Review Article

# Minimally invasive surgery in thymic malignances: the new standard of care

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**Abstract:** Surgery is the most important therapy for thymic malignancies. The last decade has seen increasing adoption of minimally invasive thymectomy (MIT) for thymic tumors. MIT for early stage diseases has been shown to yield similar oncological results while being helpful in minimizing surgical trauma, improving postoperative recovery, and reducing incisional pain. Similar surgical and oncological principles should be observed in both minimally invasive and open procedures so as to ensure radical resection and accurate staging of the tumor.

**Keywords:** Thymic malignancies; minimally invasive surgery; video-assisted thoracoscopic surgery (VATS)

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Thymic malignancies are relatively rare diseases comparing to other solid tumors in the chest (1). At the same time, the indolent nature of the disease manifested by prolonged survival even after disease progression in many thymoma patients contributes to the difficulty to carry out prospective randomized studies on a large scale so as to provide high level evidence for clinical practice. This explains the long existing controversies concerning diagnosis and management of thymic tumors (2,3). It is only in recent years that global international (International Thymic

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Malignancy Interest Group, ITMIG) and regional (the Chinese Alliance for Research in Thymomas (ChART), the Japanese Association of the Research on the Thymus (JART), and the European Society of Thoracic Surgeons (ESTS) thymic working group) cooperations (3-5) have started to appear in clinical studies for thymic tumors. Emerging results from such collaborations represent a promising start of using evidence-based medicine instead of relying on limited individual experience for the treatment of thymic malignancies.

Up till now, surgery remains the most important therapy for thymic tumors, and still carries the most chance of cure when complete resection could be achieved (6). The last decade has witnessed a rapid increase in applying minimally invasive thymectomy (MIT) for thymic tumors, including video-assisted thoracoscopic surgery (VATS), robotic surgery, and other minimally invasive surgical approaches (7,8). The retrospective database of ChART also showed that the proportion of MIT for Masaoka stage I and II tumors has reached over 40% since 2010 (5). However, MIT is still not recommended as an acceptable procedure in current clinical guidelines due to lack of high-level evidence (9).

## Benefit of MIT in peri-operative results as compared to open surgery

To establish the role of MIT in surgical treatment of thymic tumors, it is first necessary to show that MIT is beneficial for patient recovery by reducing surgical trauma comparing to open surgery. Evidences in this area have been substantial reported by a large number of clinical studies. For example, in a Shanghai Chest Hospital early experience study reported years ago, only 3 cases (6.1%) were converted to open surgery because of local tumor invasion. No perioperative major complication or mortality occurred in the MIT group. Although there was no significant difference in transfusion, or duration or amount of postoperative chest tube drainage between the two groups, operation time, blood loss during operation, and length of ICU and hospital stay were significantly less in the MIT group than in the open group (P<0.05) (10). Rückert *et al.* showed that postoperative pain after VATS thymectomy was significantly less than after median sternotomy, reflected by significantly less analgesic drugs needed by the patients in the VATS group. Moreover, their results also showed that the adverse impact of VATS thymectomy on pulmonary function was also significantly minimized than that of open surgery. Immediate reduction of lung function after surgery was 35% and 65%, respectively for the VATS and the median sternotomy groups. And spirometry indexes were completely recovered on the third postoperative day after VATS thymectomy, while in the open surgery group recovery was only 55% of the preoperative level (11).

In addition to the single-center experiences mentioned above, a meta-analysis by Hess *et al.* (12) further proved that compared to open surgery, MIT resulted in less blood loss, reduced postoperative drainage, and shortened postoperative hospital stay. A total of 2068 surgical patients in 20 related clinical reports undergoing either MIT (n=838) or open surgery (n=1,230) was involved. Resected thymomas were consistently larger in the open groups, with a mean diameter significantly larger in five studies (MIT, 29–52 mm; open, 31–77 mm). MIT was consistently associated with less estimated blood loss (MIT, 20–200 mL; open, 86–466 mL), shortened chest tube duration (MIT, 1.3–4.1 days; open, 2.4–5.3 days), and reduced length of hospital stay (MIT, 1–10.6 days; open, 4–14.6 days). There were no consistent differences in rates of perioperative complications or myasthenia gravis (MG) complete stable/remission.

A recently published propensity score matched study by JART retrospectively analyzed the data of 140 pairs of patients receiving either MIT or open surgery out of 2,835 of those with Masaoka stage I and II thymoma (4). The postoperative complication rate in the MIT group was not higher than that in the open group (6.1% *vs.* 9.6%; P=0.25). There was no difference in overall morbidity rates between the two groups, or in incidences of wound infection, or respiratory complications. In particular, by avoiding sternum splitting, severe complications after open thymectomy such as sternal infection and mediastinitis were not observed in MIT patients. MG crisis was observed in only 1.4% of MIT-treated patients, which was not significantly different from that in the open group (P=1.0).

In summary, there have been ample evidences in the existing literature recognizing the feasibility, safety and even superiority over open procedures, of MIT for thymic diseases. This will certainly lead to further increase of its application in the management of early-staged thymic tumors.

## Does MIT carry similar oncological results as open thymectomy?

In addition to superior peri-operative results, it is more important to prove that MIT has equivalent, or at least

 

non-inferior, oncological outcomes to open surgery. MIT has not become a routine practice in surgical treatment of thymic tumors until the recent decade (13). Yet, the relative indolent nature of thymic tumors requires a longer follow-up for them than for other malignant tumors in order to evaluate the effectiveness of a certain treatment. It has been recommended that a 10-year survival and more preferably recurrence rate in addition to survival results be used to evaluate oncological outcomes in such low-grade tumors. And it is until very recently has the oncological results with long-term follow-up of MIT started to appear in literature.

Up till now, there has been no prospective controlled trial comparing MIT with open thymectomy. In fact, it is basically impractical to carry out such studies in the current situation. In the retrospective study using the ITMIG global database, 266 pairs of patients were selected by propensity score matching to make comparison between MIT and open surgery among 2,514 cases with thymomas. The results showed that the radical resection rate of both groups reached 96% after adjusting the influence of tumor size, stage and histological type. And upon multivariate analysis for R0 rate, surgical approach was not associated with the possibility of complete resection, while the elapse of time (improving surgical techniques), tumor stage (the more advanced stage the lower resection rate), and the extent of thymectomy (total thymectomy is more radical) were identified as independent predictors (8). In view of the fact that resection rate, along with tumor stage and histology, has long been held the three major prognostic factors for oncological outcomes in thymic tumors (6), the ITIMG study actually suggested the oncological effectiveness of MIT indirectly by showing similar resection status between the two surgical approaches.

The afore mentioned recently JART retrospective study compared 140 pairs of patients receiving either MIT or open surgery for Masaoka stage I and II thymoma (4). There were only 3 cases and 1 case of R1 resections in the MIT and open groups respectively. Five-year overall survival was similar between the two groups, being 97.9% and 97.1%, respectively. More importantly, there was no significant difference in recurrence-free survival, being 93.9% and 95%, respectively. However, patients with thymic carcinomas were not enrolled in this study. And because of the late implementation of MIT, the median follow-up time of the MIT group (3.7 years) was significantly shorter than that of the open group (5.2 years).

An earlier retrospective study by the ChART compared 229 patients receiving MIT with 610 patients receiving open surgery with clinical Masaoka stage I–II thymic tumors (7). Both the 5-year overall survival (89.4% *vs.* 96.7%, P=0.582) and the recurrence rate (3.3% *vs.* 4.7%, P=0.579) were comparable in those patients turned out to have pathological stage I–II tumors. Although upon multivariate analysis only WHO classification, Masaoka-Koga stage, and adjuvant therapy were identified as independent predictive factors for overall survival, and surgical approach was not found to have any significant impact on long-term outcomes, the results were imperfect due to potential confounding biases. To solve this problem, 110 pairs of patients receiving either MIT or open surgery were selected with the help of propensity score matching from 1,087 cases of Union for International Cancer Control (UICC) pathological stage I (similar to Masaoka I–II) tumors in the ChART database (results reported at the ESTS 2017 Brompton session). There was no difference between the two groups in tumor size, pathological stage, histological type, or postoperative adjuvant therapies. The median follow-up time was 26 months (MIT) and 36 months (open), respectively. There was no significant difference in either overall survival (85.7% *vs.* 93.1%, P=0.539), disease-free survival (92.5% *vs.* 91.9%, P=0.773), or cumulative incidence of recurrence (7.1% *vs.* 5.8%, P=0.522) between the two groups. And improvement rate of symptoms in patients with MG was similar too (83.3% *vs.* 88.2%, P=0.589). By confirming the first ChART study on MIT, the results of this propensity-score matched study further proved that MIT could have similar long-term outcomes as open surgery in thymic tumors (14). It is noteworthy that not only thymomas but also thymic carcinomas were included in this study. Since it is difficult, if not entirely impossible, to differentiate between thymoma and thymic carcinoma before surgery, it seems that MIT could be chosen based on tumor stage or resectability, regardless of tumor histology.

It should be pointed out that although the above-mentioned international and regional collaborative studies have attempted to obtain more convincing results by aggregating large-numbers of case and using complex statistics including multivariate analysis and propensity-score matching, none of them could be exempted from the intrinsic confounding bias associated with retrospective studies and non-randomized comparisons. And the median follow-up time of the MIT patients were unanimously shorter than that of the open surgery patients, and might not be long enough to reveal the true outcome as recurrence could appear many years after surgery. Regarding the relatively rarity and indolent nature of thymic tumors,

 

prospective randomized controlled clinical studies are unlikely to be undertaken. Currently, the only feasible way to further confirm the equivalence of MIT to open surgery seems to rely on prolonged duration and improved accuracy of follow-up.

## What is the ideal resection extent in MIT, total or partial thymectomy?

The standard surgical procedure for thymic tumors has been total thymectomy through median sternotomy, which gives an excellent exposure of the anterior mediastinum. After splitting the sternum, it is convenient to remove the entire thymus along with an early-staged tumor without invasion, guaranteeing radical resection. Besides, the adult thymus is no longer functional as an immune organ, causing little loss to the patient when completely removed. The development of MIT in treating thymic tumors has somehow challenged this concept. Similar to anterior or posterior thoracotomy, MIT such as thoracoscopic surgery and robotic surgery are usually performed via a lateral approach in which difficulty exists in exposing the upper horns or the contralateral margin of the thymus. Although similar resection extent as in median sternotomy could be achieved with the help of refined thoracoscopic vision and special instruments, there is also some degree of difficulty during operation and also the risk of accidental injury to the innominate veins, necessitating conversion to open surgery. In recent years, it has been reported that partial thymectomy in MIT might have similar results as total thymectomy (15-17). An important issue is that all these three reports were retrospective single-center studies with small number of cases and inadequate time of follow-up, making it difficult to confirm the oncological outcomes of partial thymectomy.

Interestingly, all these studies came from Asian countries, which might be related to the fact that historically surgeons in Asia have been more accustomed to partial thymectomy via lateral thoracic approach. This was clearly reflected in the ITMIG retrospective study by Fang *et al.* comparing surgical approaches in Asia, Europe, and the United States (13). The results showed that in 1,430 patients with Masaoka-Koga stage I–II thymic tumors, the proportion of MIT in the Asian group exceeded 30%, significantly higher than those of the North American (15.9%) or the European group (9.6%). This was accompanied by a significantly higher proportion of partial thymectomy in Asian patients (31.7%) than in North American (5.4%) or European patients (2.4%). Multivariate analysis showed that in addition to the geographic regions, MIT and lateral thoracotomy were independent predictors for partial thymectomy.

In fact, the ChART multi-center retrospective study better illustrated this issue (18). Nearly a quarter of the 1,047 patients with Masaoka-Koga clinical stage I–II thymic tumors in the ChART database received partial thymectomy. Total thymectomy was more often performed in median sternotomy, while partial thymectomy was mostly done in lateral thoracotomy or MIT. Upon multivariate analysis, 10-year overall survival (90.9% *vs.* 89.4%) and overall recurrence rate (3.1% *vs.* 5.4%) after total or partial thymectomies appeared to be similar. However, in stratified analysis, recurrence was significantly less after total thymectomy than after partial thymectomy for Masaoka-Koga stage II tumors (2.9% *vs.* 14.5%, P=0.001), although no significant difference was seen in Masaoka–Koga stage I diseases (3.2% *vs.* 1.4%, P=0.259). Given the difficulty in telling Masaoka-Koga stage I from stage II tumors on preoperative imaging or even upon intraoperative exploration, it is thus important to make sure that surgical and oncological principles could be observed. With the limited evidences currently available, total thymectomy should still be recommended as the standard resection extent to ensure radical removal and accurate staging of the disease. Its feasibility and effectiveness in locally advanced tumor remains to be established.

In summary, minimally invasive surgical techniques are already quite mature in the surgical treatment of thymic tumors. With reduced surgical trauma, patients can benefit from MIT by improved postoperative recovery and decreased functional loss. At present, there is already some preliminarily clinical evidences confirming the oncological effectiveness of MIT, but its long-term outcome remains to be further verified. No matter which surgical approach is used, similar surgical and oncological principles should always be observed so that patients with thymic tumors could truly benefit from the advancement of modern surgery.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

 

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