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Clinical Research

Meta-Analysis of Limited Thymectomy versus Total Thymectomy for Masaoka Stage I and II Thymoma

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Background: This meta-analysis aimed to evaluate the incidence of tumor recurrence, postoperative myasthenia gravis, postoperative complications, and overall survival after limited versus total thymectomy for Masaoka stage I and II thymoma.
Methods: A systematic search of the literature was conducted using the PubMed, Embase, MEDLINE, and Cochrane databases to identify relevant studies that compared limited and total thymectomy in Masaoka stage I–II patients. The quality of the included observational studies was assessed using the Newcastle-Ottawa Scale. The results of the meta-analysis were expressed as log-transformed odds ratios (log ORs), with 95% confidence intervals (CIs).
Results: Seven observational studies with a total of 2,310 patients were included in the meta-analysis. There was an overall non-significant difference in favor of total thymectomy in terms of tumor recurrence (pooled log OR, 0.40; 95% CI, -0.07 to 0.87; p=0.10; I^2=0%) and postoperative myasthenia gravis (pooled log OR, 0.12; 95% CI, -1.08 to 1.32; p=0.85; I^2=22.6%). However, an overall non-significant difference was found in favor of limited thymectomy with respect to postoperative complications (pooled log OR, -0.21; 95% CI, -1.08 to 0.66; p=0.64; I^2=36.1%) and overall survival (pooled log OR, -0.01; 95% CI, -0.68 to 0.66; p=0.98; I^2=47.8%).
Conclusion: Based on the results of this systematic review and meta-analysis, limited thymectomy as a treatment for stage I and II thymoma shows similar oncologic outcomes to total thymectomy.

Keywords: Limited thymectomy, Total thymectomy, Meta-analysis, Masaoka-Koga stage I & II thymoma

Introduction

Thymoma, which is the most common anterior mediastinal tumor, arises from thymic epithelial cells [1]. It usually exhibits an indolent growth pattern, but has the potential for aggressive transformation with local invasion and pleural dissemination [2]. The prognosis of these tumors is directly related to their stage at presentation and the completeness of surgical resection with negative margins [3]. Open trans-sternal thymectomy has been the standard approach for thymoma resection [4]. However, in recent years, minimally invasive methods such as video-assisted thoracoscopic surgery and robotic-assisted thymectomy have been advocated, with proven benefits [5,6]. In cases where thymoma is associated with myasthenia gravis (MG), extended thymectomy is the surgical choice to remove the "germinal centers" in the surrounding thymus gland, which play a major role in the pathogenesis of MG [7]. However, the extent of resection is a topic of debate, particularly for non-myasthenic stage I and II thymoma. Many authors have argued that the extent of surgery for thymoma should be total thymectomy, defined as resection of the tumor en bloc with the remnant gland, surrounding fatty tissue in the mediastinum, and bilateral pericardial fat pads, with dissection into the neck up to the thyro-thymic ligament [8]. Proponents of total thymectomy claim any less extensive surgery to be a "non-anatomical resection,"

which is against the principles of oncological resection, elevates the rate of loco-regional recurrence [9], and also increases the incidence of postoperative MG (POMG) [10]. However, a few authors have questioned the need for total thymectomy and have proposed thymomectomy/partial thymectomy for stage I and II thymomas [11], claiming oncologic equivalence.

No randomized controlled trials have evaluated the validity of thymomectomy. Nevertheless, several observational studies have assessed the efficacy and safety of thymomectomy/partial thymectomy [12-17]. Propensity score matching was used by some authors to address the issue of selection bias, in view of the retrospective nature of these studies [18,19]. Although most reports suggested no difference between total thymectomy and partial thymectomy, multi-institutional studies with large numbers of patients revealed a higher local recurrence rate after partial thymectomy, particularly for stage II disease, which is difficult (if not impossible) to assess preoperatively [20]. Therefore, the currently available evidence to address the research question is inadequate, which limits the applicability of limited thymectomy in clinical decision-making and day-to-day practice. Hence, this meta-analysis was initiated to assess and interpret the evidence base with adequate power, to determine whether limited thymectomy is an adequate/safer option for stage I and II thymoma in comparison to total thymectomy.

Methods

Literature search strategy

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. The studies were selected and identified by electronic searches of various databases (PubMed, Google Scholar, Embase, MEDLINE, and the Cochrane Database of Systemic Reviews) from the date of their inception until April 2020. The search terms/key words used were a combination of "thymomectomy" OR "limited thymectomy" OR "partial thymectomy" AND "total thymectomy" OR "extended thymectomy" OR "radical thymectomy" OR "thymothymectomy" AND "thymoma" OR "thymic neoplasms." Only articles that were published in English were considered for review in this meta-analysis. The references of all the retrieved articles were also reviewed to identify more relevant studies.

Study selection

The inclusion criteria for studies to be eligible for this meta-analysis included (1) comparative studies in which patients underwent limited thymectomy or total thymectomy by open or minimally invasive methods for thymoma; (2) studies with patients who had Masaoka stage I and II thymoma; (3) studies with patients who had not previously received treatment for thymoma; (4) studies with outcomes including tumor recurrence, occurrence of POMG, overall survival, and postoperative complications; and (5) studies on human subjects.

The exclusion criteria were (1) individual case reports, (2) review articles, (3) editorials and expert opinions lacking presentation of original data, (4) studies/trials that lacked a control cohort, and (5) studies that reported no/unclear outcomes of interest.

Data extraction and critical appraisal of evidence

All data required for the meta-analysis were extracted from the articles' tables, texts, and figures. One investigator (M.V.P.) independently reviewed each included article under the supervision of 2 senior investigators (A.K., B. B.A.). Any discrepancies regarding interpretation of data were discussed in detail and resolved. The analyzed data included the first author, year of publication, total number of patients included in the study, country of origin of the study, interventions done, the total duration of follow-up, tumor recurrence, the occurrence of POMG, postoperative complications, and overall survival.

Statistical analysis

Statistical analysis was carried out using Stata ver. 14.0 (Stata Corp., College Station, TX, USA). Depending on the presence or absence of significant statistical heterogeneity, the meta-analysis was performed using a random-effects or fixed-effects model. Heterogeneity among studies was evaluated by the I^2 test [22]. If the I^2 statistic value was between 0% and 25%, heterogeneity was interpreted as absent. An I^2 value was considered to indicate low heterogeneity if it was between 25% and 50%, moderate heterogeneity if it was between 50% and 75%, and high heterogeneity if it was between 75% and 100% [23]. A random-effects model was used if heterogeneity was confirmed, while a fixed-effects method was used in the absence of statistically significant heterogeneity [24]. Log-transformed odds ratios (ORs) was used to represent dichotomous data. For each estimate, 95%

confidence intervals (CIs) were calculated and presented in forest plots. All p-values were 2-sided. A p-value less than 0.05 was considered to indicate a significant difference.

Assessment and evaluation of quality of evidence and publication bias

Since all of the eligible studies were observational studies, the Newcastle-Ottawa Scale (NOS) was used to assess the quality of evidence of each individual study [25]. Quality was evaluated through an assessment of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration of the outcome of interest, comparability of cohorts based on the design or analysis, assessment of the outcome, and the length and adequacy of follow-up. Depending on these factors, each study was assigned a score of 0–9. Studies with a score ≥7 were considered to be high-quality articles. The risk of publication bias was assessed by asymmetry in funnel plots.

Ethical considerations

The study was approved by the institutional ethics review board of Sir Ganga Ram Hospital, New Delhi (IRB approval no., SGR/12/2020).

Results

Literature search

A total of 117 studies were identified through all database searches. After removing duplicate studies 105 studies were identified for further review. Ninety-one studies were removed after reading the full text of these articles, as they did not meet the selection criteria. In the further review, 7 more studies were also excluded due to a lack of a comparator, because they were review articles, and due to no or unclear reporting of the primary outcome. The flow diagram depicting the identification and inclusion of studies was created following PRISMA recommendations (Fig. 1). Finally, 7 studies were included in this meta-analysis, with a total of 2,310 patients [12-14,16,18-20]. All of the studies included were from Asia, including 4 from Japan and 1 each from Taiwan, South Korea, and China. The details of the studies included are summarized in Table 1.

Quality assessment

All 7 of the included studies were observational, no randomized trials have addressed this issue. Two studies followed propensity matching method to minimize the bias [18,19]. The NOS was used for quality assessment in view

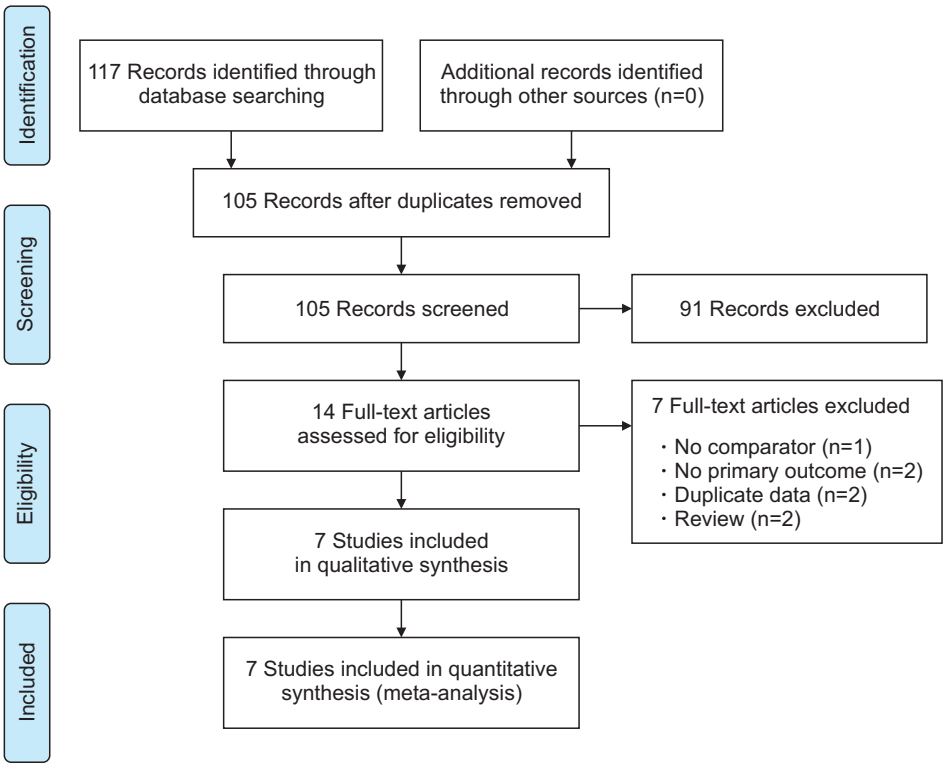

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart showing the selection process of articles.

Table 1. Newcastle-Ottawa quality assessment scale of included studies

Study	Selection				Comparability	Outcome			Total score
	Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Onuki et al. [12] (2010)	❋	❋	❋	❋	-	❋	❋	❋	7
Tseng et al. [13] (2013)	❋	❋	❋	❋	-	❋	-	❋	6
Nakagawa et al. [14] (2014)	❋	❋	❋	❋	-	❋	❋	❋	7
Sakamaki et al. [16] (2014)	❋	❋	❋	❋	-	❋	-	❋	6
Narm et al. [19] (2016)	❋	❋	❋	❋	❋	❋	-	❋	7
Gu et al. [20] (2016)	❋	❋	❋	❋	-	❋	❋	-	6
Nakagawa et al. [18] (2016)	❋	❋	❋	❋	❋	❋	-	❋	7

Table 2. Characteristics of studies included in the meta-analysis

Study	Country	Study design	No. of patients	Thymomectomy/ total thymectomy	Masaoka staging	Propensity score matching
Onuki et al. [12] (2010)	Japan	Retrospective	79	18/61	I/II	No
Tseng et al. [13] (2013)	Taiwan	Retrospective	95	53/42	I/II	No
Nakagawa et al. [14] (2014)	Japan	Retrospective	173	100/73	I/II	No
Sakamaki et al. [16] (2014)	Japan	Retrospective	82	46/36	I/II	No
Narm et al. [19] (2016)	South Korea	Retrospective	762	141/141	I/II	Yes
Gu et al. [20] (2016)	China	Retrospective	1,047	251/796	I/II	No
Nakagawa et al. [18] (2016)	Japan	Retrospective	1,286	276/276	I	Yes

of the observational nature of the studies (Table 2). Of the 7 studies, 4 had a total score of 7, implying high quality. However, 3 studies had a score of 6, suggesting a moderate risk of bias.

Publication bias

Funnel plots were used to assess publication bias in the included articles (Fig. 2). No asymmetry was observed in the funnel plots representing tumor recurrence and occurrence of POMG (Fig. 2A, B). However, the funnel plots for overall survival and postoperative complications showed asymmetries, suggesting the possible presence of publication bias (Fig. 2C, D).

Patient characteristics and perioperative outcomes

Baseline demographic data were calculated using details of the 7 included studies. Overall, 885 patients underwent limited thymectomy and 1,425 patients underwent total thymectomy. The mean age in the limited thymectomy group was 55.6 years and that in total thymectomy group was 53.2 years. The male-to-female ratio was 1,063 to 1,247. The mean size of the tumors in the limited thymectomy group was 5.79 cm and that in the total thymectomy group was 6.09 cm. Masaoka stage I thymoma was found in 1,364 patients, while 946 patients had stage II thymoma. According to the World Health Organization classification, 1,031 patients had type A and AB histology, 1,184 had type B (B1, B2, and B3) histology, and 97 had unknown histology. Perioperative outcomes are presented in Table 3.

Tumor recurrence

The meta-analysis for tumor recurrence between both groups is described in detail in Fig. 3A. No heterogeneity was observed among the 7 studies that were pooled [12-14,16,18-20]. Therefore, a fixed-effects model was used for the meta-analysis. A non-significant difference was found in favor of total thymectomy instead of limited thymecto-

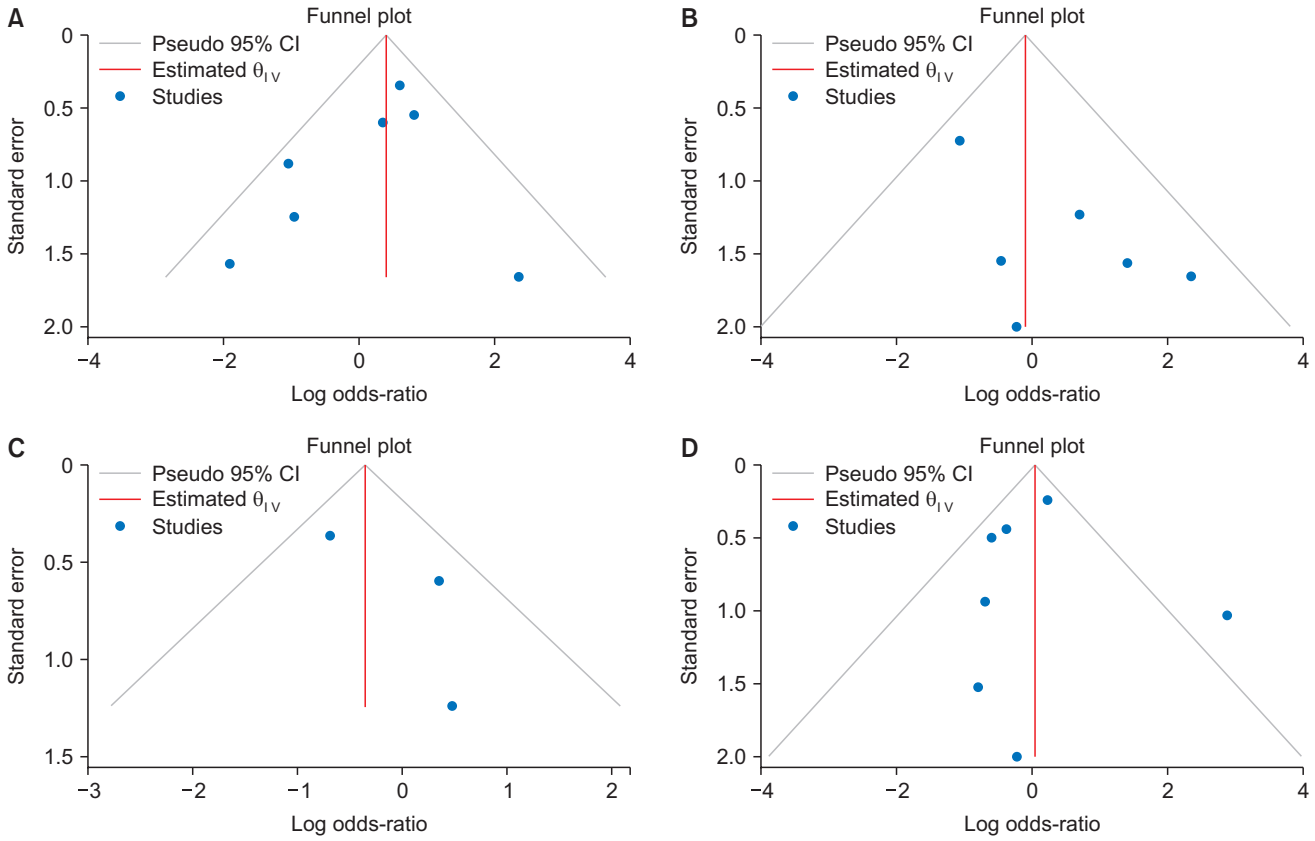

Fig. 2. Funnel plots depicting publication bias for studies evaluating tumor recurrence (A), for studies evaluating postoperative myasthenia gravis (B), for studies evaluating postoperative complications (C), and for studies evaluating overall survival (D). CI, confidence interval.

my, with a pooled log OR estimated at 0.40 (95% CI, -0.07 to 0.87; p=0.10).

Postoperative myasthenia gravis

The results of the meta-analysis for POMG are presented in a forest plot in Fig. 3B. Six studies evaluated the incidence of MG after surgery for thymoma. A mild degree of heterogeneity was observed among the 6 studies that were pooled (I^2=22.6%) [12-14,16,19,20]. No statistically significant difference was found in the incidence of postoperative MG between the limited thymectomy and total thymectomy groups (p=0.85), with a pooled log OR estimated at 0.12 (95% CI, -1.08 to 1.32).

Postoperative complications

Only 3 studies evaluated and reported postoperative complications [13,18,19]. The meta-analysis showed moderate heterogeneity among these 3 studies (I^2=36.1%). Hence, a random-effects model was preferred over a fixed-effects model. For postoperative complications, there was an overall non-significant difference in favor of the limited thymectomy group compared with the total thymectomy group with a pooled log OR estimated at -0.21 (95% CI -1.08 to 0.66; p=0.64) (Fig. 3C).

Overall survival

There was moderate degree of heterogeneity among the 7 studies that were pooled (I^2=47.8%) [12-14,16,18-20]. Therefore, a random-effects model was used for the meta-analysis of the results for overall survival. No statistically significant difference was found between the limited thymectomy and total thymectomy groups with respect to overall survival, with a pooled log OR estimated at -0.01 (95% CI, -0.68 to 0.66; p=0.98) (Fig. 3D).

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Table 3. Comparison of postoperative outcomes among included studies

Study	Postoperative complications (%)		Follow-up (mo)	Local recurrence rate (%)		Postoperative MG (%)		Overall survival (%)		Final conclusion
	TM	TTM		TM	TTM	TM	TTM	TM	TTM	
Onuki et al. [12] (2010)	-	-	76.6±58.4[a]	5	0	5	0	100	82	Similar results
Tseng et al. [13] (2013)	3.8	2.4	57[b]	1.9	4.5	0	0	100	100	Similar results
Nakagawa et al. [14] (2014)	-	-	108 (1.2–384)[c]	2	5	3	8	92.2	86.2	Similar results
Sakamaki et al. [16][d] (2014)	-	-	49[b]	0	5.6	4.3	0	95.4	91.6	Similar results
Narm et al. [19] (2016)	5	3.5	49[b]	3.7	4.1	1.4	0.7	92.2	99.3	Lower operative time and blood loss in the TM group
Gu et al. [20] (2016)	-	-	38[b]	5.4	3.1	0	0.8	89.4	90.9	Significantly higher recurrence rate in the TM group/stage II
Nakagawa et al. [18][d] (2016)	4.3	8.3	53[b]	4	1.8	-	-	97.3	96.9	Marginally significant trend (p=0.06) for a higher recurrence rate in the TM group

TM, thymomectomy; TTM, total thymectomy; MG, myasthenia gravis.
[a]Expressed as mean±standard deviation. [b]Expressed as median. [c]Expressed as mean (range). [d]Reported 5-year survival rates; the others all reported 10-year survival rates.

Discussion

The traditional treatment of thymic tumors was excision of the tumor along with the thymus gland (total thymectomy/thymothymectomy). However, in recent years, some researchers have argued against the removal of the whole thymus gland in early-stage (stage I and II) thymoma patients, suggesting that tumor resection alone is sufficient for oncologic clearance. Proponents of the total thymectomy/thymothymectomy emphasized the higher local recurrence rate of tumors, the possibility of POMG [10], and the occurrence of multiple thymomas in the remaining thymus gland after limited thymectomy [26].

To help resolve this controversy, this meta-analysis evaluated the tumor recurrence rate, incidence of POMG, overall survival rate, and postoperative complication rate in patients who underwent limited thymectomy or total thymectomy using the best available evidence to date to determine whether any significant differences exist. All studies included were retrospective observational studies. The results showed a non-significant difference in favor of total thymectomy in terms of tumor recurrence and the incidence of POMG with no/minimal heterogeneity in the pooled data. The meta-analysis results of postoperative complications and overall survival should be interpreted with caution in view of the moderate degree of heterogeneity in the pooled data. A higher degree of heterogeneity corresponds to greater variation in the actual effect sizes due to confounding factors.

Local tumor recurrence is a major factor to consider when deciding upon the extent of surgery in patients with stage I and II thymoma. In this meta-analysis, all 7 studies evaluated the outcome of tumor recurrence. The major concern with limited thymectomy is possibility of incomplete resection with the corresponding risk of loco-regional recurrence. Tseng et al. [13] reported no local recurrence among 53 patients and Onuki et al. [12] reported only 1 local recurrence among 18 patients. In a multi-institutional study of the Korean Association of Research on Thymus database by Narm et al. [19], the incomplete resection rate was reported as 3.5% of cases in the limited thymectomy group and 4.3% of cases in the total thymectomy group; all cases of incomplete resection were due to the proximity of the tumor to the phrenic nerve. Locoregional recurrence was observed in 6 patients (4.2%) in the limited thymectomy group and in 3.5% of those in the total thymectomy group. The Japanese Association of Research on Thymus (JART) database study by Nakagawa et al. [18], also reported a tendency for a higher incomplete resection rate as well

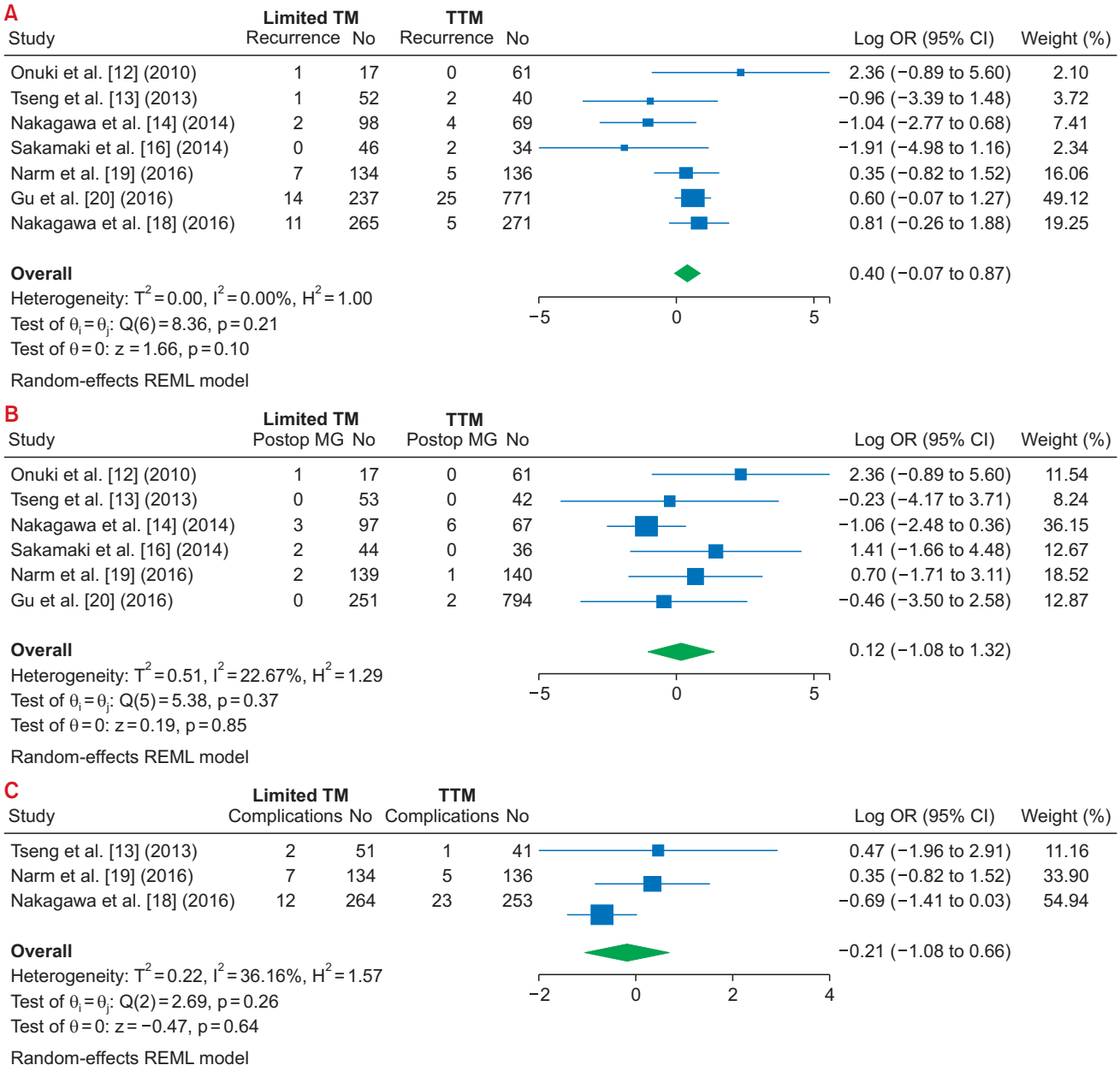

Fig. 3. Forest plots evaluating meta-analysis results for tumor recurrence (A), postoperative myasthenia gravis (B), postoperative complications (C), and overall survival (D). TM, thymomectomy; TTM, total thymectomy; OR, odds ratio; CI, confidence interval; REML, restricted maximum likelihood; MG, myasthenia gravis; Postop, postoperative. (Continued on next page).

as a higher loco-regional recurrence rate (3.6% versus 1.5%) in the limited thymectomy group. In the results published by the Chinese Alliance for Research on Thymoma [20], a stratified analysis could not find any significant difference in recurrence rates in Masaoka stage I tumors (3.2% versus 1.4%, p=0.259). However, this changed dramatically with stage II tumors, wherein the recurrence rate was significantly lower after thymectomy than after limited thymectomy (2.9% versus 14.5%, p=0.001). In this meta-analysis, local recurrence was observed more commonly after limited thymectomy than after total thymectomy, but this difference did not reach statistical significance. Based on these results, it can be concluded that limited thymectomy may be comparable, but not completely equivalent, to total thymectomy with respect to tumor recurrence.

POMG has also been suggested to be an important factor with a higher likelihood of occurring after thymomectomy. The hypothesis of an increased incidence of POMG in thy-

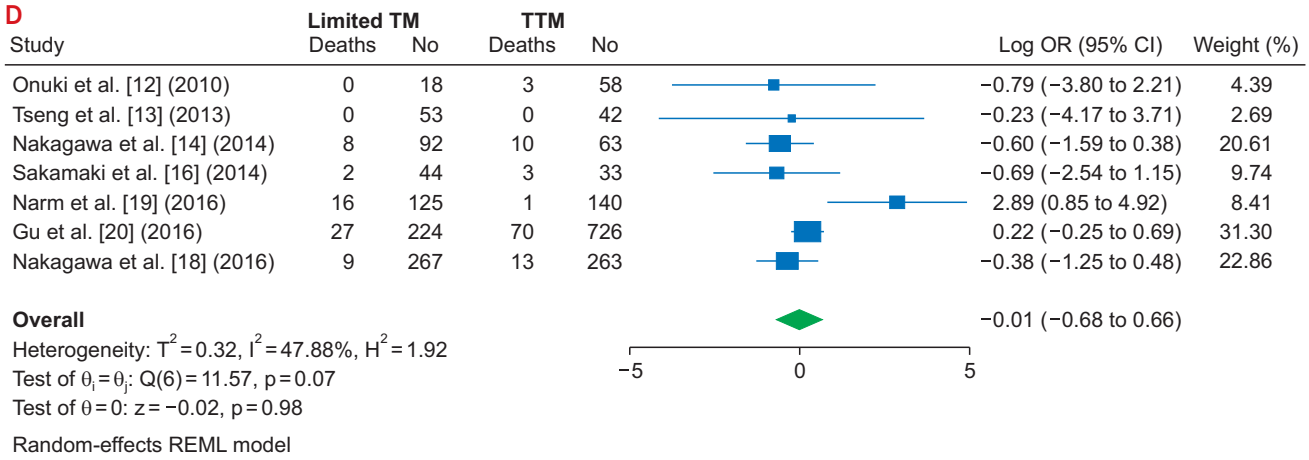

Fig. 3. (Continued; caption shown on previous page).

momectomy patients has been questioned by many authors [10,27], who claimed that the incidence of POMG is rare and its exact mechanism is not known. Onuki et al. [12] reported that POMG occurred in 3% of patients after limited thymectomy and in no patients after thymectomy. Narm et al. [19] observed POMG incidence rates of 1.4% and 0.7% in limited thymectomy and total thymectomy groups, respectively. Conversely, Nakagawa et al. [14] reported a higher incidence of this entity in the total thymectomy group (3% versus 8%). Six studies included in this meta-analysis evaluated this outcome. Overall, the meta-analysis showed a non-significant difference favoring total thymectomy regarding POMG. The proponents of total thymectomy cite the difficulty of performing completion thymectomy if a patient develops POMG. However, in light of the rarity of POMG, this point is debatable, particularly in view of the lower rate of postoperative complications. Tseng et al. [13] reported better postoperative outcomes in the limited thymectomy group, with a shorter duration of surgery, a lower rate of admission to the intensive care unit, a shorter duration of intercostal drain placement, and shorter hospital stays. The analysis of the JART database by Nakagawa et al. [18] showed significantly lower complication rates in the limited thymectomy group than in the total thymectomy group (4.3% versus 8.3%). A multi-institutional study from South Korea by Narm et al. [19] reported that the limited thymectomy group had a shorter duration of surgery and less blood loss. However, the rate of postoperative complications, duration of intercostal drain placement, and length of hospital stay were not different between the 2 groups. In this meta-analysis, only 3 studies evaluated and compared postoperative complications between the 2 groups, and a non-significant difference was found favoring thymomectomy with regard to postoperative complications. However, the small number of studies with moderate heterogeneity of the pooled data may significantly reduce the statistical power of this observation.

In thymoma, overall survival may not be considered an ideal measure of treatment efficacy because it includes many thymoma-unrelated deaths. Instead, freedom from recurrence (FFR) should be considered as the best prognostic marker after thymoma surgery. This was also recommended by the International Thymic Malignancy Interest Group [28]. However, overall survival was used as an outcome measure in this meta-analysis because of the paucity of FFR data in the included studies. The heterogeneity in the pooled data of overall survival was due to differences in follow-up duration, surgical approach, and the size and Masaoka stage of the tumors in the selected studies. Therefore, the findings of this meta-analysis for overall survival should be interpreted with great caution. The incidence of multiple thymomas in the remaining gland was reported in between 0% and 3.1% of patients following resection of thymoma [27,29]. Due to the rarity of this situation, it is very difficult to estimate its correlation with locoregional recurrence and survival. Therefore, this parameter was not analyzed in this meta-analysis.

This meta-analysis is limited by the inclusion of only retrospective, non-randomized observational studies. In fact, there were no randomized controlled trials or prospective studies comparing limited thymectomy with total thymectomy in the literature. The major drawbacks of all the included studies were a relatively short follow-up and a relatively lower frequency of outcomes of interest, such as death and recurrence, which makes the detection of statis-

tically significant differences very difficult. The relatively high heterogeneity significantly reduced the statistical power of the analysis. Another major limitation is the inclusion of myasthenic patients in some studies. None of these studies revealed any specific reason for the inclusion of such patients or analyzed those patients separately.

In conclusion, according to this systematic review and meta-analysis, limited thymectomy as a treatment for stage I and II thymoma shows similar oncologic outcomes to those of total thymectomy. More homogeneous data and prospective studies or randomized controlled trials with long-term follow-up are required further to prove the oncologic safety of limited thymectomy.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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