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CLINICAL STUDY

The comparison of modified minimally invasive and open surgical approaches in the treatment of epithelial thymic tumours

Juhos P[1], Janik M[1], Lucenic M[1], Tarabova K[2], Komarc M[3]

Department of Thoracic Surgery, Slovak Medical University, University Hospital Bratislava, Bratislava, Slovakia. **peter.juhos@gmail.com**

ABSTRACT

OBJECTIVES: Exploring the efficacy of a modified combined minimally invasive approach in patients with thymoma regardless of myasthenia gravis involvement in contrast to open surgery as the mainstay of treatment.

BACKGROUND: Primary epithelial thymic tumours are rare malignancies of the anterior mediastinum, often present with myasthenia gravis, and with good prognosis when assuming complete surgical resection. We present a modified mini-invasive technique (MIT) that is unique in its extent.

METHODS: Fifty-two patients were included in this retrospective study. Two groups of patients who had undergone different types of surgery were compared using the Mann-Whitney test (ordinal variables) and Fisher's exact test (binary variables). Changes after completing the surgical learning curve were observed.

RESULTS: There was a statistical difference when comparing early Masaoka stages (I–II) with later stages in favour of the mini-invasive method (p = 0.013). The duration of surgery was longer in the mini-invasive group with a median value of 260 vs 133 min (p = 0.001). The analysis of operation times revealed that after overcoming the learning curve period, the duration of surgery decreased (2008–2012: 297 min; 2013–2018: 199 min; p = 0.005). The systemic complication rate was lower in the mini-invasive method (26.1 % vs 3.4 %; p = 0.035).

CONCLUSION: Our results showed the modified maximal minimally invasive thymectomy to be an effective and safe method, and after overcoming the learning curve, even superior to open surgery in cases with lower tumour stages in terms of its extent *(Tab. 3, Fig. 1, Ref. 49).* Text in PDF *www.elis.sk*

KEY WORDS**:** thymoma, thymic carcinoma, myasthenia gravis, minimally invasive surgery, VATS, thymectomy.

Introduction

Primary epithelial thymic tumours are a group of rare oncologic conditions including thymoma, thymic carcinoma and neuroendocrine tumours of the thymus (NET). Prevalent among them are thymomas with an age-specific incidence of 0.17–0.22 per 100,000 person years (1–4). Despite this seemingly low incidence, thymomas are responsible for more than 50 % of anterior mediastinal masses in adult population with its peak age over 65 years and age median of 53 years (5). In the view of biological behaviour, thymomas are relatively indolent tumours with good prognosis, assuming complete surgical resection with low occurrence of extrathoracic metastases and locoregional lymph node involvement (6,7). The 5- and 10-year survival rates of a locally noninvasive thymoma vary between 90 % and 80 %, respectively as compared with the 5-year survival rate of 55 % in case of thymic carcinoma. Survival rates decrease with local invasion and higher histopathologic type and grading. Nevertheless, when compared to other solid malignancies, they remain favourable (8–11). These attributes predestine patients with thymomas to be perfect candidates for primary surgical treatment and because of different concurrent paraneoplastic conditions such as myasthenia gravis (MG), these patients should be treated in a multidisciplinary fashion and in high-volume centres (12–15). Myasthenia gravis symptoms are present in 40–45 % of patients with thymoma.(16) Myasthenia gravis-associated thymoma (MGAT) differs from seropositive MG associated with thymic hyperplasia in imunopathogenesis, clinical manifestation and treatment response (16–19). With the advent of minimally invasive and robotic techniques, these advances were introduced also into thoracic surgery and surgical treatment of thymic pathology (20–24). In this light, the comparison of these novel techniques with standard care represented by longitudinal sternotomy became the aim of many studies (25–28). In the Department of Thoracic Surgery in Bratislava we perform a combined mini-invasive method of maximal minimally invasive thymectomy (MMIT) in patients with thymomas regardless of myasthenia gravis involvement (29, 30). We learned the original method from its author M. Zielinskí and became successful in applying it in non-thymomatous MG patients at first. By using a dual sternal traction, this technique provides extent, excellent overview, and manipulation in the operation field necessary for radical tumour resection in the mediastinum. We have slightly modified the method originally described by its author by removing the transthoracic

[1]Department of Thoracic Surgery, Slovak Medical University, University Hospital Bratislava, Bratislava, Slovakia, [2]First Department of Anaesthesiology and Intensive Care Medicine, Faculty of Medicine, Comenius University in Bratislava, University Hospital Bratislava, Bratislava, Slovakia, and [3]Department of Methodology, Faculty of Physical Education and Sport, Charles University, Prague, Czech Republic

Address for correspondence: P, Juhos, MD, Department of Thoracic Surgery, University Hospital Bratislava, Ruzinovska 6, SK-826 06 Bratislava, Slovakia.

part of the operation while leaving just the transcervical and subxiphoid approach with the aim of postoperative pain reduction. In this paper we present our short-term peri- and post-operative results over a period of 10 years with special consideration of the surgeons' learning curve. To our knowledge, there is no study in the available literature comparing this kind of extensive minimally invasive method with open surgery (OS).

Materials and methods

The primary aim of this study was to investigate the effect of a unique modified minimally invasive technique of thymectomy on short-term results as compared with the open approach in patients with thymic epithelial tumours with or without MG involvement. The modified maximal minimally invasive thymectomy is a surgical technique that provides the highest level of resection extent of thymic tissue as required by Jaretzki (31). This property is especially important in patients with MGAT (28). All the patients were checked and assessed for symptoms of MG and blood autoantibodies at the Centre of Neuromuscular Diseases which is a centralized and one-of-a-kind facility in Slovakia. MG patients were first stabilized on immunosuppressive therapy. Because of this collaboration, during the observed period, the majority of patients suffering from thymic pathology in Slovakia were treated at our department and are part of this study. All the patients went through a thorough preoperative anaesthesiology examination with attention paid to the neuromuscular nature of MGAT, and had a reserved ICU bed.

Strict inclusion criteria were defined because of the retrospective nature of our study. The presence of an epithelial thymic malignancy in the definitive histopathologic report was the baseline criterion. Special attention was paid to patients with paraneoplastic MG (MGAT). Another criterion was the surgical technique. The open surgical technique was carried out by longitudinal median sternotomy only. As previously mentioned, among patients treated with different minimally invasive techniques, we chose only those who had undergone surgery using the maximal minimally invasive thymectomy. Patients with other histologic results of thymic pathology (i.e. thymic cysts, metastasis, lipomas, hyperplastic thymus, non-thymomatous MG) treated using the above-mentioned techniques or patients with thymic malignancies but operated on with other surgical approach were excluded. The rationale behind choosing the MMIT was our experience with the technique in the treatment of myasthenia gravis patients. One of the controversial issues of surgical treatment of thymic tumours is the extent of resection (32). Despite the lack of randomized studies, professional societies recommend not only to achieve an R0 resection of the tumour (thymomectomy) but also to remove the thymus gland and perithymic lymphatic and adipose tissue in the anterior mediastinum especially in the case of MGAT where the extensive thymectomy according to Jaretzki and Masaoka should be performed (33–36). Out of 79 patients meeting the above-mentioned criteria, 52 patients were included in our study. Twenty-nine patients were treated using MMIT, while 23 patients underwent extended thymectomy via longitudinal sternotomy. Tumour stages were defined based on a definitive histopathologic report.

We calculated basic descriptive statistics (location, variability) for all variables of interest. The above-mentioned two groups of patients undergoing different types of surgery were compared using the Mann–Whitney test (ordinal/interval variables) and Fisher's exact test (categorical/binary variables). The same procedures were used to contrast two different time periods (2008–2012 and 2013–2018) in order to explore a potential learning curve needed to master the technique. We calculated standardized effect sizes along with 95 % confidence intervals in form of log odds ratios (for binary outcomes) and standardized mean differences (for continuous outcomes) to facilitate the comparison of our results with those described in the literature. P values below 0.05 were considered to be statistically significant. Statistical analyses were performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA).

Results

Out of 52 patients, 23 had thymoma without proven paraneoplastic MG while 29 patients with MGAT received immunosuppressive therapy. In overall demographics, the sex ratio was slightly in favour of females, namely 29 females (55.8 %) to 23 males (44.2 %). The median age was 57 years (min 24; max 77). Twenty-eight patients with MGAT (96.6 %) were diagnosed with the seropositive form of MG, either generalized (n = 20) or ocular (n = 8). One patient was diagnosed with the seronegative form of the disease (3.4 %). Following the Masaoka-Koga staging system (37), the patients were mainly distributed in stages I and IIA (82.7%) (Tab. 1). After conversion to the new TNM classification (8th edition), 90.4 % of the patients were in stage I. The surgical technique distribution per clinical stage of the oncologic disease is detailed in Table 1.

When comparing Masaoka stage I with higher stages, there was no statistically significant difference in the chosen surgical approach. On the other hand, when stages I and II were compared together with later stages, there was a significant difference (p = 0.013) in favour of MMIT in lower stages, and in favour of OS in later stages of the disease, which could be explained with the natural tendency to prefer sternotomy in locally advanced tumours. The conversions to OS were done due to bleeding in 2 patients, while 3 patients were converted for oncologic reasons. The median tumour size was 55 mm overall (min 18 mm; max 130 mm). The median tumour sizes in the MMIT and open surgery groups were 50 mm, and 70 mm, respectively while the difference was statistically significant (standard mean difference: –1.16; CI: –1.78 to –0.53;

Tab. 1. Distribution of stages according to Masaoka-Koga system in two types of surgery.

Masaoka stage	MIT	OS	Total
I	15 (51.7%)	9 (39.1%)	24 (46.2%)
IIA	10 (34.5%)	9 (39.1%)	19 (36.5%)
IIB	4 (13.8%)	0 (0.0%)	4 (7.7%)
III	0 (0.0%)	3 (13.0%)	3 (5.8%)
IVA	0 (0.0%)	1 (4.3%)	1 (1.9%)
IVB	0 (0.0%)	1 (4.3%)	1 (1.9%)
Total	29 (100.0%)	23 (100.0%)	52 (100.0%)

mini-invasive – MIT, open – OT

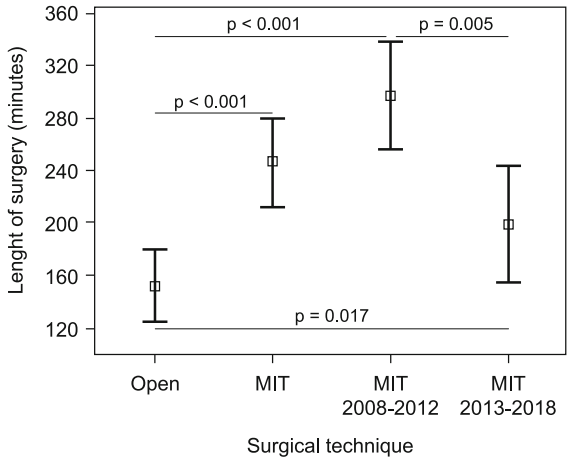

Fig. 1. Duration of surgery depending on operating technique in minutes.

p = 0.001). R0 resection was achieved in 49 patients (94.2 %). The comparison of resection radicality between these two techniques could not be done because of low frequency of the variable.

The diagnosis-specific distribution of surgical techniques was as follows: MMIT was carried out in 79.3 % of MGAT patients while 73.9 % of patients with non-MG thymoma were treated with OS, which represented a significant difference (log OR: 1.04; CI: 0.47–1.60; p < 0.001). An interesting and statistically significant finding was noted in the observed time periods (2008–2012 and 2013–2018) when we operated on almost the same number of patients using the minimally invasive technique (n = 14 and n = 15, respectively) but an increase in the open approach was detected from 4 to 19 (log OR: –0.65; CI: –1.21 – 0.08; p = 0.038). Also, the conversions took place in the later time period. From the surgeons' perspective, the comparison of the duration of surgery is one of the most important short-term variables. The median value for the whole observed period for MMIT was 260 minutes and 133 minutes for OS, which proved to be significant (standard mean difference: 1.22; CI: 0.62–1.81; p < 0.001). The initially longer operation times coincided with the introduction of the new mini-invasive method, and the learning curve surely contributed to this difference. Taking these data into consideration, we decided to analyse the previously mentioned two different time periods where the operating times for MIT significantly differ (2008–2012: 297 min; 2013–2018: 199 min; p = 0.005) (Fig. 1). As to the duration of drainage (MMIT = 3 days; OS = 4 days) and LOS (MMIT = 5 days; OS = 5 days) there was no significant difference (p = 0.418; p = 0.461).

Tab. 2. Specific complications of surgical technique.

Complication	MIT	OS	Total
Myastenic crisis	0	1	29
Tracheostomy	0	3	52
Phrenic nerve lesion	1	3	52
Phrenic nerve lesion with diaphragm plication	0	2	52
Recurrent nerve palsy	1	0	52

Average blood loss was 118.97 ml for MMIT, and 269.57 ml for sternotomy with no significant difference (standard mean difference: –0.48; CI: –1.03 – 0.09; p = 0.172). The systemic complication rate (pneumonia, atrial fibrillation, pneumothorax, embolization) was lower with the mini-invasive method (26.1 % vs 3.4 %; log OR: –0.99 CI: –1.95 – –0.04; p = 0.035). There was no difference in the observed disease-specific complications (Tab. 2). Neoadjuvant therapy was administered to 4 patients in the OS group with no statistical significance (p = 0.080). No perioperative mortality was documented.

Comparing our results with those described in literature

The latest study of larger scale to compare minimally invasive thymectomy (MIT) and open surgery for thymic malignancies was designed by Friedant et al 2016 (Tab. 3) (26). It is a systematic review and meta-analysis of 30 studies from 1995–2014. Its limitation is that only nonrandomized retrospective works were included. The reason behind this is the total absence of prospective studies on the topic that would meet the inclusion criteria of the authors. The short-term targets the authors focused on were demographics, length of surgery, blood loss, LOS, tumour size, completeness of resection, conversion rate, respiratory and cardiac complications. The average tumour size in both MIT and OS was larger in our study. From the studies assessing the oncologic stage, patients with Masaoka stages I and II were similarly distributed. There was almost no difference in demographic parameters. When comparing the length of surgery, Friedant et al. found no significant difference between MIT and OS groups (164.92 min vs 147.18 min, standard difference = 0.13, 95 % CI: –0.28 to 0.54, p = 0.53). On the other hand, in our study, the overall operation time was significantly lower in the OS group. A decrease was noted in the later time period after completing the learning curve. The time difference could be explained also with the fact that our MMIT is a more extensive surgical method compared with the majority of minimally invasive techniques, and the resected tumours were larger. In contrast with our work, there was a significant difference in the duration of stay (LOS), namely 8 days in the MIT group and 9 days in the OS group (standard difference = –0.88, 95 % CI: –1.52 to –0.24; p < 0.01). In our study, LOS was 5 days in both groups.

It has to be stressed that this is a brief comparison and that it was not our aim to provide a profound analysis.

Tab. 3 Comparison of our results with those described in literature (Friedant et al) using standardized effect sizes along with 95% CI.

Variable	Technique (Friedant)		Technique (our results)	
	MIT	OS	MIT	OS
Tumour size (mm)	40.9	48	50	70
Masaoka stage I. II (%)	94.89	78.62	100	78.2
Age (years)	52.34	52.72	55.17	53.43
Conversion rate (%)	2.36		9.61	
Blood loss (ml)	169	226	118.97	269.57
Duration of surgery (min)	164.92	147.18	260 (199)*	133
Duration of stay (days)	8	9	5	5

*duration of surgery considering the learning curve

Discussion and conclusion

Minimally invasive surgical approaches expanded recently into various fields of thoracic surgery and in some types of surgery such as lung resection even replaced the golden standard of open surgery and became the mainstay of treatment. Mini-invasive surgery of thymic malignancies was not "spared" the novel techniques like VATS, subxiphoid approach, combined methods, and robotic VATS resection (38, 39). Even though the course is set in favour of these techniques, there are still doubts and uncertainty about the efficacy of mini-invasive treatment compared with open surgery represented by longitudinal sternotomy or thoracotomy (40–42). Due to these issues, the topic is still ongoing and controversial. When considering the rare incidence of thymic malignancies and lack of randomized controlled trials (RCT) we deem our results with a modified technique worthwhile sharing with the professional community. As it is ever the problem with rare diseases, the chance of conducting a thorough RCT is slim and less likely. Due to these matters, the most prudent way to outsource any data for comparison is to analyse the largest and best-quality retrospective database of the International Thymic Malignancies Interest Group (ITMIG) (16, 43–45). The recommendations and guidelines published by this group are considered as accepted standards in the treatment process. Doubts about the efficacy of mini-invasive surgical methods stem from the possibility of a less radical resection, tumour capsule compromise, and therefore cancer cell dissemination in the mediastinum and pleural cavities resulting in increased locoregional recurrence, worse prognosis and survival (46–48).

The majority of recent studies exploring this matter conclude the equality even superiority of various, although less extensive minimally invasive approaches regarding short-term results (21, 25–27). Another important issue are the long-term results, i.e. disease recurrence, 5- and 10-year survival rates, and disease-free interval. Taking into consideration the relatively short period that MIT are used and overall small numbers of patients, these results are mostly unavailable or scarce. The long-term results in our study are still being collected and analysed and will be presented in the near future. Naturally not all patients are candidates for MIT. These techniques are usually proposed to patients in lower stages of the disease (Masaoka I and II) with the tumour well encapsulated, localized in the anterior mediastinum, and not exceeding 5–6 cm in diameter, with clear plane between large vessels of the mediastinum on radiologic imaging, no sign of local tumour compression, and unilaterally confined disease (49). Conversely, the invasion of phrenic nerves, left brachiocephalic vein or other major vessels is regarded as a contraindication. Any uncertainty in achieving complete radical resection (R0) needs to be met with a stern resolution to convert to open surgery. The fact that in large reviews, the conversion rates are low attests to the correct patient selection. The arguable advantages of MIT are better cosmetic effect, less intense pain, smaller blood loss, shorter durations of hospital and ICU stay, faster convalescence, and a similar rate of R0 resection as the main long-term prognostic factor of survival and recurrence. More recently, the time of surgery is deemed to be an independent variable affecting the completeness of resection in correlation with the learning curve of surgeon (21).

There are limits to our study, namely its retrospective design and the natural bias against selecting patients with locally advanced tumours that are more likely to be indicated for open surgery. The higher conversion rate and median tumour size attest to the fact, that after conquering the learning curve of a new modified method, more advanced stages of thymomas are attempted to be resected in a minimally invasive way. In the later period of our study, we observed that the more experienced the surgeons get, the shorter the duration of surgery, almost achieving time typical for the open method especially considering the higher level of MMIT extent.

Consequently, according to our results, we consider MMIT to be an effective, extensive, safe and even superior alternative approach in cases with lower clinical stages of thymic malignancies especially for patients with myasthenia gravis symptoms, and in some regard possibly superior to less extensive mini-invasive approaches.

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