Original Article

A systematic review and meta-analysis comparing surgically-related complications between robotic-assisted thyroidectomy and conventional open thyroidectomy

Running title: Robotic poses higher nerve injury risk

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Keywords: robotic surgery; robotic thyroidectomy; neck dissection; papillary thyroid carcinoma; hypoparathyroidism; recurrent laryngeal nerve

ABSTRACT

Background: Despite gaining popularity, robotic-assisted thyroidectomy (RT) remains controversial. This systematic review and meta-analysis aimed at comparing surgically-related complications between RT and conventional open thyroidectomy (OT).

Methods: A systematic review of the literature was performed to identify studies comparing surgically-related outcome between RT and OT. Studies which compared ≥1 surgically-related outcome between RT and OT were included. Outcomes included operating time, blood loss, complications and hospital stay. Meta-analysis was performed using a fixed-effects model.

Results: Eleven studies were eligible but none were randomized controlled trials. Of the 2375 patients, 839 (35.3%) underwent RT while 1536 (64.7%) underwent OT. RT was significantly associated with longer operating time (p<0.001), hospital stay (p=0.023) and higher temporary recurrent laryngeal nerve (RLN) injury (p=0.016). Although there was no correlation between number of RT reported in the study and rate of temporary RLN injury (ρ=-0.486, p=0.328), routine perioperative laryngoscopy was performed in only 2 of 11 studies. Blood loss (p=0.485), temporary (p=0.333) and permanent hypocalcemia (p=0.599), hematoma (p=0.602), and overall morbidity (p=0.880) appeared comparable. Two (0.2%) brachial plexus injuries in RT were reported in one study.

Conclusions

Relative to OT, RT was associated with significantly longer operating time, longer hospital stay and higher temporary RLN injury rate but comparable permanent complications and overall morbidity. Given some of the limitations with the literature and the potential added surgical risks and morbidity in RT, application of the robot in thyroid surgery should be carefully and

thoroughly discussed before one decides on the procedure.

SYNOPSIS

Relative to cervical open thyroidectomy, robotic-assisted thyroidectomy (RT) was associated with significantly longer operating time, longer hospital stay and higher temporary RLN injury rate but comparable permanent complications and overall morbidity. Therefore, RT should be carefully and thoroughly discussed before one decides on the procedure.

INTRODUCTION

Thyroidectomy is a common surgical procedure and the standard cervical open thyroidectomy (OT) is a safe and effective procedure.[1] However, to improve cosmesis and patient satisfaction, various endoscopic approaches have been developed.[2] Unlike OT, these endoscopic approaches often require making incisions away from the neck so as to leave no visible neck scar.[2,3] In experienced hands, similar outcomes to OT have been reported.[3] However, these endoscopic techniques are generally technically challenging because of the small working space and limitations with current endoscopic instruments.[3] To overcome these problems, a South Korean group pioneered the use of the *da Vinci* robot (i.e. "robotic-assisted thyroidectomy" or RT). Despite higher cost, it offers better manipulations and stereoscopic visual field.[4] Since 2009,[5] there has been much interest both in the US and other parts of the world with several groups publishing their initial successful experience[6-9]. However, despite the initial enthusiasm, RT remains controversial. In October 2011, the FDA in the US revoked the approval on the use of the robot for thyroidectomy.[10] This has led some to abandoning RT and questioning its clinical benefits[10-12]. To date, there has been no randomized trial comparing outcomes between RT and OT and given the current controversies, a multi-center trial is unlikely in the near-future. Although studies have shown similar outcomes between RT and OT, they were mostly single-institution based and might have insufficient statistical power to demonstrate a significant difference. To date, two meta-analyses have been published with one reporting similar outcomes between RT and OT.[13,14] However, some of the included studies came from the same dataset. Given the increasing number of publications on this controversial procedure, we conducted a systematic review and meta-analysis to compare the surgically-related complications between RT and OT.

METHODS

This systematic review and meta-analysis was conducted in accordance with the PRISMA statement.[15]

Search strategy

Studies comparing surgical-related outcomes between patients who underwent RT and OT were retrieved from the Scopus, Medline (PubMed) and Cochrane Library electronic databases on 19th June 2013. We used the following free text search terms in "All fields"

#1: 'robotic thyroidectomy'

#2: 'robotic assisted thyroidectomy'

#3: 'robot thyroidectomy'

#4: #1 OR #2 OR #3

There was no language restriction or methodological filters. The bibliographies of two previous meta-analyses on RT were searched for other additional relevant references.[13,14]

Study selection

All titles identified by the search strategy were independently screened by three authors (BHL, JST, KPW). Search results were compared, and disagreements were resolved by consensus. Abstracts of potentially relevant titles were then reviewed for eligibility and full-length articles were selected for closer examination. Any prospective or retrospective study comparing at least one surgically-related outcome between RT and OT was considered. However, we excluded case reports, editorials, expert opinions, reviews without original data, studies on pediatric population, studies comparing outcomes between RT and endoscopic (i.e. non-robotic) thyroidectomy and studies evaluating patients undergoing concomitant robotic-assisted lateral neck dissection. Surgically-related outcomes include operating time, intraoperative blood loss, recurrent laryngeal nerve (RLN) injury, hypoparathyroidism after total thyroidectomy (TT), hematoma formation, seroma, chyle leakage, pain, nausea / vomiting, flap sensation and cosmetic result. Multiple reports of the same dataset were assessed and the most representative or updated report of a study was included.

Data extraction

All data were extracted onto a standardized form. The primary data extracted from each article included: type or design of study, first authorship, country of origin, year of publication, patient demographics, selection method for RT and OT, weight / size of excised thyroid gland, extent of surgery (TT or less than total thyroidectomy (LTT)), pathology, operating time, volume of blood loss, rate and definition of any surgically-related complications. TT included near-TT, TT and TT with CND whereas LTT included hemithyroidectomy and subtotal thyroidectomy. Operating time was the duration in minutes from skin incision to closure. For studies which had both TT and LTT, only the mean operating time for TT was used. Hypocalcemia rate was calculated by dividing total number of patients with hypocalcemia over total number of TTs. RLN injury rate was calculated in two ways, by dividing total number of injuries over total number of patients or over total number of nerves-at-risk. In TT, two RLNs were considered at risk whereas in LTT, one RLN was considered at risk. For simplicity, the overall morbidity rate was calculated by dividing total number of morbidities over total number of patients and so if one patient suffered from 2 different morbidities, it was counted as two.

Statistical analysis

For comparison of dichotomous variables between RT and OT, chi-square tests and Fisher's exact tests were used. Student t-test was used for comparison of continuous variables. The Pearson's correlation test was used to correlate two continuous variables. All the individual outcomes were integrated with the meta-analysis software Review Manager Software 5.0 (Cochrane Collaborative, Oxford, England). Standardized mean differences (SMD) were calculated for total operating time, volume of blood loss, length of hospital stay and tumor size. Odds ratios (OR) were examined for the other surgical outcomes. Results were aggregated and analyzed using a fixed-effect model. Publication bias was estimated by Begg's rank correlation test and Egger's regression test.[16,17] This meta-analyses were conducted using IBM SPSS Version 20.0 for Window and Comprehensive Meta-Analysis Version 2.2.064 (Biostat, Inc.)

RESULTS

Of the 452 titles initially identified from the database search (Appendix 1), 19 full-length articles were assessed for inclusion. Eight were excluded and 11 studies[18-26] were determined to be eligible for inclusion. Table 1 lists these 8 articles[27-34] and the reason for their exclusion. No additional study was found from our search of the two bibliographies in previous meta-analyses.[13,14]

Patient selection

Ultrasonography was a routine preoperative imaging modality in most studies.[18-24,26,35] The inclusion and exclusion criteria for RT or OT were similar. Inclusions included age between 21–65 years old, malignant tumor size ≤2–4cm, thyroid lobe size ≤6cm and body mass index ≤ 36.[18-26,35,36] Exclusions included previous neck irradiation, presence of lateral lymph node and distant metastases, thyroiditis, Graves' disease and posteriorly located carcinoma.[18,21,22,26] In terms of selection for RT or OT, 3 studies were based on patient preference[18,23,24] while other 8 studies did not specify.[19-22,25,26,35,36] In one study, patients in the OT group were selected in reverse, chronological consecutive order from the time when the robot was first implemented (i.e. historical controls).[19]

Baseline characteristics

Table 2 shows a comparison of the baseline characteristics between the 11 eligible studies (retrospective:9, prospective:2). Of the 2375 patients included, 839 (35.3%) had RT while 1536 (64.7%) had OT. Overall, OT had a significantly higher TT:LTT ratio than RT (p<0.001). Eight studies evaluated outcomes of RT using the trans-axillary approach (TAA)[18-25] while 3 studies evaluated outcomes of RT using the bilateral axillo-breast approach (BABA)[26,35,36]. Of the 11 studies, two originated from the US while the other 9 studies were from South Korea.

Age and sex ratio were matched in 4 studies[18,19,22,36] while the other 7 studies[20,21,23-26,35] had significantly younger patients and a higher female to male ratio in RT. The overall mean age was comparable (*p*=0.173) but the female/male ratio in RT was significantly higher (*p*<0.001). One study [19] reported comparable gland size while the other study[24] reported lighter gland in RT. In terms of pathology, 7 studies[18,20,21,23,24,26,35] comprised DTC only while 2 comprised had both benign and malignant diseases[19,22] and 2 were unknown[25,36]. In the two studies with benign and malignant diseases, the disease ratio in RT and OT were 26/15 and 31/24, respectively.

Surgical outcomes

Table 3 shows a comparison of outcomes between the two groups. Figure 1a shows the forest plot for operating time. The OT group had an overall mean reduced operating time of 55.8 (95%CI= 53.1 – 58.5)mins and this difference was statistically significant (SMD=1.56,95%CI: 1.45 to 1.68,*p*<0.001). The potential publication bias was not significant, as confirmed by the Begg analysis (Kendall's tau= 0.417, *p*=0.118) and the Egger regression test (z=1.052,*p*=0.328). When TAA and BABA were analyzed separately, the mean operating time of RT via TAA was still significantly longer than OT (*p*=0.006) and the same was observed with BABA (*p*=0.021). However, there was no significant difference between the two approaches (*p*=0.120). The overall mean blood loss was comparable (SMD = -0.111,95%CI= -0.421 – 0.200,*p*=0.485). Figure 1b shows the forest plot for hematoma. The rate of hematoma was reported in 8 studies[18-24,26] and was comparable (OR=1.316, 95%CI=0.469 – 3.689, *p*=0.602). Figure 1c and d show the forest plot for overall morbidity and hospital stay. The overall morbidity was comparable (OR=0.981, 95%CI=0.766 – 1.257, *p*=0.880) but hospital stay in RT was significantly longer (SMD=0.123, 95%CI=-0.017 – 0.228, *p*=0.023, respectively).

The definition used for postoperative hypocalcemia and RLN injury for the 11 studies are listed in Appendix 2. Four studies defined permanent hypocalcemia as failure to have postoperative parathyroid hormone and/or adjusted serum calcium normalized within 6 months.[21,22,24,26] Figure 2a and 2b show forest plots for temporary and permanent hypocalcemia. Of the 11 studies, 6 studies[18,20-22,24,26] reported their temporary postoperative hypocalcemia rate while 7 studies[18,20-24,26] reported permanent postoperative hypocalcemia rate. Assuming they adopted similar definitions of hypocalcemia, the overall temporary and permanent hypocalcaemia in RT were comparable to OT (OR=1.159, 95%CI=0.859 – 1.564, *p*=0.333 and OR=1.325, 95%CI=0.464 – 3.782, *p*=0.599, respectively).

The definition for temporary and permanent RLN injury also varied between studies (see appendix 2). Three studies[18,21,26] defined permanent RLN injury as persistent impairment in vocal cord function > 6-month. Routine perioperative laryngoscopy was performed in only 2 studies[18,21] while selective laryngoscopy was reported in 2 other studies[24,26]. Figure 2c and 2d show forest plots for temporary and permanent RLN injury. The cumulative temporary RLN injury rate in RT was significantly higher (OR=2.444; 95%CI=1.178 – 5.068, *p*=0.016). Potential publication bias did not appear significant, as confirmed by the Begg analysis (Kendall's tau=0.001, *p*=1.000) and the Egger regression test (z=0.437, *p*=0.685). Even after excluding one study with <40 RT cases[19], temporary RLN remained significantly higher in RT (*p*=0.010). When the cumulative temporary RLN injury was calculated based on number of nerves-at-risk, the rate became even more significant (OR=2.833, 95%CI=1.371 – 5.855, *p*=0.005). To see if this was a case-volume dependent phenomenon, the number of RT cases reported was correlated with temporary RLN injury rate. However, there was no significant correlation between the number of RT cases reported and temporary RLN injury observed (ρ=-0.486, *p*=0.328). The cumulative permanent RLN injury was comparable (OR=1.641; 95%CI=0.268 – 10.026, p=0.592).

Other reported outcomes

Postoperative voice quality and swallowing sensation were compared and one study found that RT had significantly less swallowing complaints at 1- and 3-month than OT.[18] Despite the more extensive tissue dissection, two studies reported similar pain score at 1-week, 1-month and 3-month.[18,21] Chest paresthesia was significantly worse initially in RT but normalized after 3 months.[18,21] Postoperative nausea/vomiting was significantly less in RT in one study[25] but two brachial plexus injuries in TAA/RT were reported in another study[19]. Ipsilateral shoulder discomfort after TAA was reported in 12.2% of patients at one week.[19] RT had better cosmetic result and higher patient satisfaction in two studies.[19] One study evaluated the effect of CO2 insufflation on intraoperative pressure (IOP) in BABA and found the CO2 insufflation increased IOP significantly when compared to OT.[36]

DISCUSSION

Despite gaining immense interest in the surgical community and wide-acceptance in South Korea, RT remains a controversial procedure in the West.[10-12] Apart from the higher initial cost, the issue of safety has been questioned.[10-12] However, due to the relatively small and few studies comparing outcomes between RT and OT, it is unclear whether the two are equivalent in terms of safety. To our knowledge, this is the largest and most comprehensive meta-analysis comparing outcomes between RT and OT. Unlike previous meta-analyses, to avoid data duplication, studies which utilized the same dataset were excluded.

Despite being a very good risk group due the exclusion criteria, RT required a significantly longer operating time than OT and this was irrespective of which of the two robotic approaches (TAA or BABA). The overall operating time was prolonged by an average of 55.8minutes which was slightly longer than the one observed in a recent cost comparison[31]. This is attributed to the need for a more extensive skin flap preparation and docking of the robot. More interesting was that, for the first time, we showed that RT was associated with significantly greater risk of temporary RLN injury than OT. The temporary RLN injury rate in RT was almost 3 times that of OT (3.8% vs. 1.3%, p=0.016) and this became even more significant when it was calculated based on number of nerves-at-risk (2.5% vs. 0.7%, p=0.005). Since this could potentially be related to both the surgeon's experience and case-volume, we performed two further analyses. In the first analysis, we excluded one study[19] which had <40 RT cases as this may represent an early part of the learning curve[37]. However, the cumulative temporary RLN injury rate remained significantly higher in RT (2.9% vs. 1.0%, p=0.010). Even when the pooled result came exclusively from several high-volume South Korean centers, the temporary RLN injury in RT was still significantly higher. The second analysis was to see if there was a correlation between the number of cases performed and the rate of temporary RLN injury. We correlated the number of RT cases reported in each study and the number of temporary RLN injury observed. However, we could not find any significant correlation (ρ=-0.486, p=0.328). These findings meant that the higher temporary RLN injury was probably independent of experience or higher case-volume per se. The reason for the higher temporary RLN injury in RT remains unexplained but since higher permanent RLN injury was not observed, it may have been caused by mild traction injury. It is also worth noting that RT represents a very different anatomic approach from OT and so traction injury risk might be higher. Other surgically-related outcomes such as blood loss, hypocalcemia, hematoma and overall morbidity were comparable. Although there were three reports of brachial plexus injury after TAA/RT, it may be potentially preventable by positioning the arm with the patient awake.[19,38,39] Other outcomes such as pain, paresthesia, nausea and vomiting, cosmesis and voice/swallowing quality were difficult to assess as there are few well-accepted tools available.

However, despite these findings, our data should be interpreted cautiously because all 11 eligible studies were non-randomized and so were subjected to selection biases. Fewer TT and lighter excised gland could potentially have favored RT. Furthermore, only 2 studies reliably assessed postoperative RLN injury by routine laryngoscopy. Since OT has been well-established many years before RT, our study might also represent a comparison of two different learning curves and due to the lack of data on complication trend, learning curve was not properly accounted for.

Conclusion

RT was associated with a significantly longer operating time, longer hospital stay and higher risk of temporary RLN injury than OT but appeared to have comparable permanent complications and overall morbidity as OT. Given the lack of standardization on complications with the current literature and the potential added surgical risks and morbidity of RT, application of the robot in thyroid surgery should be carefully and thoroughly discussed before one decides on the procedure. Further prospective studies are required to confirm our findings.

ACKNOWLEDGMENTS

None

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

BHH Lang / CKH Wong / JS Tsang / KP Wong / KY Wan were involved in the review of literature, acquisition of data and drafting and completing the manuscript. BHH Lang / CKH Wong / JS Tsang were also involved in the review of literature and drafting the manuscript. BHH Lang / CKH Wong / JS Tsang / KP Wong conceived the study, participated in the co-ordination and the acquisition of data and helped to draft the manuscript. All authors read and approved the final manuscript.

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Table 1. The eight articles which were excluded after reviewing the full-length text

First Author	Journal	Publication year, country	Title	Main reason for exclusion
Kang[27]	Surgical Endoscopy	2009, Korea	Robot-assisted endoscopic surgery for thyroid cancer: experience with the first 100 patients	Data from this study were included in a later study[20]
Lee[28]	Annals of Surgical Oncology	2011, Korea	Multicenter study of robotic thyroidectomy: short-term postoperative outcomes and surgeon ergonomic considerations.	There was no open thyroidectomy group for comparison.
Tae[29]	Surgical Endoscopy	2011, Korea	Robotic thyroidectomy by a gasless unilateral axillo-breast or axillary approach: our early experience	Data from this study were included in a later study[21]
Broome[30]	Archives of Surgery	2012, USA	Expense of robotic thyroidectomy: a cost analysis at a single institution	This study did not compare outcomes between robotic and open approaches
Cabot[31]	Surgery	2012, USA	Robotic and endoscopic transaxillary thyroidectomies may be prohibitive when compared to standard cervical thyroidectomy: a cost analysis	This study did not compare outcomes between robotic and open approaches
Foley[32]	Surgical Endoscopy	2012, USA	Robotic transaxillary endocrine surgery: a comparison with conventional open technique	Data from this study were included in a later study[22]
Lee[33]	Annals of Surgical Oncology	2012, Korea	Postoperative functional voice changes after conventional open or robotic	Data from this study were included in an earlier but

			thyroidectomy: a prospective trial	more representative study[18]
Tae[34]	Surgical Endoscopy	2012, Korea	Functional voice and swallowing outcomes after robotic thyroidectomy by a gasless unilateral axillo-breast approach: comparison with open thyroidectomy	Data from this study were included in a later study[21]

Table 2. A comparison of patient characteristics between robotic assisted thyroidectomy (RT) and open thyroidectomy (OT). Studies were grouped according to robotic approaches.

First author (year)	**Study design**	**Number of patients**				**Mean age (±SD) (yrs)**		**Sex ratio (Male:Female)**		**Weight / size of gland**	**Final pathology**		**Match between RT and OT**
		RT		**OT**		**RT**	**OT**	**RT**	**OT**		**Benign**	**Malign.**	
		TT	**LTT**	**TT**	**LTT**								
Trans-axillary approach (TAA)													
Lee (2010)[18]	RS	26	15	26	17	39.0 ± 7.0	37.7 ± 6.5	3:38	3:40	NR	RT=0 OT=0	RT=41 OT= 43	1,2,5,6
Landry (2012)[19]	RS	0	25	0	25	*50 (22 -62)	*53(24 -75)	2:23	4:21	RT=OT	RT= 21 OT= 22	RT=4 OT=3	1-6
Lee (2012)[20]	RS	27	165	90	176	41.9 ± 9.2	48.7 ± 10.8	13:179	53:213	NR	RT=0 OT=0	RT=192 OT=266	5
Tae (2012)[21]	RS	29	46	204	22	39.6 ± 8.9	51.0 ± 12.5	5:70	37:189	NR	RT=0 OT=0	RT=75 OT=226	5,6
Aliyev (2013)[22]	RS	16	0	30	0	48 ± 4	51 ± 3	0:16	2:28	NR	RT=5 OT=9	RT=11 OT=21	1-3,5,6
Ryu (2013)[23]	RS	45	0	45	0	39.0 ± 7.8	48.9 ± 10.3	3:42	9:36	NR	RT=0 OT=0	RT=45 OT=45	2,5,6
Yi (2013)[24]	RS	98	0	423	0	42.2 ± 8.2	51.8 ± 10.5	0:98	0:423	OT>RT	RT=0 OT=0	RT=98 OT=423	2,4-6

Yoo (2013)[25]	PS	65	20	68	17	39.2 ± 7.1	44.8 ± 8.0	0:85	0:85	NR	NR	NR	2
TAA overall	-	306	271	886	257	41.0 ± 8.3	49.7 ± 10.6	26:551	108:1035	-	RT=26 OT=31	RT=466 OT=1027	-
Bilateral Axillo-Breast Approach (BABA)													
Kim (2011)[26]	PS	69	0	138	0	41.3 ± 7.8	51.8 ± 8.9	6:63	34:104	NR	RT=0 OT=0	RT=69 OT=138	5,6
Lee (2011)[35]	RS	174	0	237	0	39.9 ± 8.8	51.1 ± 11.1	20:154	50:187	NR	RT=0 OT=0	RT=174 OT=237	5,6
Kim (2013)[36]	RS	13	6	12	6	41.4 ± 6.0	43.5 ± 6.7	0:19	2:16	NR	NR	NR	1-3,6
BABA subtotal	-	256	6	387	6	40.4 ± 8.4	51.0 ± 10.2	26:236	86:307	-	RT=0 OT=0	RT=243 OT=375	-
Overall	-	562	277	1273	263	40.8 ± 8.3	50.0 ± 10.5	52:787	194:1342	-	RT=26 OT=31	RT=709 OT=1402	-

Matching: 1 = age; 2 = sex; 3 = body mass index (BMI); 4 = weight of excised thyroid gland; 5 = final pathology; 6 = extent of thyroidectomy

*median (range)

Abbreviations: PS = prospective study; RS = retrospective study; NR = not reported; TT = total thyroidectomy; LTT = less than total thyroidectomy

Table 3. A comparison of surgical outcomes between robotic-assisted thyroidectomy (RT) and open thyroidectomy (OT). Studies were grouped according to robotic approaches.

First author (year)	**Operating time (mins)**	**Blood loss (mls)**	**Hypocalcemia# (%)**		**RLN injury (%)**		**Hematoma + (%)**	**Overall morbidity ^ (%)**	**Other reported outcomes**	**Hospital stay (days)**
			Temp	**Perm**	**Temp**	**Perm**				
Trans-axillary approach (TAA)										
Lee (2010)[18]	RT=128.6 ± 36.3 OT=98.0 ± 22.2	RT=3.5 ± 3.0 OT=4.9 ± 3.6	RT=5 (19.2) OT=4 (15.3)	RT=0 (0.0) OT=0 (0.0)	RT=1 (2.4) OT=0 (0.0)	RT=0 (0.0) OT=0 (0.0)	RT=0 (0.0) OT=1 (2.3)	RT=8 (19.5) OT=7 (16.3)	Voice, pain, cosmesis, swallowing, sensation	RT=2.5 ± 1.2 OT=3.2 ± 1.8
Landry (2012)[19]	*RT=121 (74 – 199) *OT=68 (41 – 112)	*RT=10 (0-150) *OT=0 (0 – 25)	NR	NR	RT=5 (20.0) OT=4 (16.0)	RT=0 (0.0) OT=1 (4.0)	RT=3 (12.0) OT=1 (4.0)	RT=15 (60.0) OT=10 (40.0)	Brachial plexus injury	NR
Lee (2012)[20]	RT=148.8 ± 29.9 OT=98.0 ± 46.0	NR	RT=12 (44.4) OT=36 (40.0)	RT=0 (0.0) OT=3 (3.3)	RT=5 (2.6) OT=1 (0.4)	RT=3 (1.6) OT=0 (0.0)	RT=0 (0.0) OT=1 (0.4)	RT=24 (12.5) OT=45 (16.9)	Oncological outcome	RT=3.3 ± 0.8 OT=3.3 ± 1.0
Tae (2012)[21]	RT=168 ± 42.5	NR	RT=8 (27.6)	RT=0 (0.0)	RT=6 (8.0)	RT=0 (0.0)	RT=2 (2.7) OT=5 (2.2)	RT=22 (29.3)	Pain, cosmesis,	RT=6.1 ± 1.8

	OT=133 ± 46.6		OT=112 (54.9)	OT=4 (2.0)	OT=7 (3.1)	OT=1 (0.4)		OT=143 (63.3)	flap sensation	OT=5.9 ± 2.5
Aliyev (2013)[22]	RT=183 ± 11 OT=139 ± 8	RT=11 ± 2 OT=12 ± 1	RT=2 (12.5) OT=3 (10.0)	RT=0 (0.0) OT=1 (3.3)	NR	NR	RT=1 (6.3) OT=0 (0.0)	RT=3 (18.8) OT=4 (13.3)	Pain, oncological outcome	RT=1.1 ± 0.1 OT=1.1 ± 0.1
Ryu (2013)[23]	RT=121.8 ± 22.9 OT=99.8 ± 19.5	NR	NR	RT=0 (0.0) OT=0 (0.0)	NR	RT=0 (0.0) OT=0 (0.0)	RT=0 (0.0) OT=0 (0.0)	RT=0 (0.0) OT=0 (0.0)	Pain, shoulder discomfort	RT=3.1 ± 0.5 OT=3.2 ± 0.6
Yi `(2013)[24]	RT=175.8 ± 33.7 OT=99.2 ± 20.9	NR	RT=52 (53.1) OT=182 (43.0)	RT=3 (3.1) OT=3 (0.7)	RT=1 (1.0) OT=2 (0.5)	NR	RT=0 (0.0) OT=2 (0.5)	RT=61 (62.2) OT=194 (45.9)	Oncological outcome	RT=4.0 ± 1.9 OT=3.4 ±1.2
Yoo (2013)[25]	RT=122.3 ± 33.1 OT=101 ± 27.3	NR	NR	NR	NR	NR	NR	NR	First 24-hour nausea and vomiting, pain	NR
TAA overall	RT=149.4 ± 32.7 OT=106.9 ±	RT=5.9 ± 2.6 OT=7.4	RT=79 (40.3) OT=337	RT=3 (1.2) OT=11	RT=18 (4.2) OT=14	RT=3 (0.8) OT=2	RT=6 (1.2) OT=10 (0.9)	RT=133 (27.0) OT=403	-	RT=3.7 ± 1.3 OT=3.8 ±

	34.7	± 3.0	(43.6)	(1.3)	(1.4)	(0.3)		(38.1)		1.5
Bilateral Axillo-Breast Approach (BABA)										
Kim (2011)[26]	RT=196 ± 45 OT=81 ± 16	NR	RT=23 (33.3) OT=38 (27.5)	RT=1 (1.4) OT=4 (2.9)	RT=1 (1.4) OT=1 (0.7)	RT=0 (0.0) OT=0 (0.0)	RT=0 (0.0) OT=0 (0.0)	RT=29 (42.0) OT=45 (32.6)	Drain output, oncological outcome	RT=3.1 ± 0.7 OT=2.8 ± 0.9
Lee (2011)[35]	NR	NR	NR	NR	NR	NR	NR	NR	Surgical completeness , oncological outcome	NR
Kim (2013)[36]	RT=174.2 ± 38.7 OT=98.3 ± 44.7	RT=29.7 ± 11.1 OT=33. 6 ± 30.7	NR	NR	NR	NR	NR	NR	Intraocular pressure	NR
BABA overall	RT=191.3 ± 43.8 OT=83.0 ± 21.2	RT=29.7 ± 11.1 OT=33. 6 ± 30.7	RT=23 (33.3) OT=38 (27.5)	RT=1 (1.4) OT=4 (2.9)	RT=1 (1.4) OT=1 (0.7)	RT=0 (0.0) OT=0 (0.0)	RT=0 (0.0) OT=0 (0.0)	RT=29 (42.0) OT=45 (32.6)		RT=3.1 ± 0.7 OT=2.8 ± 0.9
Overall	RT=155.2 ± 34.4 OT=104.0	RT=11.8 ± 6.0 OT=12.	RT=102 (38.5) OT=375	RT=4 (1.3) OT=15	RT=19 (3.8) OT=15	RT=3 (0.7) OT=2	RT=6 (1.1) OT=10 (0.8)	RT=162 (28.9) OT=448		RT=3.7 ± 1.2 OT=3.7 ±

		6 ± 13.8	(41.2)	(1.6)	(1.3)	(0.3)		(37.5)		1.5

Abbreviations: NR = not reported; RLN = recurrent laryngeal nerve; temp = temporary; perm = permanent

*only median (range) was provided

only total thyroidectomy was analyzed

^a sum of all complications including hypocalcemia, RLN injury, hematoma, seroma, infection, burn, brachial plexus injury and chyle leakage within that group

+with or without re-exploration

Figure 1a

Operating time

1st author & year	RT mean	RT SD	OT mean	OT SD	Statistics for each study: Std diff in means	Lower limit	Upper limit	p-Value
Lee (2010)	128.6	36.3	98.0	22.2	1.02	0.57	1.48	0.00
Lee (2012)	148.8	29.9	98.0	46.0	1.27	1.07	1.47	0.00
Tae (2012)	168.0	42.5	133.0	46.6	0.77	0.50	1.04	0.00
Aliyev (2013)	183.0	11.0	139.0	8.0	4.82	3.66	5.97	0.00
Ryu (2013)	121.8	22.9	99.8	19.5	1.03	0.59	1.47	0.00
Yi (2013)	175.8	33.7	99.2	20.9	3.22	2.92	3.51	0.00
Yoo (2013)	122.3	33.1	101.0	27.3	0.70	0.39	1.01	0.00
Kim (2011)	196.0	45.0	81.0	16.0	3.96	3.48	4.44	0.00
Kim (2013)	174.2	38.7	98.3	44.7	1.82	1.05	2.59	0.00
					1.56	1.45	1.68	0.00

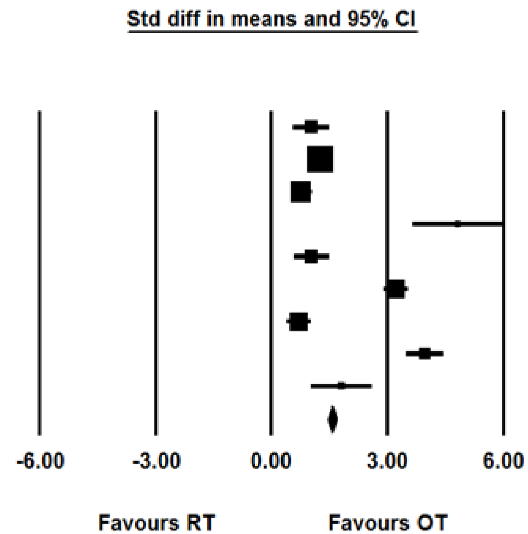

Figure 2c

Temporary RLN injury

1st author & year	Temp RLN Injury / Total: RT	OT	Statistics for each study: Odds ratio	Lower limit	Upper limit	p-Value
Lee (2010)	1 / 41	0 / 43	3.222	0.128	81.383	0.478
Landry (2012)	5 / 25	4 / 25	1.313	0.308	5.598	0.713
Lee (2012)	5 / 192	1 / 266	7.086	0.821	61.144	0.075
Tae (2012)	6 / 75	7 / 226	2.720	0.885	8.367	0.081
Yi (2013)	1 / 98	2 / 423	2.170	0.195	24.176	0.529
Kim (2011)	1 / 69	1 / 138	2.015	0.124	32.704	0.622
			2.444	1.178	5.068	0.016

Odds ratio and 95% CI