Systematic Review and Meta-Analysis

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Thymectomy via open surgery or robotic video assisted thoracic surgery

Can a recommendation already be made?

Judith Buentzel, MD[a], Carmen Straube, MD[a], Judith Heinz, PhD[b], Christian Roever, PhD[b], Alexander Beham, MD[c], Andreas Emmert, MD[d], Marc Hinterthaner, MD[e], Bernhard C. Danner, MD[e], Alexander Emmert, MD[e,*]

Abstract

Background: Robot-assisted minimally invasive surgery (RVATS) is a relatively new technique applied for thymectomies. Only few studies directly compare RVATS to the mainstay therapy, open surgery (sternotomy).

Methods: A systematic search of the literature was performed in October 2016. The meta-analysis includes studies comparing robotassisted and open thymectomy regarding operation time, length of hospitalization, intraoperative blood loss, and chest-in-tube days, postoperative complications, reoperation, arrhythmic events, pleural effusion, and postoperative bleeding.

Results: Of 626 studies preliminary screened, 7 articles were included. There were no significant differences in comparison of operation time (−3.19 minutes [95% confidence interval, 95% CI −112.43 to 106.05]; $P=.94$), but patients undergoing RVATS spent significantly less time in hospital (−4.06 days [95% CI −7.98 to −0.13], $P=.046$). There were fewer chests-in-tube days (−2.50 days [95% CI −15.01 to 10.01]; $P=.24$) and less intraoperative blood loss (−256.84 mL [95% CI −627.47 to 113.80]; $P=.10$) observed in the RVATS group; due to a small number of studies, these results were not statistically significant. There were also less post-operative complications in the RVATS group (12 complications in 209 patients vs 51 complications in 259 patients); however, this difference was not statistical significant (odds ratio 0.27, 95% CI 0.07–1.12; $P=.06$).

Conclusions: Patients undergoing RVATS spent less time in hospital than patients treated by open surgery (sternotomy). These patients tended to have less postoperative complications, less intraoperative blood loss, and fewer chest-in-tube days. We found evidence for the safety and feasibility of RVATS compared with open surgery, which has to be further confirmed in randomised controlled trials.

Abbreviation: RVATS = Robot-assisted minimally invasive surgery.

Keywords: robot-assisted minimally invasive surgery, thoracic surgery, thymectomy

1. Introduction

Thymectomy is considered the standard of care in younger (<50 years) nonthymoma patients with myasthenia gravis [1] and cornerstone of treatment for thymoma patients.[2] In thymoma, the therapeutic approach depends mainly on the Masaoka classification,[3] which combines perioperative and histopathological findings. However, due to the rarity of thymoma, no prospective randomized trials on thymoma are available and the potential improvement of new treatment methods has mainly got to be evaluated in collaborative studies.[2] Surgical thymectomy is nowadays considered the mainstay of treatment in thymoma and thymic carcinoma.[4]

Robotic video assisted thoracic surgery (RVATS) was first established as a new operation technique in thoracic surgery 2003 for lobectomy [5] and other complex thoracoscopic procedures.[6] When operating with the da Vinci surgical system, the surgeon's movements are transferred to the tip of the instruments via a console, making use of highly sensitive motion sensors.[7] Advantages and disadvantages of the da Vinci Surgical System have been summed up by the Ontario Health Technology Advisory Committee [8] as follows: "The main advantages of use of the robotic device are: 1) the precision of the instrument and improved dexterity due to the use of "wristed" instruments; 2) three-dimensional imaging, with improved ability to locate blood vessels, nerves and tissues; 3) the surgeon's console, which reduces fatigue accompanied with conventional laparoscopy surgery and allows for tremor-free manipulation. The main disadvantages of use of the robotic device are the costs including instrument costs ($2.6 million in US dollars), cost per use ($200 per use), the costs associated with training surgeons and

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[a] Department of Haematology and Oncology, [b] Department of Medical Statistics, [c] Department of General, Visceral and Pediatric Surgery, University of Goettingen, University Medical Center Goettingen, Goettingen, [d] Westklinikum Hamburg, Department of General and Visceral Surgery, Hamburg, [e] Department of Thoracic and Cardiovascular Surgery, University of Goettingen, University Medical Center Goettingen, Göttingen, Germany.

[*] Correspondence: Alexander Emmert, Department of Thoracic and Cardiovascular Surgery, University Medical Center Goettingen, University of Goettingen, Robert-Koch-Str. 40, D-37075 Göttingen, Germany (e-mail: alexander.emmert@med.uni-goettingen.de).

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operating room personnel, and the lack of tactile feedback, with the trade-off being increased visual feedback.“

There have been a number of studies establishing a role of RVATS in surgery of the pelvis, for example, in benignant gynecology and rectal and colonic cancer.[9–11] Also, there has recently been evidence for a potential role of RVATS in the treatment of lung cancer; in lobectomy, RVATS was associated with shorter hospital stay, shorter chest tube duration, and less blood loss compared with open lobectomy.[12–14]

A first series of mediastinal resections including 9 thymectomies was published in 2004,[15] suggesting suitability of the procedure for complete thymectomy, and thereby also for the treatment of thymoma. In 2006, the authors of a case series of 22 thymectomies [16] concluded that the mediastinum should remain an area of special interest for robotic surgeons.

In 2013, a case series of 100 patients undergoing robotic thymectomy was published and described the procedure as safe and effective; they also observed a neurological benefit for the majority of patients, especially in early stages of myasthenia gravis.[17] A multicenter observational study [18] described RVATS thymectomy in 79 patients with stage I and II thymoma as a safe procedure with a short hospital stay, low postoperative complication rate, and good oncologic outcomes at a median follow-up of 40 months.

According to our literature search, no randomized trials comparing RVATS to open surgery in thymectomy or treatment of thymoma have as yet been performed. Therefore, we hereby attempt to offer the best available evidence by reviewing data from all relevant comparative studies available. We will also perform meta-analyses wherein data quality is accordingly sensible.

2. Methods

2.1. Search strategies and data collection

To identify relevant studies, a systematic literature review was performed by searching PubMed on October 25, 2016, using the search terms *((“thymectomy” OR “thymoma” OR “thymus”) AND (“open” OR “open surgery” OR “sternotomy” OR “transsternal” OR “thoracotomy”) AND (“robotic” OR “robot” OR “robot assisted” OR “da Vinci” OR “daVinci”))*. No language restriction and no filters were applied. In addition, the following literature databases were screened: The Cochrane Library, BioMed Central and Science Direct, and the “MEDLINE related articles” option was used to identify further relevant studies. All abstracts were screened for inclusion and exclusion criteria by 2 investigators (CS and AE). The basic inclusion criterion was the comparison of outcomes in robot-assisted versus open surgery thymectomy. Detailed inclusion criteria were suitable reporting of the surgical outcomes, operation time, length of hospitalization, intraoperative blood loss, and chest-in-tube days, postoperative complications, reoperation, arrhythmic events, pleural effusion, or postoperative bleeding. Studies were excluded if no data suitable for statistical analysis were available. Only data of already published studies found through online research were used for meta-analysis, and we did not require the approval of the local ethics committee.

After a preliminary screening of 626 potentially relevant articles by 2 researchers, we considered 10 studies for meta-analysis. Three studies were excluded for the following reasons: In the study of Orsini et al,[19] there was no separation between patients treated with RVATS and patients treated with VATS; in another study, only patients treated with RVATS were included without control group [20]; and the study of Cakar et al[21] was excluded as no data on patients characteristics were available. Details on study identification and selection are shown in Fig. 1.

Data extraction was performed by 1 investigator (JH) and independently verified by another (CS); disagreements were resolved by consensus between these 2 researchers.

Data were extracted on the surgical outcomes as well as study characteristics, including the number of patients, age, proportion of females and males, and types of surgery method.

2.2. Statistical analysis

Meta-analyses were conducted separately for each surgical outcome. If the outcome was a continuous measure (e.g., operation time, length of hospitalization, intraoperative blood loss, and chest-in-tube days), the number of patients in each group, the mean value and standard error, and the mean differences were used (inverse variance method).

For dichotomous variables (e.g., postoperative complications, reoperation, arrhythmic events, pleural effusion, and postoperative bleeding), the number of events and the number of patients in the groups were used. The groups were compared by considering logarithmic odds ratios.

Due to the clinical and methodological heterogeneity between studies, random-effects models were used to allow the combination of data from different studies.[22] In the case of zero counts (zero count per cell) in a contingency table, a continuity correction of 0.5 was added to all cells.[23] In 1 study, only the *P* value relating to the mean differences for continuous outcomes was given but not the standard deviation.[24] In this case, standard deviations were obtained from the *P* value and t value according to the description in the Cochrane Handbook. Between-study variance and its uncertainty was estimated by the method proposed by Paule and Mandel [25,26] and the Cochran Q test to assess heterogeneity was used. In order to account for the small number of studies available for the meta-analyses and varying studies' precisions, the modified Knapp–Hartung approach was used to combine effect estimates and to derive associated confidence intervals.[27] Computations were performed using R [28] and the metafor package.[29] Forest plots were generated with forestplot package [30] in R.

3. Results

3.1. Study characteristics

Seven retrospective studies published between 2010 and 2016 were analyzed for this study. Characteristics are listed in Table 1.[31–36] Of a total of 489 patients, 215 (44%) were undergoing RVATS, while 274 (56%) experienced open surgery. The number of patients included into these studies varied between 6 and 100 per study for RVATS and between 15 and 100 for open sternotomy. Mean (or in some cases median) age of patients included ranged from 40 to 58 years for RVATS and 27.9 to 59 years per study for open surgery. Two out of seven studies used propensity score matching to reduce bias.[31,32] Indication for open surgery or RVATS were anterior mediastinal masses,[31,32] thymoma [33–36] (classified using the Masaoka [33] or the WHO classification),[34] thymic cysts, thymic hyperplasia, [34,35] or myasthenia gravis.[24] Out of 215 interventions performed by RVATS (7 studies included), 4 were converted to open sternotomy. The following parameters were included into

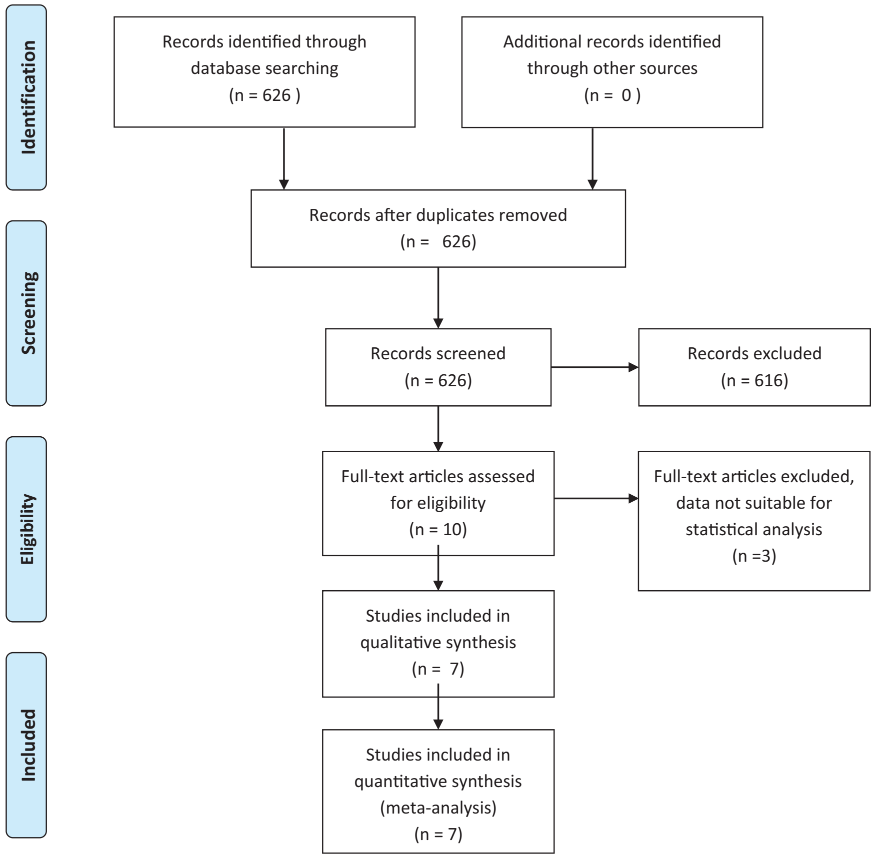

Figure 1. Flow diagram of studies identified, included, excluded.

meta-analyses: operation time, length of hospitalization, intraoperative blood loss, chest-in-tube days, postoperative complications, reoperation, arrhythmic events, pleural effusion, and postoperative bleeding.

A high risk of bias of the studies is most likely, as the included studies are retrospective studies with small sample sizes. A selection bias due to missing randomization and biased allocation to the treatment groups, a performance bias due to knowledge of the allocated interventions by participants and personnel during the study, and a reporting bias due to possible selective outcome reporting cannot be excluded. Two studies reported data on propensity score matching analyses.[31,32] In this case, the matched data were used for meta-analysis.

3.2. Surgery outcomes

Mean operation time was reported in 5 studies. In the RVATS groups, the operation time ranged between 97 and 224.2 minutes [N (RVATS) = 177], and in open surgery groups, between 55 and 243.8 minutes [N (open) = 222]. The estimated mean differences are shown in Fig. 2. Comparing operation time between both approaches resulted in a mean difference of -3.19 minutes [95% confidence interval, 95% CI -112.43 to 106.05]; $P = .94$, indicating no substantial difference between the RVATS and open surgery group. We observed a substantial between-study heterogeneity (tau = 85.8; $I^2 = 98.9\%$; $P < .0001$).

Four studies reported data on hospitalization [N (RVATS) = 77, N (open) = 122; Fig. 3]. Mean number of days in hospital were reported between 3.7 and 9.6 days in the RVATS group and 5.5 and 11.8 days in the open surgery group. Patients undergoing RVATS spent significantly less time hospitalized than patients undergoing sternotomy [-4.06 days (95% CI −7.98 to −0.13); $P = .046$]. Between the studies, we also found a significant heterogeneity (tau = 2.1; $I^2 = 79.9\%$; $P = .007$).

Intraoperative blood loss was reported in 3 studies ranging from 41.7 to 100.9 mL and from 151.4 to 466.1 mL for RVATS

Table 1

Study characteristics.

Author/ Reference	Study design	Database	Study period	N RVATS	N open	RVATS age, y	Open age, y
Balduyck et al[34]	Retrospective	Own patients	01/2004–12/2008	14	22	49	56
Kang et al[32]	Retrospective	Own patients	01/2006–06/2015	100	100	52.1	52.3
Renaud et al[24]	Retrospective	Own patients	01/1998–03/2010	6	15	40	27.9
Seong et al[31]	Retrospective	Own patients	05/2008–08/2012	34	34	53.7	52.4
Weksler et al[35]	Retrospective	Own patients	02/2001–02/2010	15	35	56.8	50.7
Wilshire et al[36]	Retrospective	Own patients	01/2004–03/2014	23	17	58	59
Ye et al[33]	Retrospective	Own patients	01/2009–12/2012	23	51	52.5	50.1

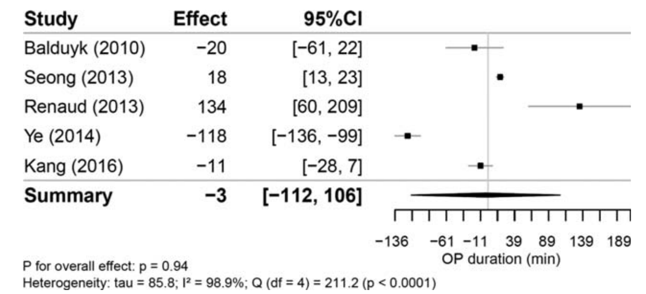

Figure 2. Mean differences of operation time (in min) between robotic and open thymectomy and combined estimate of the operation time.

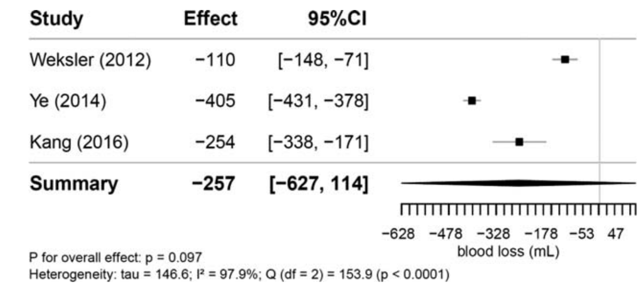

Figure 4. Mean differences in intraoperative blood loss (in mL) between robotic and open thymectomy and combined estimate of the intraoperative blood loss.

versus sternotomy [N (RVATS) = 138, N (open) = 186]. The analysis of these studies resulted in a pooled mean difference of -256.84 mL (95% CI −627.47 to 113.80; P = .10) and a between-study heterogeneity of tau = 146.6 (I^2 = 97.9%; P < .0001) (Fig. 4).

Two studies reported chest-in-tube days [N (RVATS) = 57, N (open) = 85], which was shorter for patients undergoing RVATS [−2.50 days (95% CI -15.01 to 10.01); P = .24], although this difference is statistically not significant. A significant between-study heterogeneity (tau = 1.4; I^2 = 98.3%; P < .0001) was present.

Six studies reported data on postoperative complications [N (RVATS) = 209, N (open) = 259]. Overall, there were fewer complications observed in the RVATS group, which is also apparent in the pooled odds ratio (OR) [0.27 (95% CI 0.07–1.12)]; however, this is not significant (P = .06). It has to be noted that in the study of Weksler et al,[35] a high proportion of complications in the open surgery group was observed compared with the other studies (Fig. 5). The recorded complications in the study of Weksler et al[35] were supraventricular arrhythmia, atelectasis, respiratory failure, renal failure, sternal dehiscence, change in mental status, severe subcutaneous emphysema, and chyle leak. In a sensitivity analysis, this study was excluded of the meta-analysis; however, the results did not change substantially (OR 0.37, 95% CI 0.09–1.68; P = .15).

Out of all observed postoperative complications, arrhythmic events, pleural effusion, and postoperative bleeding were reported separately as follows.

Atrial fibrillation and supraventricular arrhythmia were classified as arrhythmic events. In total, 4 studies reported arrhythmic events and 3 events were recorded for RVATS [N (RVTAS) = 166] and 7 for open surgery [N (open) = 192]. We did not detect significant difference between both approaches (OR 0.76, 95% CI 0.07–7.69; P = .72).

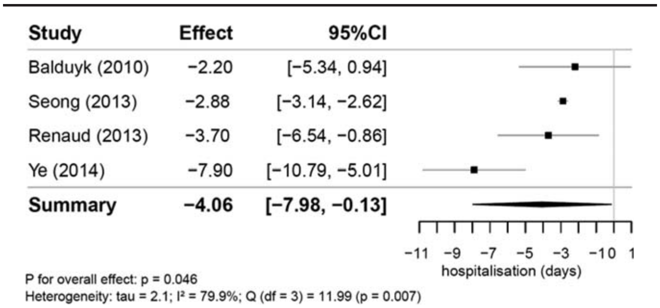

Figure 3. Mean differences in length of hospitalization (in d) between robotic and open thymectomy and combined estimate of the length of hospitalization.

Pleural effusion and postoperative bleeding [3 studies, N (RVATS) = 157 and N (open) = 151] were observed solely in the open surgery group, although this did still not result in statistically significant differences between the 2 treatment groups [postoperative bleeding (OR 0.21, 95% CI 0.004–11.46; P = .24) and pleural effusion (OR 0.29, 95% CI 0.005–17.71; P = .33)].

4. Discussion

Decisions about the operative strategies for a thymectomy should depend on the size, location, local invasion of the lesion, experience of the surgeons, and condition of the patient. Until recently, sternotomy was the only approach to guarantee complete removal of the thymus. But in the last years, robotic-assisted thoracoscopy has become more commonplace.[2,37]

Robotic assistance using the da Vinci system allows a more delicate approach to the mediastinum. The excellent 3D vision with magnification is utilized, and the endoscopic "arms" with their 7 degrees of freedom are more maneuverable than typical thoracoscopic instruments.[38] This seems to suggest the possibility of less potential trauma to mediastinal structures and less postoperative pain while still allowing complete resection of the thymus. RVATS is described as a safe and feasible technique for thymectomy. Overall, 15 to 20 thymectomies may be required for a surgeon to learn and adequately perform this technique.[39]

Several systematic reviews and meta-analysis have evaluated the efficacy and safety of robotic-assisted surgery versus open surgery in lung cancer, rectal cancer, and kidney surgery.[40–42] During the past 5 years, many authors from established general thoracic centers reported studies that supported the feasibility, reproducibility, effectiveness, and safety of the robotic-assisted procedures compared with the open thymectomy.[24,31–36] To the best of our knowledge, this is the first meta-analysis comparing these 2 surgical techniques of thymectomy.

In the present study, we analyzed data of 215 and 274 patients undergoing either RVATS or open surgery. Seven observational studies were included into this meta-analysis. No difference in operation time was found indicating that not the approach used for thymectomy but other factors, for example, the experience of the surgeon, the equipment of the operation theater, or patients chosen for surgery influence operation time. It should be considered that the definition of "operation time" differed between studies, for example, Balduyck et al described room occupation time.

Patients undergoing RVATS spent significantly less time in hospital than patients undergoing sternotomy. Although a lower

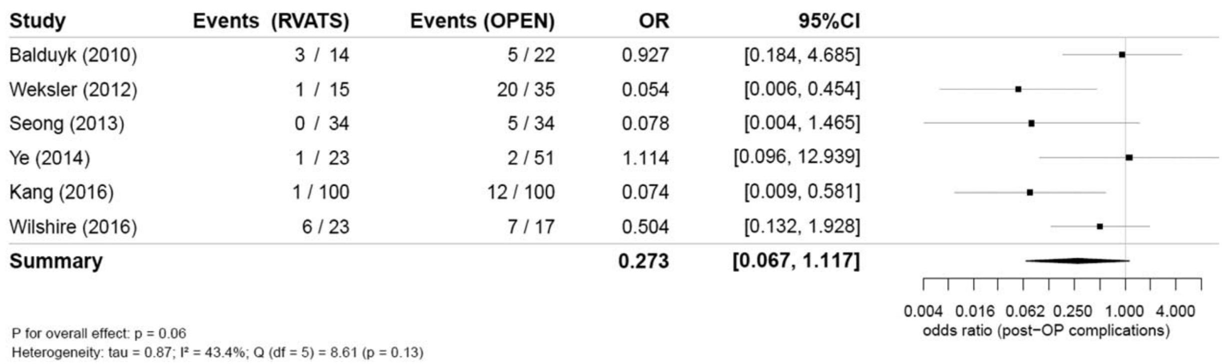

Figure 5. Combined postoperative complications (odds ratio) in robotic and open thymectomy and combined estimate of the complications.

hospitalization rate might be used as an argument for RVATS, one should consider that hospitalization rates are not generalizable. Length of stay standards may vary between countries, as does medical training insurances coverage, cultural and societal values as well as hospital-specific protocols all influencing discharge timing.[43]

While the difference of intraoperative blood loss between those 2 approaches was not significant, less intraoperative blood loss was observed for RVATS (mean range 41.7–100.9 mL for RVATS, 151.4–466.1 mL for open surgery). We also observed a shorter chest-in-tube time for patient treated with RVATS (mean range RVATS 1.3–1.53 days, mean range open surgery 3–4.8 days). The studies reporting intraoperative blood loss and chest-in tube days indicated that RVATS is favorable to open surgery. Due to the small number of studies included and the appropriate use of the modified Knapp–Hartung approach, a conservative approach yielding a large confidence interval, the advantageous effects of RVTAS were statistically not significant. A larger number of studies are required to determine if this observation might be significant.

A further advantage of RVATS is the smaller complication rate than open surgery thymectomy (12 complications in 209 patients vs 51 complications in 259 patients), albeit this difference was not significant.

There are only few studies comparing RVATS to open surgery. Mostly data on early follow-up were reported. For example, Seong et al[31] observed no recurrence in either group, albeit their follow-up period ranged between 1.11 ± 0.21 years for RVATS and 1.85 ± 0.19 years for open surgery. Kang et al[32] described a 3-year follow-up with 3 recurrences in the RVATS group and none in the open group. These results were not significant. Weksler et al[35] described 1 postoperative death in the open group. The median follow-up of Balduyck et al[34] was 44 months; 1 recurrence in the sternotomy group after 54 months was described. More long-term follow-up studies are required to address the question whether the long-term out-come of RVATS is different from the outcome of patients undergoing open surgery. Furthermore, there are no sufficient data available comparing incomplete to complete resection of the thymus. Overall complete resection of the thymus is the gold standard to achieve cure. Complete resection is a prognostic factor for recurrence helping to improve survival.[44]

As described above, small number of studies is a limitation of this meta-analysis. All studies included in this analysis were retrospective, and only 2 were propensity matched. Indications of patients included and patient characteristics were rather variable. As, therefore, performance bias and reporting bias cannot be excluded, our findings point out the necessity and usefulness of randomized studies comparing RVATS with open surgery to better define the potential advantages of the minimally invasive approaches for thymectomy.

The results of our meta-analyses show that patients undergoing RVATS spent less time in hospital than patients treated by open surgery. Although the results for chest-in-tube days, intraoperative blood loss, and postoperative complications were not significant, RVATS may potentially favorable compared with sternotomy. However, further randomized and controlled studies are necessary to support this hypothesis. We found evidence for the safety and feasibility of RVATS compared with open surgery. Thus, we suggest that RVATS is an appropriate alternative to open surgery for thymectomy. In the absence of randomized controlled trials comparing RVATS with open surgery, our findings represent the highest level of clinical evidence in the current literature on this issue.

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