Minimally Invasive versus Open Thymectomy for Thymic Malignancies: Systematic Review and Meta-Analysis

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ABSTRACT

Complete resection is the standard of care for treatment of thymic malignancies. The use of minimally invasive surgery remains controversial. We searched online databases and identified studies from 1995 to 2014 that compared minimally invasive to open thymectomy for thymic malignancies. Study end points included operative blood loss, operative time, respiratory complications, cardiac complications, length of hospital stay, R0 resection, and recurrence. We summarized outcomes across studies using random-effects meta-analysis to account for study heterogeneity. We calculated ORs for binary outcomes and standardized mean differences for continuous outcomes. We calculated incidence rate ratios for the number of recurrences, accounting for total person-time observed in each study. Of 516 potential reference studies, 30 with a total of 2038 patients met the inclusion criteria. Patients with Masaoka stage I or II thymic malignancy constituted 94.89% of those in the minimally invasive surgery (MIS) group and 78.62% of those in open thymectomy (open) group. Mean tumor size was 4.09 cm (MIS) versus 4.80 (open). Of the 1355 MIS cases, 32 were converted to open cases. Patients in the MIS group had significantly less blood loss; however, no significant differences in operating time, respiratory complications, cardiac complications, or overall complications were identified. Length of stay was shorter for patients in the MIS group. When patients with Masaoka stage I and II thymic malignancy only were analyzed, there was no difference in rate of R0 resection or overall recurrence rate. One postoperative death occurred in the open group. The results of this unadjusted meta-analysis of published reports comparing minimally invasive with open thymectomy suggest that in selected patients with thymic malignancy, minimally invasive thymectomy is safe and can achieve oncologic outcomes similar to those of open thymectomy.

Keywords: Thymoma; Thymectomy; VATS; Robotic assisted surgery; Minimally invasive surgery; Thymic malignancy

Introduction

Thymic malignancies (thymomas and thymic carcinomas) are rare cancers whose etiologies and risk factors are not well understood.[1–13] Complete (R0) surgical resection is the standard of care for thymic malignancies, but the safest and most effective method of resection is controversial.[7,9,13–26] Minimally invasive surgery (MIS), including robotic-assisted thoracoscopic surgery (RATS) and video-assisted thoracoscopic surgery (VATS), is a newer alternative to open approaches such as median sternotomy and thoracotomy. Many surgeons are reluctant to adopt minimally invasive approaches because they are concerned that such techniques may be associated with increased manipulation of the tumor and a corresponding risk for capsular disruption, tumor seeding of the pleura, incomplete resection, and increased risk for local recurrence.

Current research suggests that minimally invasive thymectomy for early-stage thymic malignancies may be correlated with shorter length of hospital stay (LOS) and lower intraoperative blood loss than is open thymectomy.[27–34] The literature suggests that minimally invasive surgery may be as effective as or better than

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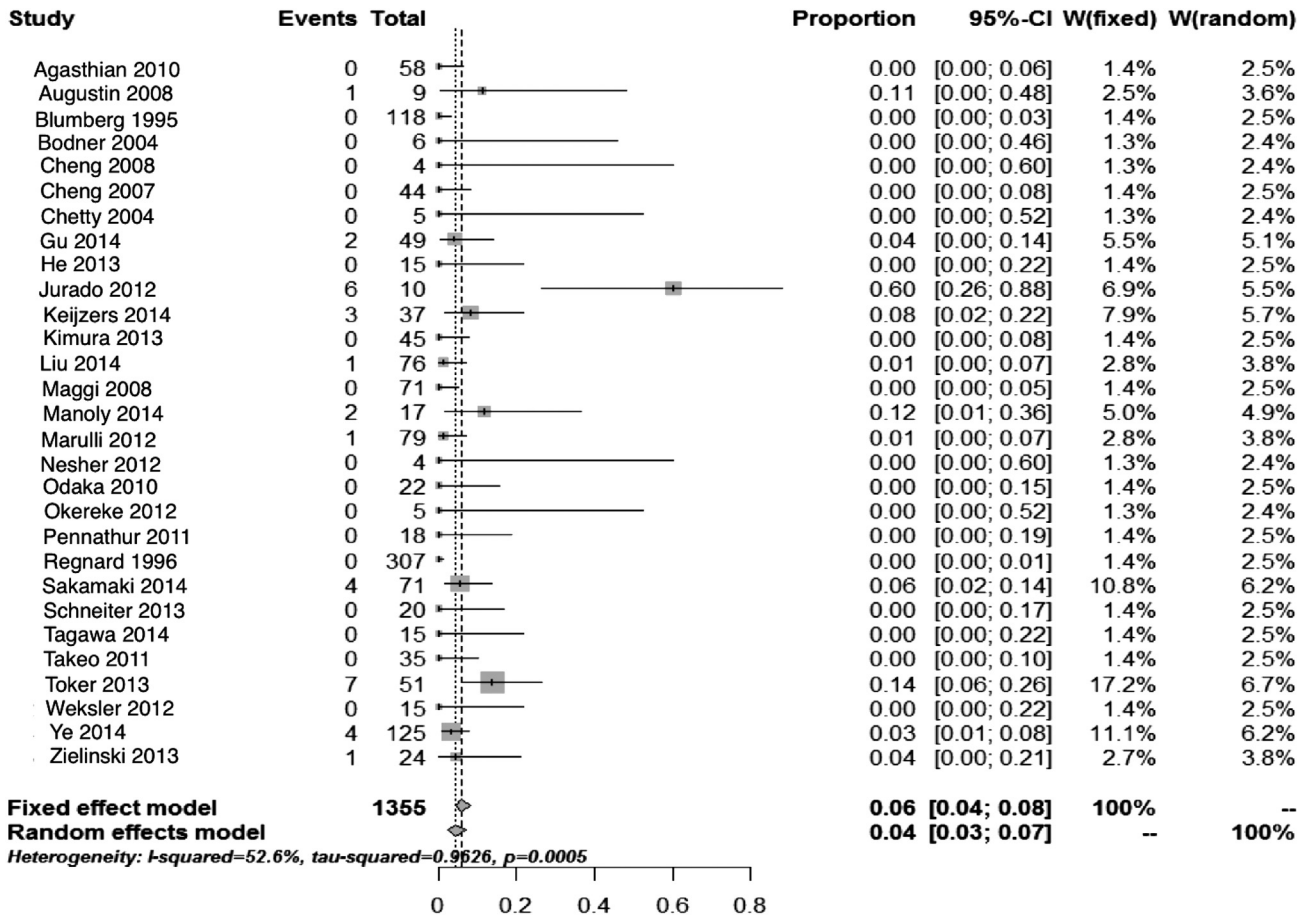

Figure 1. Minimally invasive versus open thymectomy, open conversion.

open thymectomy in treating small, early-stage thymic malignancies.[25,26,32,33,35,36] Studies have shown comparable survival data and oncologic outcomes between the two procedures[30,37,38]; however, such claims are limited by small sample size and lack of long-term follow-up comparisons between patients who have undergone MIS and those who have undergone open thymectomy. In addition, fewer studies focus on thymectomy performed for thymic malignancies as opposed to including thymectomy performed for myasthenia gravis.[7,8,12,16,19,21,33,36,38–40]

The purpose of this meta-analysis is to compare perioperative and long-term outcome variables between minimally invasive and open thymectomy for thymic malignancies by using the current body of literature to determine whether minimally invasive thymectomy is as safe and oncologically effective as open surgery.

Materials and methods

Search strategy

A thorough literature review of the following online databases was performed: PubMed, Science Direct, Oxford Journals, Springer, Sage Journals, and Ovid. References and related PubMed citations for retrieved articles were also reviewed for potential inclusion in our meta-analysis. The search period lasted from May 2014 to September 2014, and we used appropriate free text terms, including *thymoma*, *thymectomy*, *minimally invasive thymoma*, *minimally invasive thymectomy*, and *minimally invasive thymic carcinoma*, in our search.

Study selection

All the studies included in our meta-analysis of thymectomy for thymic malignancies were published in English. Studies were analyzed if they detailed a comparison between any type of minimally invasive thymectomy and any type of open thymectomy for thymoma, thymic carcinoma, or both. Not all studies were included in the analyses for each end point. Studies with only one arm were included in the evaluation for demographics (age and gender), tumor characteristics (stage and size), and open conversion rate.

Any studies indicating minimally invasive thymectomy, open thymectomy, or both for other benign conditions alone (myasthenia gravis and thymolipomas) or nonthymic malignancies alone (germ cell tumors, lymphoma, and lung cancer) were excluded.

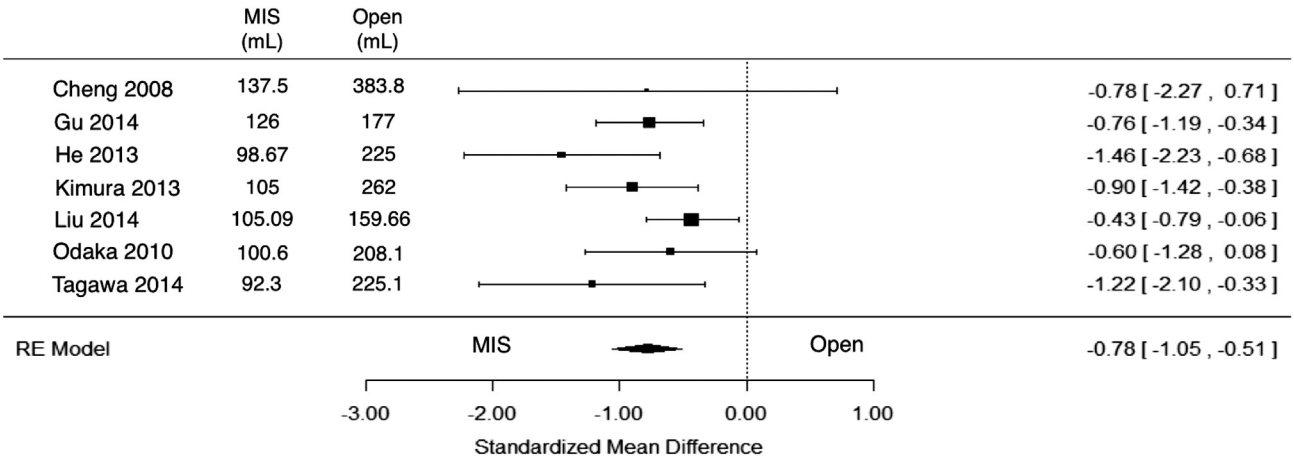

Figure 2. Minimally invasive versus open thymectomy, blood loss (mL).

Data extraction

One investigator independently reviewed each included article under the guidance of two faculty members from the same center. Study end points included some or all of the following: age (years), gender, mean blood loss (milliliters [mL]), open conversion rate, R0 resection rate, mean operative time (minutes), mean tumor size (cm), respiratory complication rate, cardiac complication rate, overall complication rate, LOS (days), perioperative mortality, mean follow-up time (months), and locoregional recurrence.

Statistical analysis

To determine quality, the Methodological Index for Non-Randomized Studies was applied first to all the included studies and then to the comparative studies only.[41] Outcomes were summarized across studies using random-effects meta-analysis to account for study heterogeneity. We calculated ORs for binary outcomes and standardized mean differences for continuous outcomes. Incidence rate ratios (IRR) were calculated for the number of recurrences, accounting for total person-time observed in each study.

Results

We identified 516 references through the aforementioned search criteria. A total of 30 studies, with publication dates ranging from 1995 to 2014, contained pertinent perioperative and long-term outcome information regarding one or both modalities of thymectomy for thymic malignancy. All the included articles were nonrandomized and retrospective. Methodological Index for Non-Randomized Studies criteria were applied to all 30 studies (mean 9.87) and then to the 16 comparative studies exclusively (mean 17.93).

Demographics were calculated using the subset of 16 comparative studies. Mean tumor size was 4.09 cm

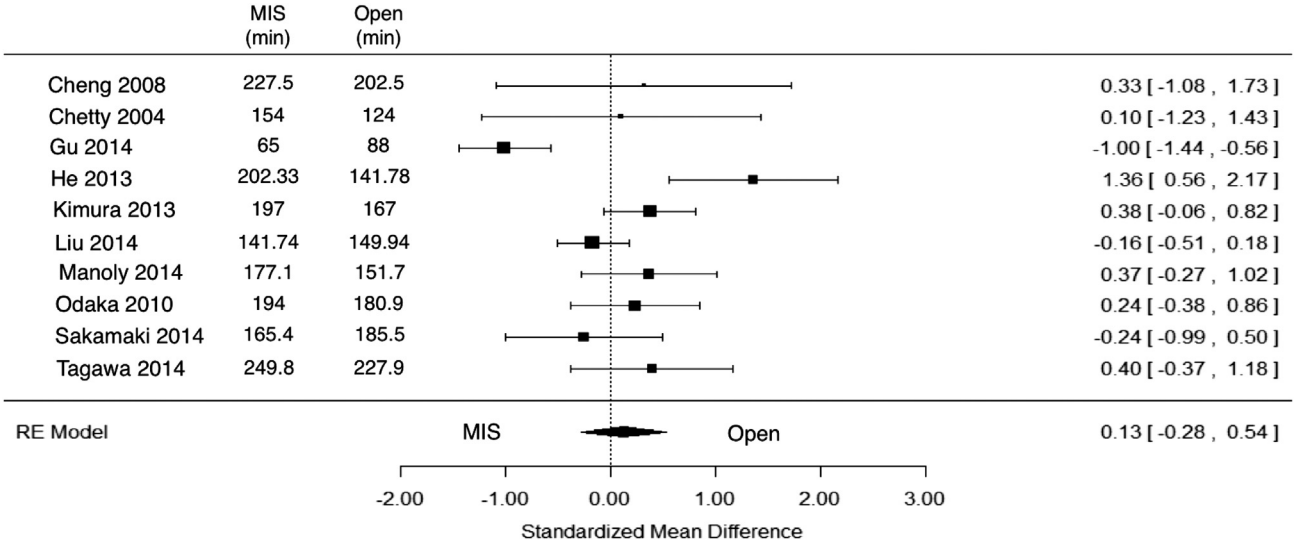

Figure 3. Minimally invasive versus open thymectomy, operative time (minutes).

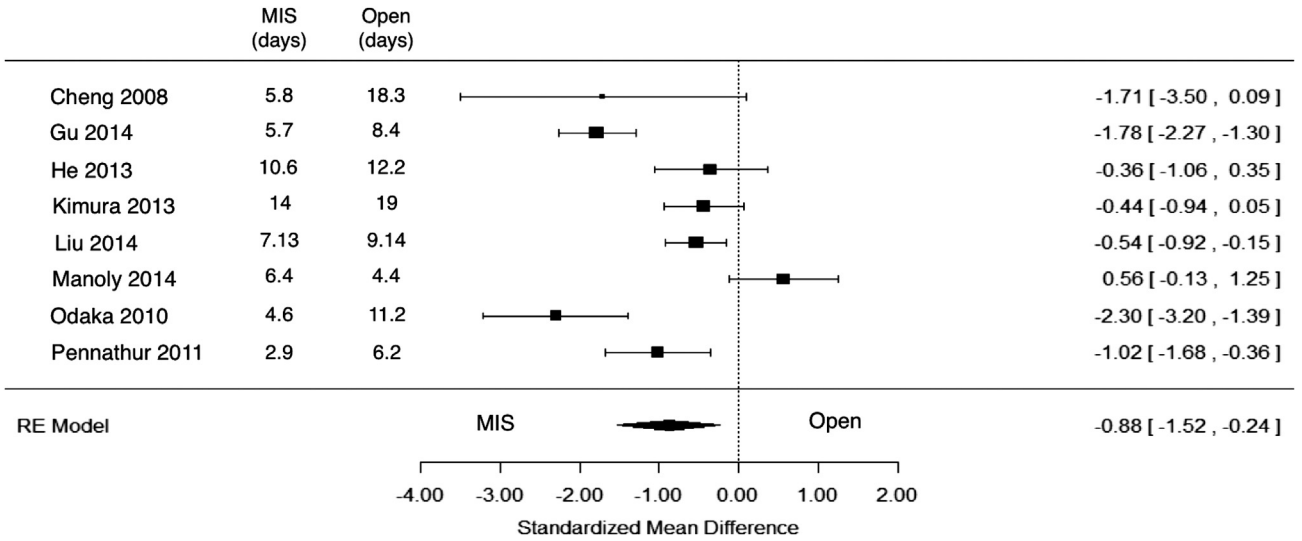

Figure 4. Minimally invasive versus open thymectomy, length of hospital stay (days).

(range 3.23 to 5.76 cm) for MIS and 4.80 cm (range 3.76 to 7.47 cm) for open procedures. Of the 16 comparative studies, seven examined patients with Masaoka I or II disease only. For the other nine comparative studies, 80.49% (n = 82) of patients in the MIS group and 66% (n = 164) of patients in the open group had either Masaoka stage I or II thymic malignancy. In all 16 comparative studies, 94.89% (n = 841) of patients in the MIS group and 78.62% (n = 870) of patients in the open group had Masaoka stage I or II thymic malignancy. The mean age was 52.34 years (range 47 to 63.1 years) for patients in the MIS group and 52.72 years (range 47 to 65.4 years) for patients in the open group; 48.52% (range 35.29% to 63.64%) of patients in the MIS group and 47.14% (range 16.67% to 61.11%) of patients in the open group were men.

Of the 1355 cases in the MIS group, 32 (2.36%) were converted to open cases, as shown in Figure 1. We found mean blood loss to be significantly less in patients in the MIS group than in patients in the open group (226 versus 169 mL, standard difference = −0.78, 95% confidence interval [CI]: −0.97 to 0.57, $p < 0.01$), as shown in Figure 2. There was no significant difference between patients in the MIS group and patients in the open group with regard to operative time (164.92 versus 147.18 minutes, standard difference = 0.13, 95% CI: −0.28 to 0.54, $p = 0.53$), as shown in Figure 3. LOS was shorter for patients in the

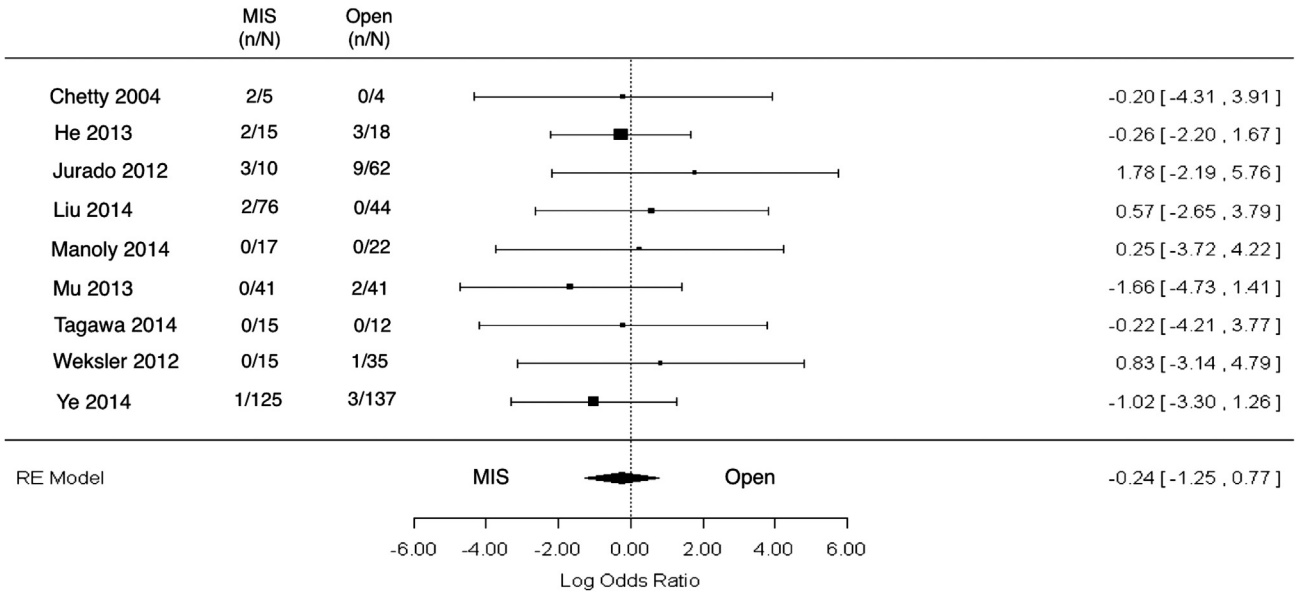

Figure 5. Minimally invasive versus open thymectomy, respiratory complications.

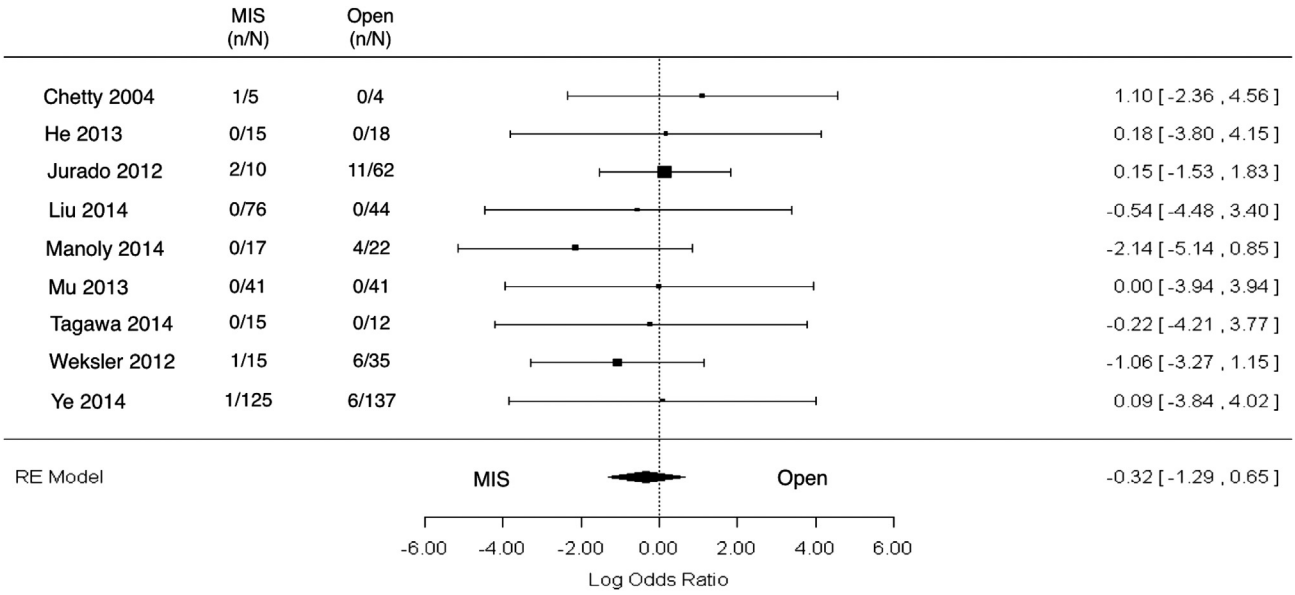

Figure 6. Minimally invasive versus open thymectomy, cardiac complications.

MIS group (8 days for the MIS group versus 9 days for the open group, standard difference = −0.88, 95% CI: −1.52 to −0.24, $p < 0.01$), as shown in Figure 4. There was no significant difference between respiratory complications (10 in the MIS group versus 18 in the open group, OR = 0.79, 95% CI: 0.29–2.16, $p = 0.64$), as shown in Figure 5. There was also no difference in terms of cardiac complications (5 in the MIS group versus 27 in the open group, OR = 0.73, 95% CI: 0.28–1.92, $p = 0.52$), as shown in Figure 6. Finally, there was no significant difference between patients in the MIS group and patients in the open group from the standpoint of overall complication rate (32 in the MIS group versus 63 in the open group, OR = 0.90, 95% CI: 0.41–1.93, p = 0.78), as shown in Figure 7.

Additionally, there was no significant difference in R0 resection rate (OR = 0.82, 95% CI: 0.38–1.73, $p = 0.60$), as shown in Figure 8. There was no significant difference in rate of locoregional recurrence (IRR = 1.57, 95% CI: 0.47–5.26, $p = 0.46$), as shown in Figure 9. In the subset of patients with Masaoka stage I or II thymic malignancy, there was no difference in R0 resection rate (n = 711, 97.36% versus 97.25%, OR = 0.98, 95% CI: 0.23–4.14, $p = 0.88$) or locoregional recurrence rate (n = 234, 2.86% versus 2.91%, IRR = 2.10, 95% CI: 0.39–11.25, $p = 0.39$), as shown in Figures 10 and 11.

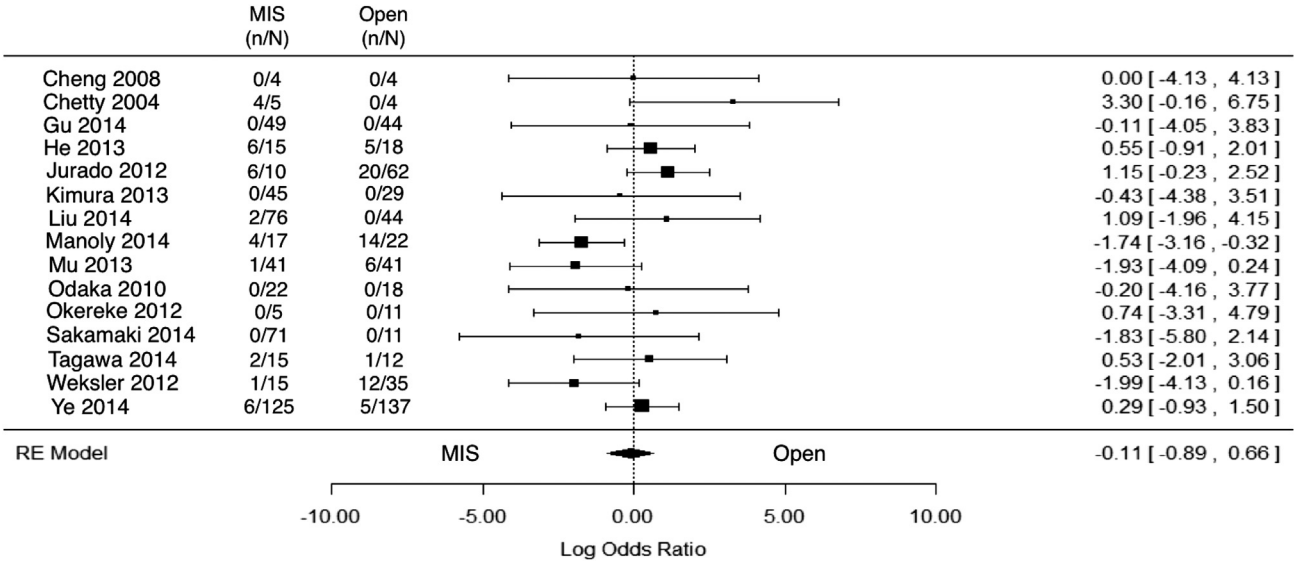

Figure 7. Minimally invasive versus open thymectomy, all complications.

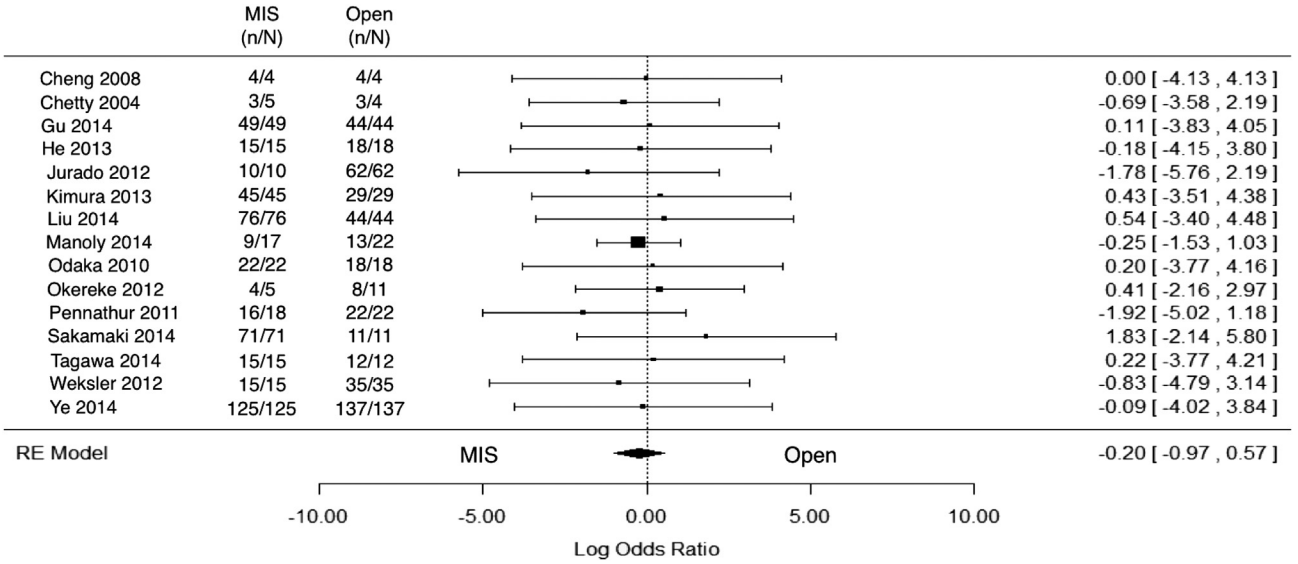

Figure 8. Minimally invasive versus open thymectomy, R0 resections.

Discussion

Minimally invasive surgical techniques have become more widely adopted in some areas of thoracic surgery as the results of clinical series of patients with lung and esophageal cancers have become more mature. However, many surgeons remain reluctant to adopt minimally invasive surgical techniques for the treatment of patients with thymic malignancies for several reasons. Perhaps most commonly, critics have stated that MIS could lead to incomplete resection or tumor seeding and therefore to higher local recurrence rates and lower overall survival rates. We systematically identified and evaluated the existing data comparing the clinical outcomes of minimally invasive thymectomy to open thymectomy by using the techniques of meta-analysis. Because of the scarcity of available data on long-term survival and inasmuch as complete resection is an important determinant of recurrence-free survival in patients with thymic malignancy,[12,14] we focused on complete resection rates and limited local recurrence data as surrogate oncologic outcome measures.

We found that there is no statistically significant difference in R0 resections overall in either the MIS or open groups, although the trend favored patients in the MIS group. The only statistically significant clinical outcomes that we observed were decreased blood loss and shorter LOS, both of which favored the minimally invasive group. We observed no differences in operating time or complications between the two groups. Because patients with larger tumors would more likely be assigned

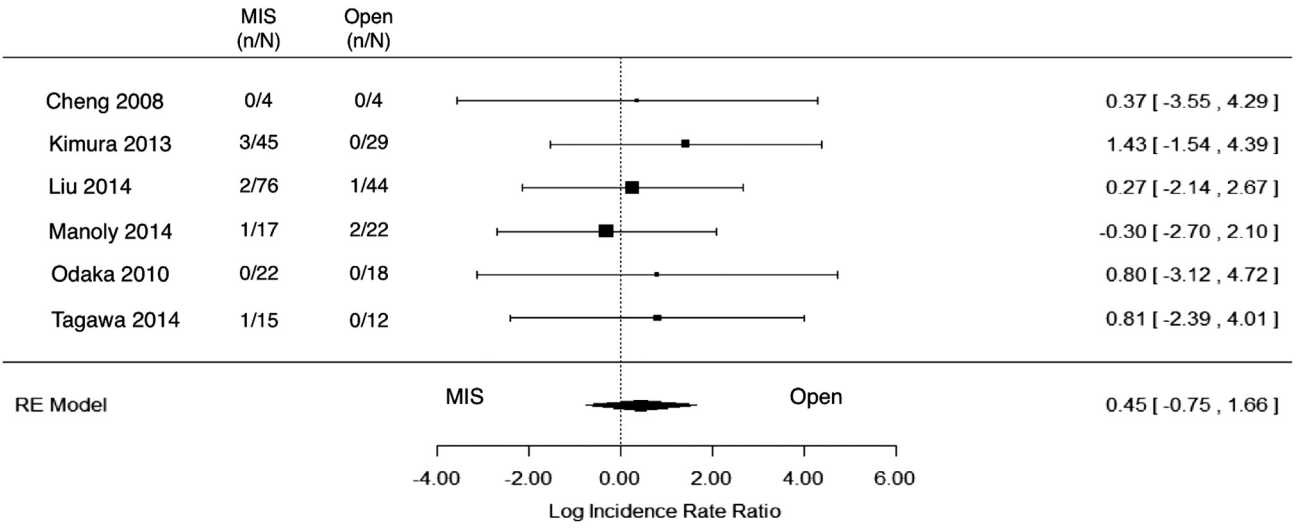

Figure 9. Minimally invasive versus open thymectomy, locoregional recurrences.

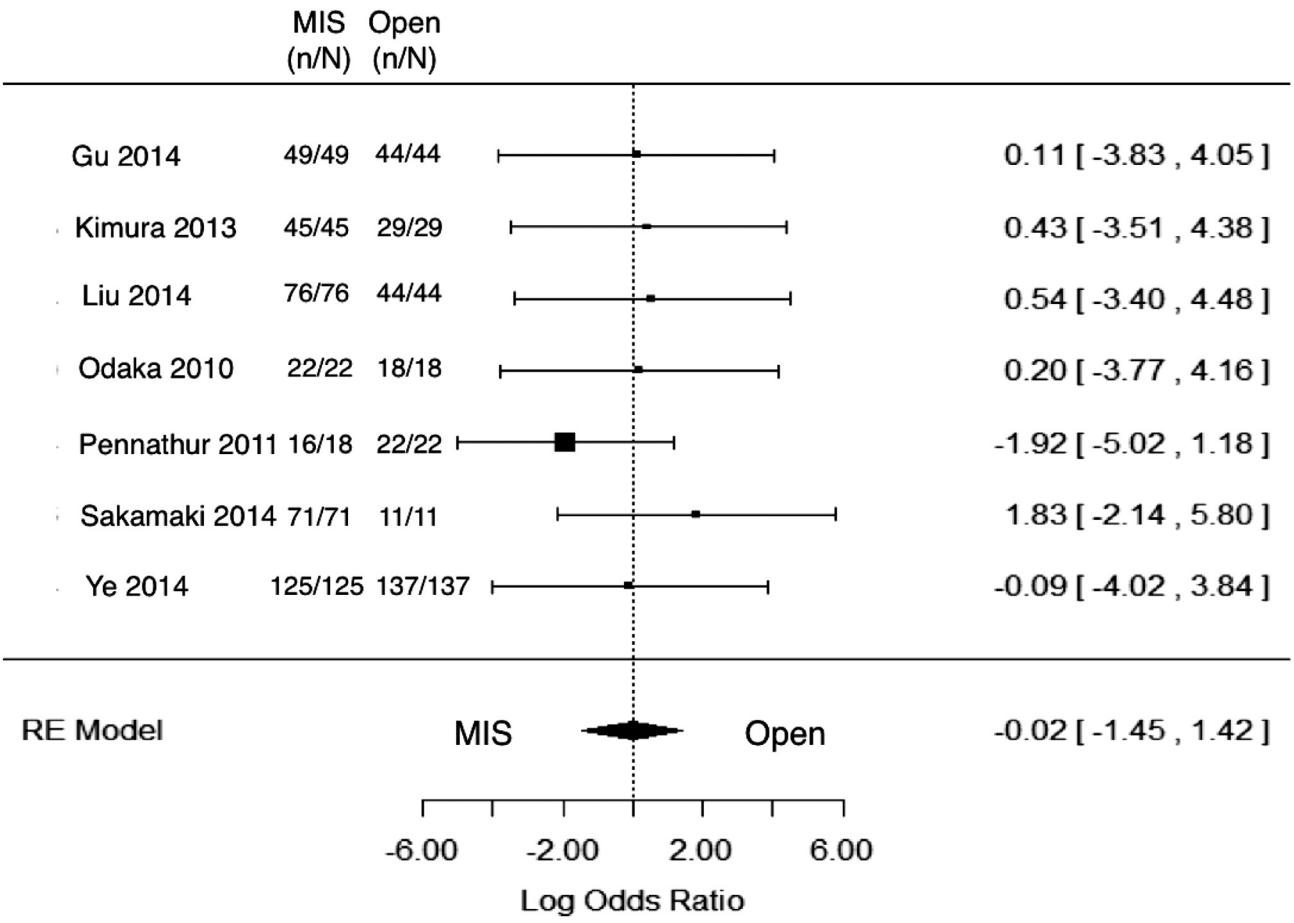

Figure 10. Minimally invasive versus open thymectomy, Masaoka stage I–II subset, R0 resections.

to undergo open surgery, we performed a separate evaluation of patients whose malignancy was clinically staged by the investigators of the various trials as Masaoka I and II disease and found no difference between R0 resection rates in this smaller subset of patients. Data on local recurrence was mentioned in only a few of the published reports on patients with tumors at an early clinical stage. On the basis of these limited data, we observed no difference between the two groups from the standpoint of local recurrence rates, although subsequent examination of recurrence in patients whose minimally invasive surgical procedure was converted to open should be explored.

In addition, our meta-analysis is limited by the inclusion of only nonrandomized, retrospective studies. In our literature review we found no randomized or prospective studies that met our criteria. Furthermore, there is a paucity of long-term follow-up data for patients who have undergone thymectomy for thymic malignancies. Our analysis was constrained by the inability to perform propensity matching because of small aggregate sample size and difficulty in obtaining individual patient information from the included studies. These factors led to increased heterogeneity within the analysis. Finally, the decision to pursue total versus subtotal, or partial, thymectomy is another factor to be considered. Although subtotal thymectomy for thymoma has shown results comparable to those of total thymectomy,[42] further analyses should be performed to confirm these findings. We generally recommend total thymectomy in all cases of thymoma.

From this analysis we were unable to identify factors that would help surgeons select appropriate patients for minimally invasive as opposed to open thymectomy approaches. Certainly, if initial attempts at minimally invasive surgical resection are deemed by the surgeon to be unlikely to lead to a complete resection or to violate any other principles of oncologic surgery, then conversion to open thymectomy surgery should be performed. Interestingly, conversion to open surgery was reported in only 2.4% of cases in our review, thus suggesting that given similar rates of R0 resection, most of the surgeons had appropriately selected patients for minimally invasive thymectomy. On the basis of the findings of this meta-analysis, we conclude that for selected patients, minimally invasive thymectomy is safe and can achieve

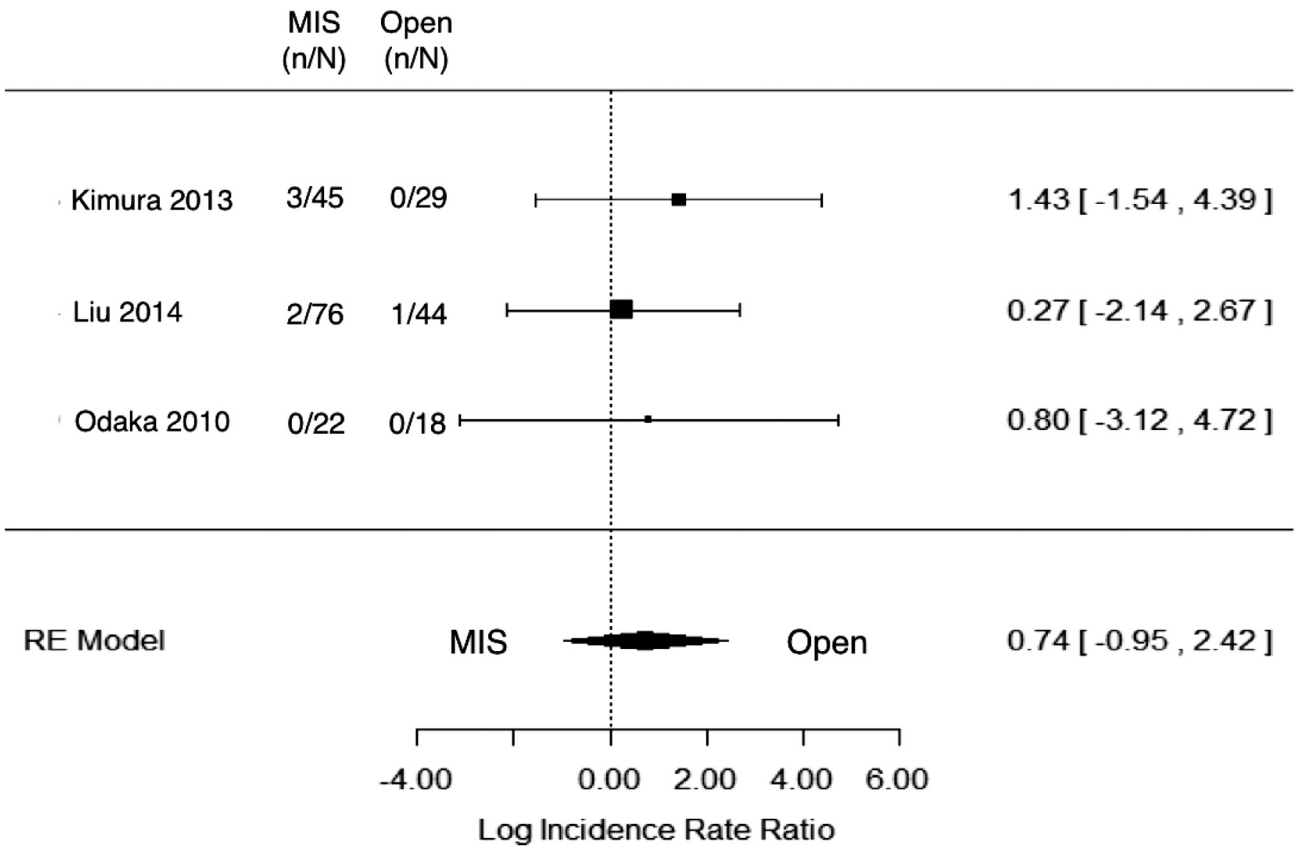

Figure 11. Minimally invasive versus open thymectomy, Masaoka stage I–II subset, locoregional recurrences.

rates of complete (R0) resection comparable to those of open thymectomy operations. Because of the indolent nature of thymic malignancies, long-term follow-up is especially critical in determining efficacy of surgery. Data on long-term cancer-specific outcomes awaits the mature results of longitudinal studies and international efforts such as the International Thymic Malignancy Interest Group database.

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