Surgical treatment of thymic epithelial tumors: a narrative review

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Background and Objective: Thymic epithelial tumors (TETs) are scarce neoplasms of the prevascular mediastinum. Included in this diverse category of lesions are thymomas and thymic carcinomas (TCs). Surgery is the mainstay of treatment of tumors that are deemed resectable. However, up till now, optimal surgical access has been a subject of debate. The advent of new techniques, such as video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS), challenged the median sternotomy which was traditionally considered the access of choice. This review aims to demonstrate the current evidence concerning the surgical treatment of TET and to enlighten other controversial issues about surgery.

Methods: PubMed research was conducted using the terms [surgery] AND [thymic epithelial tumors] OR [thymomas] and [surgical treatment] AND [thymic epithelial tumors] OR [thymomas]. Papers concerning pediatric cases and non-English literature papers were excluded. Individual case reports were also excluded.

Key Content and Findings: Minimally invasive surgical techniques (MIST) such as VATS and RATS are increasingly applied in early-stage TET. Although numerous published studies have demonstrated better perioperative outcomes in early-stage TET, long-term follow-up data are still required to demonstrate the oncological equivalent of MIST to open surgery. Resection of stage III TET is more challenging. Thymectomy can be expanded en bloc to include the major vascular structures, lung, pleura, phrenic, or vagus nerve in these individuals. There is no agreement on the ideal surgical access and traditionally these patients underwent open sternotomy, sometimes combined with a thoracic access. Evidence concerning the treatment of stage IVA disease is mainly derived from retrospective case series which are highly heterogeneous in terms of the number of enrolled patients, histology, degree of pleural involvement, and timing of presentation.

Conclusions: New techniques in the field of minimally invasive surgery are gaining acceptance for early-stage TET but longer follow-up periods are warranted to prove their oncological outcomes. On the contrary, these techniques should be used cautiously in case of locally advanced tumors. Surgeons must not forget that the main objective is the complete resection of the lesion, which is one major predictive factor for increased survival.

Keywords: Thymoma; thymic carcinoma (TC); robotic surgery; thoracoscopic surgery

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Introduction

Thymic epithelial tumors (TETs) are scarce neoplasms of the anterior (prevascular) mediastinum (1). Included in this diverse category of lesions are thymomas and thymic carcinomas (TCs). Thymomas have in general an indolent course and until recently, they were considered to be benign lesions (2). On the contrary, TC are more aggressive tumors that tend more frequently to invade adjacent organs and metastasize (2,3). Consequently, TC have a worse prognosis than thymomas (2). Many staging classification systems have been suggested and put into practice. The most popular staging system is that developed by Masaoka in 1981 and modified by Koga in 1994 (4-6). The World Health Organization (WHO) histological classification (1999) was accepted on a global scale. The revised WHO classification in 2015 classified these tumors as A, AB, B1, B2, and B3 thymomas and TC (7,8). The Masaoka-Koga stage classification and the WHO histological classification, however, are not directly correlated (4-9). The International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancies Interest Group (ITMIG) created a new tumor-node-metastasis (TNM) staging system in 2014 (9). Consequently, thymic malignancies were matched to other solid tumors using a TNM method.

Surgery is the mainstay of treatment of tumors that are deemed to be resectable. Indeed, many studies have shown that one of the major predictive factors of survival is the completeness of resection (10). However, up till now, optimal surgical access has been a subject of debate. The rarity and histological heterogeneity of TET preclude the conduction of large-scale randomized trials and this problem is also applicable to the choice of surgical technique. The available body of evidence is mainly derived from retrospective series and thus robust recommendations are difficult to define. The advent of new techniques, especially in the field of minimally invasive surgery, such as video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS), challenged the median sternotomy which was traditionally during decades considered the access of choice for the resection of TET (11). Nowadays, still many surgeons consider median sternotomy to be the preferred surgical approach. Transcervical or subxiphoid access has also been proposed as an alternative to the trans-sternal and intercostal techniques, involving sometimes sternal lifting (12). This review aims to demonstrate the current evidence concerning the surgical treatment of TET by providing an appraisal according to the stage of the lesions and to enlighten other controversial issues about surgery. For demonstrative and educational reasons, two perioperative photos and one photo of an operative specimen of three different cases operated in the University Hospital of Antwerp are provided in the main text, without elements that could reveal the identity of the patients. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-44/rc).

Methods

The current recommendations on the quality assessment of narrative review articles were followed in the elaboration of this review (13). Research from PubMed was done with the terms [surgery] AND [thymic epithelial tumors] OR [thymomas] and [surgical treatment] AND [thymic epithelial tumors] OR [thymomas]. Papers concerning pediatric cases and non-English literature papers were excluded. Individual case reports were also excluded. Papers were chosen based on relevance because the current study is not a systematic review. The majority of studies were retrospective case series and consequently, papers with higher levels of evidence have not been identified. The references of selected papers were sought to find other pertinent articles. The search strategy is demonstrated in *Table 1*.

An overview of the surgical treatment of TET

The surgical treatment of TET is presented for each stage according to the Masaoka-Koga staging system. The treatment of recurrent disease, the extent of lymphadenectomy, the place of salvage surgery and the extent of resection (total versus limited thymectomy or thymomectomy) are the subjects of separate analysis.

The histological heterogeneity of TET inevitably creates inhomogeneous studies in terms of WHO histological classification and the Masaoka-Koga clinical stage. In addition, patients with thymomatous myasthenia gravis (MG) are added to the population. This innate heterogeneity is aggravated by the difference in definitions, because by using the term “thymectomy”, the extent of resection is sometimes considerably variable. Toker *et al.* provided definitions to standardize surgical practice and research (12). These definitions have been endorsed by ITMIG members. More specifically, a complete

Table 1 The search strategy summary

Items	Specification
Date of search	01/09/2023
Databases and other sources searched	PubMed
Search terms used	[surgery] AND [thymic epithelial tumors] OR [thymomas] and [surgical treatment] AND [thymic epithelial tumors] OR [thymomas]
Timeframe	No date restriction
Inclusion and exclusion criteria	Inclusion: all types of studies
	Exclusion: papers concerning pediatric cases and non-English literature papers were excluded. Individual case reports were also excluded
Selection process	The literature research and selection process were conducted independently by four of the authors (L.B., S.K., D.V., R.W.)
	Any discrepancies were resolved after a discussion between the researchers, if no consensus was obtained, the opinion of the designers of the study (A.C.A., J.M.H.H., P.E.V.S.) was sought

thymectomy (complete removal of the thymic gland) is advised for patients without MG, and an extended thymectomy (removal of the contiguous right and left mediastinal pleura, mediastinal and pericardiophrenic fatty tissues, and dissection of the aorto-pulmonary window in addition to a complete thymectomy) is advised for patients with MG (12). Therefore, unless it is in the context of a clinical trial, surgical resection of anything less than a complete thymectomy is seen to be unsuitable at this time. Onuki *et al.* and Bae *et al.* used the term "limited thymectomy", described as the removal of the thymoma (thymomectomy) along with the fatty tissue and surrounding tissue, leaving behind residual thymic tissue (14,15). Even if encouraging results in terms of recurrence are presented, however, these should be interpreted cautiously because long follow-up periods are warranted in order to draw robust conclusions. The indolent course of TET renders mandatory the establishment of longer follow-up programs. For all these reasons, limited thymectomy is highly debated.

The anatomic position of the thymus in the anterior (prevascular) mediastinum reasonably led the thoracic surgical community to consider median sternotomy as the optimal surgical access that could provide easy and complete resection of thymic lesions (11). Thymectomy may also be performed by cervicotomy and thoracotomy but there are concerns raised about the completeness of resection that can be achieved. Median sternotomy remains the primary surgical method for resectable lesions (stage I, II, and selected stage III cases), according to the European Society of Medical Oncology (ESMO) recommendations on thymic tumors (grade IV, level A) (16). Nevertheless, minimally invasive techniques are considered to be an alternative for assumed stages I and II, according to the ESMO guidelines, if local technical expertise exists.

Stage I and II

Minimally invasive surgical techniques (MIST) such as VATS and RATS are increasingly applied in early-stage TET (17-20). There are many papers, mainly retrospective series, that provide excellent complete resection rates in favor of MIST. There are also studies comparing these techniques with open sternotomy, however, the absence of randomized controlled trials must be underlined. In order to compare MIST and open surgery in TET, Friedant *et al.* conducted a systematic review and meta-analysis of the relevant literature (21). Individuals in the MIST group had smaller tumors and were expected to be in stage I/II than individuals in the open surgery group (95% *vs.* 78%). Patients in the MIST group had less blood loss during surgery, but there were no significant differences in the length of the procedure, or the incidence of pulmonary, cardiac, or other complications. Patients in the MIST group had shorter lengths of stay. When only patients with Masaoka stage I and stage II thymic malignancies were examined, neither the rate of R0 resection nor the total recurrence rate differed (21). In the systematic review of Hess *et al.*, the tumors removed by open surgery were

larger than the ones in the MIST group (22). Decreased intraoperative blood loss, faster removal of the chest tube, and shorter hospital stay were all related to MIST resection. The two groups did not vary in terms of surgical complications or thymoma recurrence (22).

As for the size, traditionally MIST were considered to be indicated only for smaller tumors (23). Tumor size is a significant consideration when considering a VATS thymectomy (24). Originally set at 3 cm, the cutoff was later raised to 5 cm (25). According to Kimura and colleagues, patients were most frequently found to have tumor capsule damage during VATS in case of thymomas 5 cm in diameter or larger (26). However, numerous researchers concur that VATS thymectomy is theoretically possible for thymomas with a diameter of up to 5 cm (27). Girard and colleagues commented that large tumors were not candidates for VATS treatment due to the technical challenge of managing the tumor intraoperatively (28). According to some reports, thymoma invasion into the great veins and pericardium is a more important factor in determining the indications for VATS thymectomy than tumor size itself (29). Agatsuma *et al.* conclude that there is indeed no agreement on the largest tumor size that can be removed through VATS thymectomy, however, larger thymomas should still get cautious consideration to prevent capsule damage (30). MIST have been reported to be successful in the removal of bigger tumors when combined with enhanced technology resources and robotic resection (31). Therefore, it appears from the available data that tumor dimension does not always preclude MIST as long as the fundamentals of TET resection are upheld. (avoidance of capsule rupture and complete resection) (31).

In terms of postoperative morbidity, loco-regional recurrence rates, overall and recurrence-free survival, MIST are comparable to open surgery. Furthermore, MIST are linked to a shorter hospital stay and less intraoperative blood loss. Gu *et al.* studied patients who were included in the ChART (Chinese Alliance for Research in Thymomas) database in order to compare VATS with open surgery for stage I TET (32). It was a propensity score-matched study with 110 patients in each group (after matching). Their analysis showed no significant difference in overall survival (OS), disease-free survival (DFS), cumulative incidence of recurrence, and improvement of MG between the two groups. However, it has to be taken into consideration that the median follow-up was 26 and 36 months for VATS and open surgery, respectively. In conclusion, according to the Guideline Committee of the Japan Lung Cancer Society (JLCS) for Thymic Tumors, for clinical stage I–II TET, thoracoscopic resection may be considered, although there is insufficient scientific evidence (grade C1) (33).

A retrospective study using data derived from 32 Japanese institutions, compared VATS and sternotomy for the surgical treatment of Masaoka I and II stage thymomas (30). Using propensity scores, the study evaluated postoperative complications, positive surgical margins, location of recurrence, and survival in 140 patients who underwent VATS and 140 patients who underwent sternotomy. There was no statistically significant difference in the recurrence rate, the recurrence-free survival, and OS rates between groups. According to the authors, the risk of pleural spreading is not increased with VATS thymectomy.

The advent of RATS has revolutionized surgical resection of TET mainly because of the better visualization of the anterior mediastinal compartment (especially in distal areas such as the superior thymic horns) offering better and more precise dissection (34,35). These advantages demonstrate that RATS can overcome the limitations of VATS. A meta-analysis published in 2017 compared RATS and VATS for TET. More particularly, surgical outcomes, operative time, length of stay, intra-operative blood loss, conversion to sternotomy, and postoperative complications were investigated (36). Five articles were included and a total of 450 patients were analyzed (169 by RATS and 281 by VATS). The quantitative analysis revealed no significant differences between the RATS and VATS. There were no significant differences in terms of conversion rates, operative time, and length of hospitalization. There was a slightly higher blood loss in the RATS group. Another meta-analysis included 350 patients (182 and 168 patients treated by RATS and VATS thymectomy, respectively). In terms of conversion to open surgery, hospital stay time, or postoperative pneumonia, there was no statistically significant difference. The RATS thymectomy group had a longer operative time (37). A third study included a total of 489 patients, of whom 215 underwent RATS and 274 open surgery. Patients undergoing RATS spent less time in the hospital than patients treated by open surgery. The differences in pleural drainage days, intraoperative blood loss, and postoperative complications were not significant between the two groups (38). Soder *et al.* conducted a propensity-score matching analysis of two groups of patients, operated by RATS or open procedures (39). RATS was associated with decreased operative time, complications, chest tube duration, and length of stay. The completeness of resection was similar between the two groups. OS was

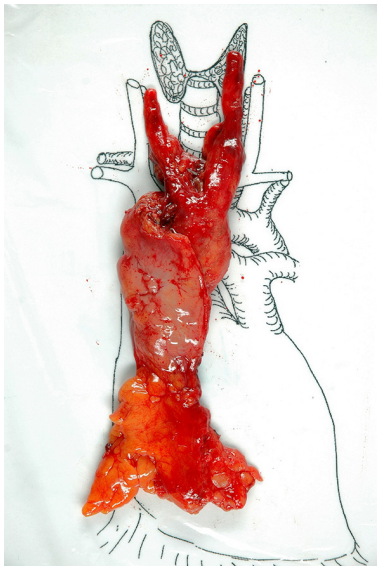

Figure 1 Operative specimen of a small thymic carcinoma removed by robotic-assisted thoracoscopic surgery.

85.3% in the open surgery group and 96.8% in the RATS group (the median OS was not reached in the two groups), however, it has to be mentioned that the median follow-up was significantly shorter in the RATS group.

Consequently, RATS seems a valid alternative for open surgery in terms of perioperative outcomes but longer follow-up is needed in order to support the oncological outcomes. Another issue that has to be taken into account is the high cost of the robotic platform that hinders its widespread use. On the other hand, studies comparing different techniques do not always provide a cost analysis. *Figure 1* shows the operative specimen of a small TC removed by RATS in our institution.

Li *et al.* conducted a propensity score-matching study comparing VATS and RATS (60 patients in each group) (40). The majority of tumors were stage I and II. Progression-free survival (PFS) was longer in the RATS group but not statistically significant. The surgical time in the RATS group was significantly shorter than that in the VATS group. However, there were no significant differences in postoperative complications, duration of chest tube insertion, the median volume of drainage (in the first 24 hours), or postoperative hospital stay (40).

A retrospective study from the Netherlands concluded that RATS is a safe and feasible procedure for patients with thymomatous MG (41). More particularly, the majority of myasthenic patients with a thymoma presented remission, mostly within 12 to 24 months after surgery. There was no discernible variation in the results between myasthenic and non-myasthenic patients. (41).

The entry point into the thorax is also a matter of debate in both RATS and VATS. Right-sided, left-sided, or bilateral access is applied by different groups without a consensus about the optimal strategy. Valid arguments exist to support the choice of each surgical access depending on the surgeon's and center's experience.

Subxiphoid access seems to overcome this problem by providing a surgical view equivalent to a sternotomy with visualization of both phrenic nerves and a good exposure of the upper poles of the thymus. Many groups reported excellent results (42-44), and the addition of sternal elevation further improves surgical view (44). Suda *et al.* evaluated thymectomies performed either through a single subxiphoid incision or via trans-subxiphoid RATS (43). The operative time was significantly shorter in the single-port group compared to the robotic group (135±48 and 204±40 min, respectively). The amount of blood lost during surgery, the length of the hospital stay following the procedure, and the time spent using oral analgesics afterward did not significantly differ between the groups. There were no intraoperative complications (43). Even though RATS could be applied through a subxiphoid incision, this technique is not widely adopted and thus more evidence is necessary. Song *et al.* evaluated the treatment efficacy of thymectomy for stage I and II TET performed using a subxiphoid thoracoscopic technique with a double elevation of the sternum compared to intercostal uniportal VATS (45). They gauged the degree of resection by measuring the length of the removed thymic tissues. Significantly larger specimens were resected through a subxiphoid VATS approach compared to the intercostal VATS group. No significant differences were found in the hospitalization cost, incidence of complications, or 3-year DFS between the two groups (45). The authors concluded that in comparison to intercostal VATS, the subxiphoid approach with double elevation of the sternum demonstrates the possibility for a more thorough clearing of thymic tissue (45).

There are numerous reports of the oncologic reliability of VATS thymectomy for Masaoka stage I and II tumors in terms of the oncologic outcome (46). According to Jurado and colleagues, there was no difference in 5-year recurrence-free survival (RFS) and recurrence rates between patients receiving VATS treatment and those receiving open sternotomy (47). When compared to sternotomy, VATS yielded a better 5-year OS, but the 5-year RFS did

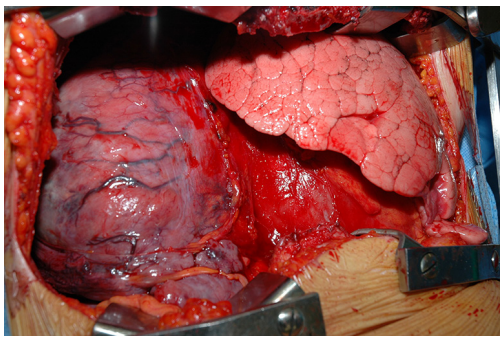

Figure 2 Intraoperative photo of a large thymoma B2 operated by clamshell incision.

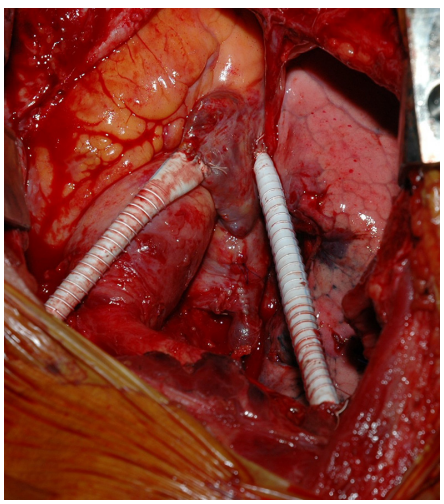

Figure 3 Intraoperative photo of another case of B2 thymoma operated by sternotomy with venous reconstruction with two ringed polytetrafluoroethylene grafts.

not change between the groups, according to Sakamaki and colleagues' research (48).

However, it is unclear whether VATS thymectomy for MG has the same operative outcomes as median sternotomy due to the lack of randomized prospective clinical research.

However, the adoption of VATS thymectomy has been hindered, particularly for large tumors, due to oncological concerns of the thoracoscopic excision associated with the potential manipulation of the tumor and consequent pleural seeding, as well as the limited working space (39).

In conclusion, median sternotomy remains the surgical access of choice for TET in the absence of large-scale randomized controlled trials (49).

Although numerous published studies have demonstrated better perioperative outcomes, long-term follow-up data are still required to demonstrate the oncological equivalent of MIST to open surgery. It has to be mentioned that in the case of histologically proven TC, the preferred surgical approach for some groups is open surgery, even for stage II lesions (50).

Stage III

Resection of stage III TET is more challenging (51). Thymectomy can be expanded *en bloc* in these individuals to include the major vascular structures, lung, pleura, phrenic, or vagus nerve (20,52). Upfront surgery is not always feasible and for that reason, multimodality protocols are applied in these cases (53,54). When surgery is performed as the first intention treatment in stage III TET, the completeness of resection is almost sub-optimal and highly variable (40–90%) according to the different series (55). Induction therapy can in fact result in tumor downstaging and render complete resection possible in case of tumors that were initially considered to be unresectable (16,55). Combined resection of involved adjacent organs is recommended, if feasible, to achieve a complete resection (33). Incomplete resection rates are increased compared to stages I and II (56).

It has been debatable how to operate on stage III TET. There is no agreement on the ideal surgical access and traditionally these patients underwent open sternotomy, sometimes combined with a thoracic access (55). In fact, in cases of involvement of posterior mediastinal structures, an extension of the incision is necessary, in the form of hemi-clamshell or clamshell incision (57). *Figure 2* shows the case of a large thymoma B2 operated by clamshell incision and *Figure 3* is another case of B2 thymoma operated by sternotomy with venous reconstruction with two ringed PTFE grafts; both cases were operated in our institution.

The study conducted by Chen *et al.* investigated the feasibility of MIST for the resection of stage III TET (58). The study included 26 individuals who underwent surgery for Masaoka stage III thymic malignancies by VATS (subxiphoid VATS and two cases of subxiphoid combined right-sided VATS) and open sternotomy. Significantly larger tumors were resected by sternotomy. Lesions more commonly affected the phrenic nerve and superior vena cava in the same group of patients. The factors that hampered successful VATS excision were determined to be the size of the tumor (>6 cm) and the involvement of the phrenic nerve and superior vena cava. The authors conclude that

in selected cases of Masaoka stage III thymic malignancies (a thymic tumor of less than 6 cm, though invading the innominate vein, pericardium, and part of the lung), MIST are acceptable (58). However, the efficiency of the VATS resection was questioned throughout the short-term follow-up period, and more research into MIST long-term oncological outcomes is required. Yokota *et al.* operated on patients with TC. MIST were performed for stage III unless a vascular invasion necessitating a reconstruction was encountered (59).

A multicenter study enrolled 134 patients who underwent RATS resection of TET (60). Whenever stage III and IV disease were encountered during surgery, a conversion to open surgery (sternotomy or thoracotomy) was performed. In case of involvement of the pericardium, the phrenic nerve, and the parietal pleura the resection was still performed by RATS. According to the authors, despite being theoretically possible, extended resections ought to be seen as experimental surgery and only used in a very small number of cancer cases. Kang *et al.* expand the indications for robotic thymectomy in stage III TET, by including cases of lung, mediastinum, and innominate vein invasions, whereas robotic thymectomy is deemed contraindicated in cases of chest wall and great vascular invasion (61).

Stage IVA

De novo stage IVA thymomas, which account for around 7% of all thymomas, present 5- and 10-year survival rates of 59% and 36%, respectively. Even while stage I to stage III thymoma relapse rates are generally low, more than half of these do so in the pleural space, and are associated with a poor prognosis (62,63). Evidence concerning the treatment of stage IVA disease is mainly derived from retrospective case series which are highly heterogeneous in terms of the number of enrolled patients, histology, degree of pleural involvement, and timing of presentation (de novo disease versus relapse) (64). The degree of pleural involvement may extend from a solitary deposit, a more extensive spread manageable by extrapleural resection, to a bulky disease not amenable to surgical resection. Patients with fewer pleural implants, representing a lower disease burden, have a better OS (52,65-67).

There are different techniques described in the case of pleural involvement, ranging from debulking surgery to extrapleural pneumonectomy (EPP) (64). Since no single surgical strategy has invariably been shown to improve survival compared to the others, many support choosing the surgical treatment in a tailored fashion according to specific factors related to the patient and the extent of the disease (64). A multimodal treatment plan is routinely adopted (16,53,68).

Case reports and case series described the initial experience of cytoreductive surgery combined with hyperthermic intrapleural chemotherapy (69-72). Yu *et al.* presented a small case series of 4 patients who underwent cytoreductive therapy combined with hyperthermic intrapleural chemotherapy (two patients with *de novo* stage IV and two patients with recurrent disease). Patients were followed up for 1–4 years. One elderly patient died of heart failure one year after surgery, whereas the remaining three patients presented no local recurrence or distant metastases (73). Belcher *et al.* retrospectively analyzed six patients who underwent cytoreductive therapy and received intraoperative hyperthermic pleural irrigation, after induction chemotherapy (74). The median follow-up was 18.8 months and 4 out of 6 patients were alive with no evidence of recurrent disease. For stage IV disease with pleural metastasis, robotic thymectomy can be performed in selective patients with oligometastatic disease (61). Yellin *et al.* evaluated surgical resection combined with heated pleural chemoperfusion as a treatment for *de novo* stage IVA thymoma and TC and for thymoma with pleural relapse (62). The goal of surgery was to completely remove any mediastinal involvement and completely remove any pleural disease. The chest wall pleura was the primary target of the partial pleurectomy. When necessary, diaphragmatic implants with partial muscle thickness were removed. Lung involvement was treated by wedge resection. A lung-sparing strategy was applied by this group. Five-, 10-, and 15-year OS were 81%, 73%, 58% for *de novo* stage IVA thymoma, 67%, 56%, 28% for thymoma with pleural relapse, and 0%, 0%, 0% for TC. Five- and 10-year PFS was 61%, 43% for *de novo* stage IVA thymoma, and 48%, 18% for thymoma with pleural relapse. The authors conclude that even though this strategy is acceptable in the case of thymoma with pleural spread, the results in the case of stage IVA TC are disappointing (62). There is an ongoing debate between pleurectomy and EPP. This choice is most of the time guided by the degree of lung involvement. The proponents of EPP underline its improved local control, nevertheless, patient selection is crucial in order to identify those who can tolerate major surgery (75-80). On the other hand, proponents of pleurectomy put forward its lung-sparing advantage and its more acceptable morbidity-mortality (76). In fact, the median PFS of 12 patients with pleural recurrence of thymoma who underwent extended

pleurectomy and decortication combined with hyperthermic intrathoracic chemoperfusion was 72.2 months (81).

The benefit of debulking still remains controversial (82,83). Debulking has been favored by some groups in cases of untreatable disease. Patients who underwent subtotal resection had better OS than those who underwent no resection at all, according to a large review by Kondo *et al.*, although this may be partially attributed to selection bias in the patients enrolled in the intervention arm (31,64,84).

Lymphadenectomy

The new IASLC/ITMIG TNM staging system in order to standardize surgical practice and communication between specialists, defined the N factor as follows: N0 No nodal involvement, N1 Anterior (perithymic) nodes, and N2 Deep intrathoracic or cervical nodes (9,85,86). The distinction between the N1 and N2 nodes supports the theory that the involvement of deep lymph nodes (N2) rather than lymph nodes near the thymus (N1) indicates a more advanced or aggressive disease (87).

In a Japanese study of 1,320 resected thymic tumors, lymph node invasion was observed in 2% of thymomas, including 1% of stage I cases, and 6% of stage III cases, and was primarily found in the anterior mediastinum (84). TC are more likely to have nodal invasion because they occur more frequently in extrathoracic sites (in 30% of cases), other intrathoracic areas (in 35% of cases), and the anterior mediastinum (in 70% of cases) (87,88). A retrospective analysis of a Chinese database including 1,617 patients demonstrated that the frequency of nodal invasion was 2.2% and resulted in worse OS. Nodal involvement was found in only seven of 1,310 (0.5%) patients with thymoma, whereas in patients with TC and neuroendocrine thymic tumors (NETTs), it was 7.9 and 16.7%, respectively (89). According to Fang *et al.*, patients with thymomas had a rate of lymph node metastasis of 2.1%, those with TC a rate of 25%, and those with NETTs a rate of 50%. The authors also identified TC, NETTs, advanced clinical stages, N2 nodal dissection, and histological WHO classification B3 as predictors of nodal involvement. As a result, they advise adding ipsilateral N2 nodes to the lymph node dissection recommendation in these circumstances (90). However, bilateral nodal dissection is typically not required apart from cases of NETTs that are associated with a high prevalence of considerable nodal disease.

According to the current recommendations, the resection of all thymomas with invasion of the surrounding structures (> T2, stage II or higher) should be associated with the routine removal of the anterior mediastinal nodes and the low anterior cervical nodes (N1 stations) routinely. Typically, the specimen is removed along with the perithymic nodes. In the event of stage III/IV thymomas, systematic sampling of the deep regional nodes is strongly advised. In the case of TC and NETTs a thorough nodal dissection of all N1 and N2 regions is warranted (16,86,91,92).

Recurrent disease

Re-resection of relapsing thymomas is an approved choice when a complete resection appears to be possible because it has been shown to improve long-term patient survival in various studies (33,93,94).

One of the mainstays of treatment for recurrent disease is a new surgical resection. Studies have demonstrated that patients who had their recurrent disease surgically removed had much better results than those who had received adjuvant therapy (66,67,95). Mizuno *et al.*, extracted 420 patients who presented a recurrent TET after resection (incidence of recurrence 14.8%) from a national Japanese database (96). Among them, 162 patients were treated surgically, and 243 were treated non-surgically. The most frequent metastatic site was the pleura (54.1%), followed by the lungs (21%). Female sex, Masaoka I–II stage, non-TC histology, absence of preoperative treatment, and longer recurrent-free interval were significantly favorable factors for survival in the surgery group. In multivariate analysis, non-TC histology and longer recurrence-free interval were recognized to be independent prognostic factors. The survival of the surgery group was significantly better compared to the non-surgery group, with 5- and 10-year survival rates of 82.7% and 68.2%, respectively, in the surgery group and 43.5% and 25.4%, respectively, in the non-surgery group (96). Okumura *et al.*, evaluated 67 patients with tumor recurrence. Among them, 22 patients underwent re-resection. The 10-year survival rate was 70% for patients who underwent a re-resection, and 35% for those who did not (93).

Salvage surgery

Salvage surgery is defined as the surgical resection of persistent or recurring tumors following local treatments with curative intent or after the administration of exclusive chemotherapy for voluminous lesions. There are no documented indications for salvage surgery in TET. Even

if this strategy could result in acceptable rates of morbi-mortality, it should be reserved in selected cases after multidisciplinary discussion and approval (57,97).

Total thymectomy vs. thymomectomy

In the case of TET, the current guidelines advocate an en-bloc resection of the tumor with the thymus gland (thymo-thymomectomy) (12,16). This recommendation is based on the theory that in the long-term follow-up, a total thymectomy would decrease the likelihood of recurrence. However, there are studies that challenge this attitude by proposing a resection of the tumor only (thymomectomy) without the necessity of removal of the entire gland in stage I and II TET without the presence of MG (14,98,99). On the other hand, a study from the ChART compared the local recurrence rate in patients with Masaoka stage I and II who underwent thymomectomy alone and thymomectomy plus total thymectomy (100). They observed a significantly higher local recurrence rate in patients with Masaoka Stage II who received thymomectomy alone. The authors draw the conclusion that, in light of their findings, total thymectomy should be performed in conjunction with tumor excision in cases of early-stage thymomas where thymomectomy alone is a suboptimal technique. A major drawback of limited resection is the difficulty of defining an adequate surgical margin while removing only the tumor, especially in the case of stage II lesions. Another limitation of the studies suggesting thymomectomy alone is the relatively short follow-up and for that reason, the results should be interpreted cautiously. In conclusion, in the absence of well-designed and adequately powered prospective studies, total thymectomy remains the treatment of choice, according to the current recommendations. Even if there are concerns about the increase in all-cause mortality and the risk of cancer in patients who underwent a thymectomy, leaving *in situ* residual thymic tissue in case of thymoma and certainly in case of TC, cannot be recommended (101). The risk of recurrence is not negligible and on the other hand, multifocal thymomas have been described. Moreover, the increase in cancer risk after thymectomy is an observation, it is not clear whether cancer development is a consequence of the thymus removal or the result of a deficient baseline immune system.

Conclusions

The rarity and histological heterogeneity of TET preclude the conduction of well-designed sufficiently powered randomized controlled trials. For that reason, the current evidence about their surgical treatment is mainly derived from retrospective case series. New techniques in the field of minimally invasive surgery are gaining acceptance for early-stage TET but longer follow-up periods are warranted in order to prove their oncological outcomes. On the contrary, these techniques should be used cautiously in case of locally advanced tumors. Surgeons must not forget that the main objective is complete resection of the lesion, which is one major predictive factor for increased survival. Surgeons are invited to adopt the new classification systems and the correct definitions in order to facilitate communication between specialists and the interpretation of the results presented in the literature. The establishment of nationwide and international databases could enhance the available data and the uniformization of the nomenclature.

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Footnote

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