidectomy; SD = standard deviation; IV = inverse variance; CI = confidence interval

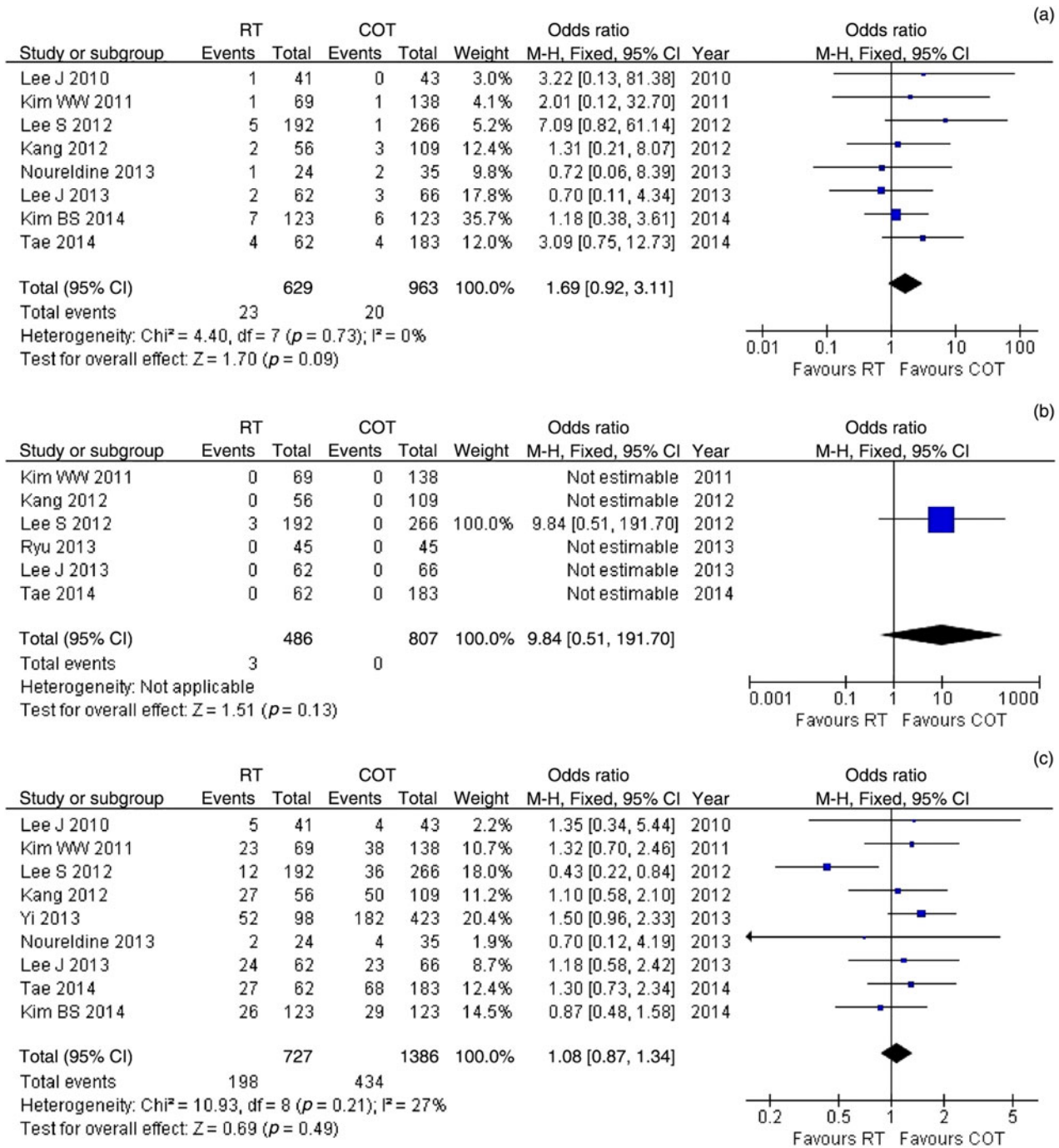


FIG. 3

Forest plots displaying incidences of (a) transient recurrent laryngeal nerve (RLN) palsy, (b) permanent RLN palsy, (c) transient hypocalcaemia, (d) permanent hypocalcaemia and (e) chyle leakage, and (f) duration of post-operative hospital stay, comparing robotic thyroidectomy with conventional open thyroidectomy. RT = robotic thyroidectomy; COT = conventional open thyroidectomy; M-H = Mantel-Haenszel; CI = confidence interval; SD = standard deviation; IV = inverse variance

With regard to lymph node dissection, as one factor of surgical radicalism for malignancy, our results also demonstrated that the robotic thyroidectomy group was associated with significantly fewer retrieved central lymph nodes. This can be attributed to the high degree of patient selection in the robotic thyroidectomy group; in contrast, the conventional open thyroidectomy group comprised more cases of bilateral cancer and multiple central node metastases.³⁸ However, analysis of only

the higher quality studies revealed no significant difference in the number of removed central lymph nodes between the two groups. This indicates that the clearance of central lymph nodes achieved by robotic thyroidectomy is similar to that of conventional open thyroidectomy. We attribute this to the magnified, three-dimensional operative views of the robotic system.¹⁹

The major complications of thyroid surgery are RLN palsy and hypocalcaemia. Our results demonstrate no

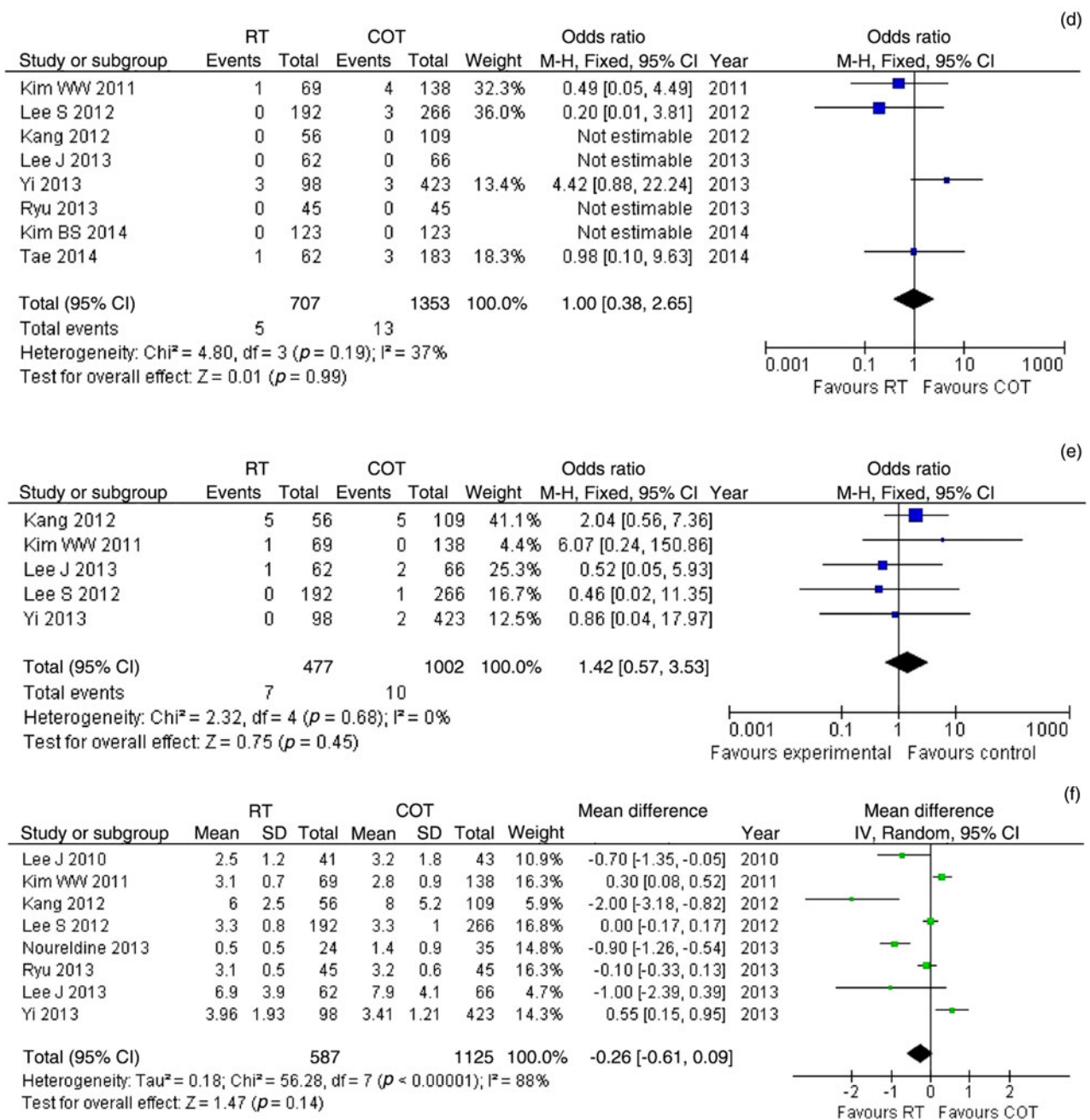


FIG. 3
(continued)

significant differences between the two groups in terms of the incidence rates of transient RLN palsy, permanent RLN palsy, transient hypocalcaemia, permanent hypocalcaemia or chyle leakage. This may largely be a result of the amplified surgical field and excellent apparatus in the robotic system, which enables identification of the RLN, parathyroid gland and thoracic duct.¹⁸

Oncological outcomes following thyroid cancer, such as completeness of thyroid resection and tumour recurrence, are a concern for surgeons. The findings revealed no significant differences between the two groups in terms of post-operative suppressed serum thyroglobulin levels and TSH-stimulated serum

thyroglobulin levels (markers of surgical completeness). This indicates that robotic thyroidectomy can be as complete as conventional open thyroidectomy.⁴⁰ Three studies reported no tumour recurrences during the 12-month follow up.^{19,35,37} However, none of the studies reported on overall long-term survival. There is still insufficient available data on long-term outcomes to adequately investigate tumour-free survival. Randomised, controlled trials with long-term follow up are needed to more precisely evaluate oncological outcomes following thyroid cancer.

Two of the studies in this analysis reported on cosmetic satisfaction and quality of life,^{39,42} but the

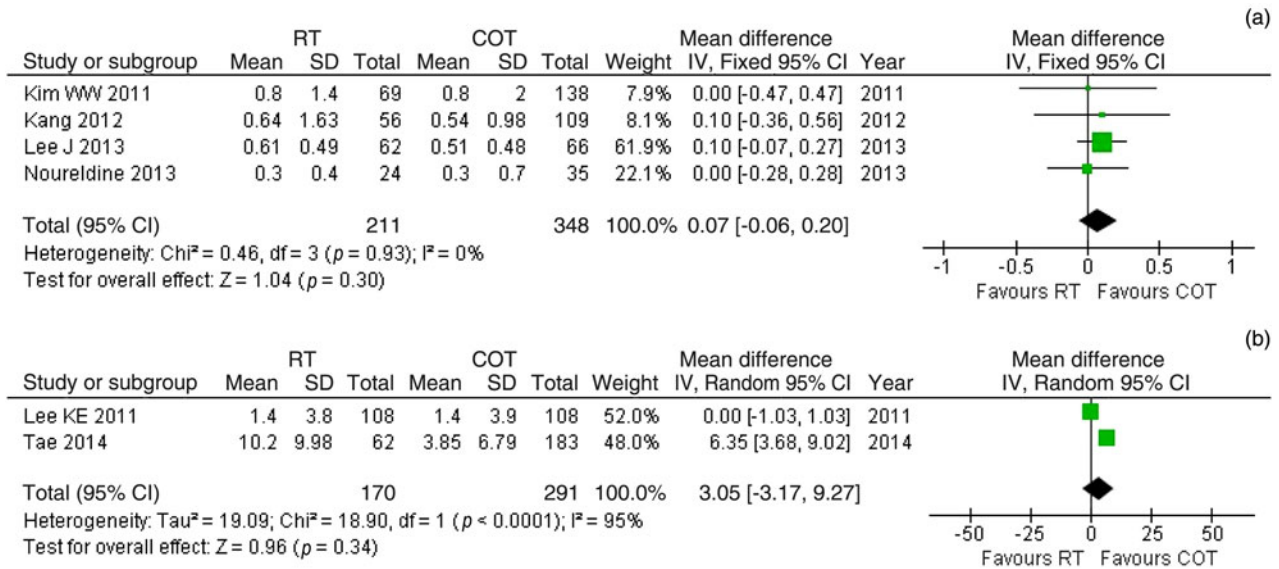


FIG. 4

Forest plots displaying (a) post-operative suppressed serum thyroglobulin levels and (b) post-operative thyroid stimulating hormone stimulated serum thyroglobulin levels, comparing robotic thyroidectomy with conventional open thyroidectomy. RT = robotic thyroidectomy; COT = conventional open thyroidectomy; SD = standard deviation; IV = inverse variance; CI = confidence interval

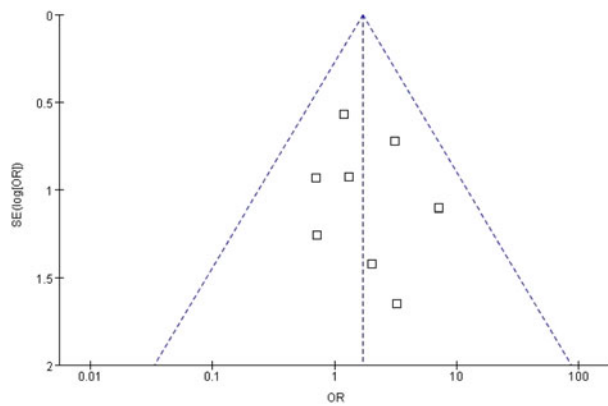


FIG. 5

Funnel plot for transient recurrent laryngeal nerve palsy. SE = standard error; OR = odds ratio

measurements of evaluation were different, making it difficult to pool the results together. Tae *et al.*³⁶ and Lee *et al.*³⁹ found that cosmetic satisfaction was significantly higher in the robotic thyroidectomy group than

in the conventional open thyroidectomy group, because there was no operative scar on the anterior neck and the incision scar in the axilla was almost shaded when the arms were in a natural position.

- **General application of robotic thyroidectomy for malignant thyroid tumours continues to be debated**
- **A meta-analysis was conducted to compare short-term outcomes of robotic thyroidectomy and conventional open thyroidectomy for differentiated thyroid cancer**
- **The results demonstrated that robotic thyroidectomy is feasible and safe for treating patients with differentiated thyroid cancer**

Of course, the meta-analysis has some limitations and hence the results should be interpreted with caution. Firstly, all studies included were non-randomised,

TABLE IV
SENSITIVITY ANALYSIS RESULTS*

Outcome	Studies (n)	Pts (n)	OR/WMD	95% CI	p	I ² (%)
Operative time (min)	3	277	33.21 (WMD)	4.47 to 61.96	0.02	88
Number of retrieved central lymph nodes	4	396	-0.48 (WMD)	-1.23 to 0.27	0.21	17
Post-op hospital stay (days)	5	882	-0.34 (WMD)	-0.91 to 0.22	0.23	88
Transient RLN palsy	4	517	1.07 (OR)	0.46 to 2.49	0.87	0
Transient hypocalcaemia	5	1038	1.21 (OR)	0.89 to 1.64	0.22	0
Permanent hypocalcaemia	4	985	4.42 (OR)	0.88 to 22.24	0.07	-
Chyle leakage	2	649	0.63 (OR)	0.09 to 4.31	0.64	0
Post-op suppressed serum thyroglobulin levels (ng/ml)	2	187	0.07 (WMD)	-0.07 to 0.22	0.32	0

*Only the higher quality studies were analysed. Pts = patients; OR = odds ratio; WMD = weighted mean difference; CI = confidence interval; post-op = post-operative; RLN = recurrent laryngeal nerve

observational clinical studies, which might either overestimate or underestimate the measured effect. Secondly, some heterogeneity was observed in certain results between the two groups. This might be explained by differences in patient selection and surgeons' experiences. Thirdly, we were unable to analyse some other important outcomes, such as cosmetic results and quality of life, because of insufficient data. Finally, the follow-up period was short in all studies, and long-term follow-up data are required to properly evaluate the survival of patients with differentiated thyroid carcinoma who undergo robotic thyroidectomy.

In conclusion, the results of this meta-analysis demonstrate that robotic thyroidectomy is feasible and safe for the treatment of patients with differentiated thyroid carcinoma, although robotic thyroidectomy is not superior to conventional techniques with respect to operative time. Further randomised, controlled trials are needed to confirm the effects of robotic thyroidectomy for differentiated thyroid carcinoma patients.

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