Editorial

Minimally invasive thymectomy for thymoma: does surgical approach matter or is it a question of stage?

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Complete (R0) surgical resection remains the primary treatment modality for thymoma in both early and advanced stage disease. Following trends seen in surgery for other malignancies, minimally invasive thymectomy (MIT) utilizing VATS or robotic approaches have increased in popularity due to the short term and cosmetic benefits associated with minimally invasive surgery. However, the efficacy of MIT for thymoma compared to open surgery (which utilizes a median sternotomy or thoracotomy) based on oncologic results or survival outcomes remains controversial. The theoretical risk of incomplete resection or capsular disruption causing recurrence and decreased survival with MIT has led many surgeons to avoid MIT for the treatment of thymoma. Because of the relative rarity of the diagnosis and the indolent course of thymoma, comparisons of surgical technique have relied mainly on small single-center retrospective reports which provide limited levels of evidence to support any specific treatment paradigm. Historically, MIT was performed using the transcervical approach popularized as a method for treating myasthenia gravis (MG), not thymoma, although one series does report their experience with the technique for thymic tumors (1). The relative difficulty of transcervical thymectomy compared to VATS or robotic approaches has resulted in the much wider adoption of VATS/Robotic MIT as the preferred minimally invasive approach. Other questions regarding thymoma management such as which staging system to use, how to utilize the World Health Organization (WHO) histologic classification, what induction or adjuvant therapies are indicated and for which stage of disease, and whether partial thymectomy, debulking surgery, or re-operative surgery are beneficial remain unanswered. These issues and the different treatment strategies employed per patient and per institution are important confounding factors whenever one analyzes any particular surgical technique.

Open Surgical resection has been the gold standard of treatment for thymoma because the overwhelming majority of thymomas are localized at the time of diagnosis and amenable to local therapy. A comprehensive review of the literature that complied studies that included at least 100 patients revealed that 40% of thymomas presented as stage I, 25% as stage II, 25% stage III, 10% stage IVa, and 1–2% stage IVb (2). Thus 65% of patients presented with disease confined to the thymus gland without invasion into adjacent structures. In that review, the ability to perform an R0 resection for early stage disease was nearly 100% for stage I, with 85% for stage II (range, 43–100%). The average rate of R0 resection rate diminished significantly with advanced stage, only 47% for stage III and 26% for stage IV. In stage III and IV disease, the rate of complete resection varied widely between studies reflecting the heterogeneity of advanced stage thymomas in terms of the degree and location of invasion and the differences in institutional practice patterns concerning aggressiveness of resection.

Survival after complete R0 resection for thymoma is excellent. In the largest retrospective analysis of thymectomy for thymoma, 92% of patients achieved an R0

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resection. Survival at 5 and 10 years for stage I thymoma was 100% and 100%, respectively (3). Stage II disease did almost as well achieving 98% 5- and 10-year survival rates. Stage III patients exhibited significantly decreased survival compared to stage I and II patients, with 89% 5-year survival and 78% 10-year survival. Stage IVa patients showed similar trends averaging 71% 5-year survival and 47% 10-year survival. This landmark study illustrated that not only do early stage patients do incredibly well, but even advanced stage patients can achieve durable long-term survival not seen in other solid malignancies. Interestingly, patients who had positive margins, either microscopic R1 or macroscopic R2 resections, had a 64% 10-year survival compared with a 36% 10-year survival in patients who had no attempt at surgical resection and underwent biopsy only, suggesting that even those with a significant volume of residual disease can survive for extended periods of time. This study illustrated that complete microscopic resection is achievable in a large proportion of thymoma patients and that survival after an R0 resection was significantly higher, establishing that complete surgical resection is the best therapeutic modality for thymoma. Similar results have been reported in other series (4-9). Interestingly, in the study by Rea *et al*., no significant survival difference was seen between those undergoing debulking surgery compared to biopsy alone, further supporting the importance of achieving an R0 resection if possible (6).

Perhaps then the most important consideration in the treatment of thymoma is how to treat stage III and IV disease. As the previous studies illustrated, the rates of R0 resection and survival decrease with advanced Masaoka stage. This phenomenon is intuitive, as the degree of invasion through the gland capsule into surrounding tissue qualifies the tumor as stage III or IV. Thymoma is both chemo and radio-sensitive. The EORTC phase II study investigating chemotherapy in metastatic thymoma revealed that response rates in 16 patients were roughly 50%, with five complete pathologic responses and four partial responses (10). Thus there has been increasing interest in multimodality approaches to advanced disease. In an effort to increase the rate of R0 resection and improve survival, several series utilizing multimodality therapy with induction chemotherapy, surgery, and postoperative chemotherapy or radiation in stage III and IV thymomas were undertaken (2). While small in size, these studies revealed excellent response rates ranging from 77% to 100% and an average R0 resection rate of 72%. Overall 5-year survival was 78%. Twenty-one percent of patients were observed to have a complete pathologic response to multimodality therapy. A recent pilot study showed comparable response rates, acceptable complication rates, and overall safety and feasibility of induction therapy for advanced stage thymomas and an R0 resection rate of 71% (11).

The first approach for a MIT was performed with a transcervical technique, popularized for treating MG, but also shown early on to be feasible for treating thymic tumors (12). More recently, Deeb *et al*. reported a small series of transcervical thymectomy for patients with known mediastinal masses (1). In that study, of 98 patients treated for MG, 14 had thymoma, 5 were stage I, 8 stage II, and 1 stage III. They had no patients recur with a mean follow up of 48 months. While the follow up time is insufficient for thymoma, where time to recurrence averages 5 years and is seen as late as 20 years after surgery (2), this study illustrated that a minimally invasive surgical approach for thymoma may be oncologically sound. Similarly, VATS and robotic approaches to thymectomy were first described for benign resections with many studies reporting less blood loss, shorter length of stay, decreased pain, and similar long term results compared to open thymectomy (13-15). Following these experiences, the use of MIT for known thymoma has increased, yet remains controversial.

A recent meta-analysis examined 30 studies that reported results for MIT either alone or compared to open surgery, with a total of 2,038 patients included in the analysis (16). Of the 30 studies, 16 had direct comparisons between MIT and open thymectomy. The mean tumor size for the MIT cohort was 4.09 cm (range, 3.23–5.76 cm) and 4.8 cm (range, 3.76–7.47 cm) in the open group. More patients with early Masaoka stage I and II thymoma were treated with MIT compared to open, 94.89% *vs*. 78.62%, respectively, illustrating that more advanced disease was preferentially treated with open surgery. Only 2.36% of MIT cases were converted to an open procedure. There was no significant difference in the rates of R0 resection or local recurrence between MIT and open surgery. In a subgroup analysis, comparing only Masaoka stage I and II patients, R0 resection rates were identical, 97.36% *vs*. 97.25%, for stage I and II respectively. In addition, local recurrence rates were also the same, 2.86% in the MIT group and 2.91% in the open group. This study suggested that there is no statistically significant difference in R0 resection or local recurrence rates between MIT or open groups. Only blood loss and length of stay were significantly different, favoring MIT. The weakness of this meta-analysis is that it is based on non-randomized retrospective studies

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with small numbers. Furthermore, the analysis of R0 resection rates and recurrence rates included only a small, select subset of studies that reported these results raising questions regarding the overall validity of the statistical conclusions. Finally, the data did not provide any guidance to help surgeons select certain patients for open or MIT procedures. It seems, that the preponderance of their data supports the use of MIT for early stage thymoma, stage I or II, but is less clear for advanced stage disease.

In the article "*Determinants of complete resection of thymoma by minimally invasive and open thymectomy: analysis of an international registry*" by Burt *et al*., the authors analyzed data from the retrospective database of the International Thymic Malignancy Interest Group (ITMIG) and reported on 2,514 patients who underwent thymectomy for thymoma by VATS/robotic or open approach (17). The objective of the study was to determine if MIT was associated with inferior R0 resection rate compared to open and to identify which factors were associated with completeness of resection.

The authors reviewed patients from a 15 year period [1997–2012] and noted that the number of MIT surgeries increased each year from 2008–2012, nearly reaching the rate of open cases by 2012, suggesting more acceptance of MIT at the institutions contributing to the database. Of important note, the majority of the MIT cases were contributed from Asia, with 227/461 MIT cases from this region, representing 50% of the cases in the MIT group. MIT patients were noted to have more favorable WHO histologic classification and less advanced Masaoka stage compared to the open group. Mean tumor size was also smaller in the MIT group, 4.0 cm (range, 0.4–15.5 cm) compared to the open group with a mean tumor size of 6.0 cm (range, 0.1–28.0 cm). This suggests that while the open group had larger tumors, sizable tumors over 10 cm nonetheless were resectable with an MIT approach. Unfortunately, the conversion rate from MIT to open surgery is not reported and it is impossible to know which patients and what tumor characteristics led to failure of MIT and how many of these cases were then included in the open cohort. Furthermore, the rate of partial thymectomy was significantly higher in the MIT group (27%) compared to the open group (9%), and much fewer patients undergoing MIT received preoperative chemotherapy or radiotherapy. Overall, 80% of thymectomies achieved an R0 resection. The MIT cohort exhibited a higher rate of R0 resection at 94% compared to the open cohort, which achieved complete resection 86% of the time.

A propensity matched analysis was then performed on a smaller subset of patients, 266 in each group, in order to account as much as possible for baseline differences between the MIT and open groups and for the likely bias that more advanced stage patients were treated in an open approach. In this analysis, there was no statistically significant difference in the rate of R0 resection, as both groups reached an R0 resection rate of 96%. Further subgroup analysis of only those patients with stage I or II thymoma also revealed nearly identical R0 resection rates for MIT and open, 96.6% and 95.1% respectively. Multivariate analysis of prognostic factors indicated that geographic region, more recent time period; less advanced Masaoka stage, total thymectomy, and no history of radiotherapy were significantly associated with achieving an R0 resection. The authors thus concluded that their data supports equivalence in the ability to obtain an R0 resection regardless of surgical approach.

These results, combined with the meta-analysis provided by Friedant *et al*., provide compelling evidence that early stage I and II thymomas are likely treated effectively with MIT and outcomes such as R0 resection and recurrence rates will likely be identical to open surgery (16). However, there should be great caution when deciding the surgical approach for more advance, stage III and IVa, disease. Firstly, the majority of the MIT cases in the ITMIG study were registered from Asia. The Friedant meta-analysis was similarly based on mainly Asian patients with 422/492 from Asian studies, raising the possibility that both studies may share patients and thus have similar results. It would be helpful to know if the ITMIG data included any patients from the previously published meta-analysis. Furthermore, the ITMIG study does not provide any data on follow up. In light of the fact that most of the MIT cases were added to the registry after 2008, the length of follow up may not be sufficient to report on recurrence rates. Finally, after propensity matching, the vast majority of patients in the ITMIG study were stage I and II, 91% and 94% in the MIT and open groups, respectively. Thus the conclusions of the paper might only apply to early stage thymoma. Only 25 patients in the MIT group and 18 patients in the open group had advanced stage III or IV disease in the propensity-matched analysis, making any real comparison to early stage cases questionable. Critical information regarding clinical stage prior to surgery, what type of extended resections were performed for invasive thymomas, and the frequency and cause of conversion to open surgery is not discussed, providing little in the way of guidance for surgeons to appropriately choose which technique may be

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best in advanced stage disease. Before MIT can be readily advocated for stage III and IVa thymoma, further study with larger numbers of patients and well matched by baseline characteristics, including detailed analysis of extent of tumor invasion into surrounding structures will help clarify this debate and provide much needed guidance for managing these patients (18,19).

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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