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Review

Optimal surgical approach to thymic malignancies: New trends challenging old dogmas

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ABSTRACT

Until recently, the surgical approach to thymic tumors has remained basically unchanged. The collaborative effort led by ITMIG with the collaboration of regional and society-based interest groups (ESTS, JART) produced an enthusiastic surge of interest in testing the new technological advances in thoracic surgery and many historical dogmas in thymic surgery have been questioned and challenged. The present review addresses the new trends in the optimal surgical management of thymic tumors based on the review of the current literature. 1. Minimally-invasive techniques (MIT) including video-assisted thoracic surgery (VATS) and robotic-assisted thoracic Surgery (RATS) are now to be considered the standard of care in early-stage thymic tumors. MIT are no inferior to open approaches in terms of postoperative complications, loco-regional recurrence rates and survival. MIT are associated with a shorter length of stay, reduced intraoperative blood loss and better cosmetic results. 2. The adoption of the ITMIG/IASLC TNM staging system for thymic tumors requires a paradigm shift among thoracic surgeons to include regional lymphadenectomy according to the IASLC/ITMIG nodal map in the surgical management of thymic tumors. 3. A limited thymectomy instead of total thymectomy along with the removal of the thymic tumor in nonmyasthenic Stage I–II tumors has been proposed by some authors, although the results are not uniform. Until more mature data is available, adherence to the current guidelines recommending total thymectomy in addition to thymomectomy is always indicated. 4. In locally-advanced Stage IVa patients with pleural involvement, major pleural resections, including pleurectomy/decortication or extrapleural pneumonectomy are indicated, provided a complete resection of the pleural deposits is anticipated, usually in a multidisciplinary setting, with excellent long-term results. The incorporation of these new concepts and techniques in the surgical armamentarium of the thoracic surgeons dealing with thymic malignancies will certainly be of help in the optimal management of these patients.

1. Introduction

Thymic tumours are rare tumors with a reported annual incidence from 1.3 to 3.2/million [1,2]. They still represent the most common anterior mediastinal tumors in the adults. Thymic tumors are classified using the recommendations of the World Health Organization (WHO) into thymomas – further divided into low-grade (A,AB) and high-grade (B1,B2,B3), thymic carcinomas (TC) and thymic tumors with neuroendocrine features (NETT) [3–5].

After few decades of relatively indolent progress in the study of thymic malignancies, the last decade witnessed a new interest which led to tremendous advancements in the diagnosis, classification, staging and management of these rare tumors [6].

The key of this success was the collaborative effort among Institutions, scientific societies, countries and continents which put together their resources in producing an extraordinary global effort. The foundation in 2010 of the International Thymic Malignancies Interest Group (ITMIG) was a landmark step [7]. In few years ITMIG produced recommendations for the standardization of terminology, outcome measures [8] and pathology [4], along with a large retrospective database [9]. In addition to ITMIG, regional society or country-based interest groups flourished, the most active being the Japanese Association for Research on the Thymus (JART) and the European Society of Thoracic Surgeons (ESTS) thymic working group. Very recently, the Chinese Alliance for Research in Thymomas (ChART) and the Korea Association for Research on the Thymoma (KART) were added. Thanks to the collaborative work of ITMIG, JART and ESTS, under the supervision of the International Association for the Study of Lung Cancer

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Table 1a
TNM classification of thymic malignancies – 8th edition (IASLC/ITMIG).

T	Descriptor
T1	Tumor encapsulated or extending into the mediastinal fat, may involve the mediastinal pleura T1a No mediastinal pleura invasion T1b Direct invasion of the mediastinal pleura
T2	Tumor with direct involvement of the pericardium (partial or full thickness)
T3	Tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or vein
T4	Tumor with direct invasion into any of the following: aorta (ascending, arch or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus
N	**Descriptor**
N0	No regional lymphnode metastasis
N1	Metastasis in anterior (perithymic) lymph nodes
N2	Metastasis in deep intrathoracic or cervical lymph nodes
M	**Descriptor**
M0	No pleural, pericardial or distant metastasis
M1	Distant metastasis M1a Separate pleural or pericardial nodule(s) M1b Distant metastasis beyond the pleura or pericardium

Table 1b
Stage grouping.

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
	Any T	N0, N1	M1a
Stage IVB	Any T	N2	M0, M1a
	Any T	Any N	M1b

(IASLC), the largest retrospective database of thymic tumors was collected and analysed, and formed the basis for the IASLC/TNM staging system of thymic tumors (Tables 1a and 1b) which was included in the 8th edition of the TNM international staging system of thoracic malignancies [10–12] and which should replace the Masaoka-Koga staging system [13,14]. Preliminary validation studies have demonstrated the value of the IASLC/ITMIG staging system [15,16].

Along with the major advancements in the diagnosis and staging, the standard surgical management of thymic tumors – which had remained basically unchanged for decades, was progressively adapted to the new thoracic surgical techniques (Video-assisted thoracic surgery – VATS, Robotic-assisted Thoracic Surgery – RATS) and new concepts have emerged and proposed for an optimal surgical approach of these rare tumors.

The present review paper will address the most recent concepts and techniques about the optimal surgical management of thymic tumors.

2. Optimal surgical approach to thymic tumors

Surgery still represents the treatment of choice in thymic tumors, despite the lack of robust evidence based on prospective, randomized trials [17] and complete resection has consistently been found to represent a powerful prognostic factor [18,19]. The anatomical location of the thymus in the anterior mediastinum has undisputedly convinced the thoracic surgeons that sternotomy was the only possible surgical approach which may provide a complete resection of the tumor. Few attempts to remove thymic tumors through cervicotomy only, or through a thoracotomy were criticized in the past for the perceived high chance not to achieve a complete resection. Very often the operation consisted only in removal of the tumor without any lymphadenectomy, under the assumption that lymphnodal spread was uncommon in thymic tumors and of little prognostic impact.

Surgical resection of capsulated or minimally invasive tumors (Masaoka Stage I–II) are usually easily achieved with a complete resection rate of nearly 100%. Resection of locally-advanced Stage III tumors is more challenging, and the decision to operate on upfront is based on the perception from the surgeon that the tumor can be completely resected. Excellent complete resection rates can be obtained even in case of tumors invading the neighboring structures (pericardium, venous great vessels, lung parenchyma), ranging from 50% to 80% [20–23]. The use of induction therapy and postoperative radiotherapy have been found to be of value in case of tumors deemed to be unresectable upfront, which is the case in most high-grade thymomas (B2–B3), thymic carcinomas and neuroendocrine thymic tumors [24–27]. Surgery in Stage IVa tumors with pleural spread in the form of pleural nodules or a diffuse carcinosis has long been considered by most surgeons of little efficacy, particularly in aggressive thymic tumors, and many authors were reluctant to extend the resection to the pleura in case of Stage IVa tumors, also based on the dismal results obtained in other tumors with pleural involvement.

This standard surgical approach has remained basically unchanged over the last 30 years with few minor changes until the first decade of the XXI century.

Then, the amazing collaborative effort led by ITMIG with the collaboration of regional and society-based interest groups (ESTS, JART and recently ChART and KART) produced an enthusiastic surge of interest in testing the new technological advances in thoracic surgery (VATS, RATS) and many historical dogmas of thymic surgery have been questioned and challenged.

The present review will focus on 4 “hot topics” in the optimal surgical approach to thymic tumors: 1. Minimally-invasive surgical techniques vs. the standard open techniques; 2. The role of lymphadenectomy in the surgical management of thymic malignancies. 3. The need of total thymectomy vs. thymomectomy only in early-stage non-myasthenic thymomas; 4. The efficacy of major pleural resection techniques in the management of Stage IVa locally-advanced thymic tumors with pleural involvement.

3. Minimally-invasive surgical techniques for thymic tumors: state-of-the-art

Surgical treatment with complete resection is the standard of care in the management of thymic tumors [19]. Traditionally, this has been achieved with open procedures. Among these, median sternotomy, either total or partial, and thoracotomy have been proposed in the past and have been proved to be successful in achieving optimal outcomes [20,28].

More recently, due to the widespread use of minimally invasive techniques (MIT) in different aspects of surgery and in thoracic surgery (Video-assisted thoracic surgery, VATS), there has been a progressive adoption of these techniques in thymic surgery. The even more recent introduction of the Robotic-assisted Thoracic surgery (RATS) has prompted many surgeons to explore the use of the robot for the resection of thymic tumours.

The debate about which technique, open surgery or MIT is the most appropriate for the treatment of thymic tumors resulted in a number of manuscripts in the last decade, most of which are retrospective case series. Unfortunately, no randomized clinical trial has been designed to address the issue and it seems unlikely, due to the rarity of the condition, that this can be done in the near future.

The correct indication of the surgical approach in thymic tumors depends on several factors: 1. The tumor stage, 2. The tumor dimension, 3. Tumor histology and 4. The individual patient’s clinical characteristics.

According to the European Society of Medical Oncology (ESMO) guidelines on thymic tumors, [29], the standard surgical approach in resectable disease remains median sternotomy (Grade IV, level A). Resectable tumors include all Stage I/II disease (according to Masaoka-

Table 2
Minimally-invasive surgical techniques for thymic tumors: state-of-the-art. Sources, results and supporting comments.

Source	Results	Supporting comments
Historical literature	Resection of early stage thymic tumors is performed with an open access (OS), including median sternotomy, either partial or total. Results are superior than using minimally-invasive techniques (MIT)	Better visualization, particularly in the neck More radical resection Risk of pleural seeding using MIT No one-lung ventilation Bilateral view of the mediastinum
Recent contributions	In early-stage thymic tumors MIT provide non inferior oncological results than open accesses. MIT are associated with a shorter length of stay, reduced blood loss, more cosmetic results, less morbidity rates.	Excellent visualization of the thymic region up to both thymic poles using MIT
	VATS and RATS provide similar oncologic and perioperative results. Subxiphoid access needs further confirmations, although the preliminary results look promising	The use of CO2 greatly improves the dissection and the operative view, even contralaterally.
Guidelines	In selected patients with Stage I–II thymoma, MIT are recommended in centers with experience in MIT. VATS or RATS are equally effective.	
Conclusions	The already mature data clearly indicates that in selected patients and in experienced centers MIT are the procedure of choice in early stage thymomas. It is desirable that a reduced cost might favour a widespread adoption of the robotic techniques.	

Koga Stage) and selected Stage III tumors. The ESMO guidelines however recognize that MIT are an option for presumed stage I and II "in the hands of appropriately trained surgeons". In particular, the authors state that "robotic resection seems to provide a better visualization of the tumor when compared to VATS". Finally, the ESMO committee emphasizes that MIT are not recommended for Stage III tumors, "given the absence of long-term follow-up". Since the publication of the ESMO guidelines in 2015, some additional contributions have appeared in the literature addressing the issue of open surgery vs. MIT in thymic tumors and will be discussed in the present review.

Friedant and colleagues [30] performed a meta-analysis and a systematic review search of articles comparing MIT to open access (OS) in thymic malignancies. Patients in the MIT group were more likely to be in Stage I/II stage than patients in the OS group (95% vs. 78%), and were more likely to have smaller tumors (4.09 cm vs. 4.80 cm). A surprisingly low conversion rate from MIT to OS was observed (2.4%). No significant difference was found between the two groups in operating time, respiratory or cardiac complications, and overall complications. A shorter length of stay was observed in the MIT group (8 days vs. 9 days) and a decreased intraoperative blood loss. Importantly, no difference was observed in the two groups in the complete (R0) resection rate and in the rate of loco-regional recurrence either overall or in the subset of patients with Masaoka stage I and II. The authors conclude that, despite the limitations of the analysis (lack of randomized trials and shorter follow-up time for the MIT group), MIT remain a safe and valuable option in selected patients with thymic tumors.

A similar methodology study was conducted by Hess and associates [31] between MIT and OS for thymic tumors. Twenty studies were included in the analysis, for a total of 2068 patients. Tumors resected by OS were larger than those resected by MIT. MIT resection was associated with a reduced intraoperative blood loss, reduced duration of chest tube, and a shorter length of stay. No difference was found between the two groups with regards to postoperative complications, thymoma recurrence, Myasthenia Gravis (MG) complete stable remission and survival.

Among the most recent retrospective series, Agatsuma and colleagues [32] reported the results of the JART database on 2835 patients from 1991 to 2010. They performed a propensity-score matching between 140 patients receiving VATS resection and 140 patients receiving OS. All patients had Stage I/II thymoma. The authors found no difference in R0 resection rate, postoperative complications (including MG crises), overall and recurrence-free survival between the two groups.

A very recent retrospective study from Wang and colleagues [33], based on the Chinese Alliance for Research in Thymomas (ChART) database compared perioperative outcomes and survival in 1117 patients with clinically early-stage (Masaoka I and II) thymic tumors operated on from 1994 to 2012, of whom 241 received VATS resection and 876 received an open approach. After a median follow-up time of 33 months, a higher percentage of total resections was observed in the VATS group. Although overall survival at 5 years was similar in the two groups (92% in each group), recurrence-free survival was significantly better in the VATS group as compared to the open group (92% vs. 83%). In a subgroup analysis considering only the pathologically-proven Masaoka I and II (229 VATS and 610 open procedures), no difference was observed either in overall survival or in the recurrence rate. The authors conclude that in clinically early-stage thymic tumors, VATS may offer better perioperative outcome and non-inferior survival as compared to open approaches.

As for the size, traditionally MIT were considered indicated only for smaller tumors [34]. The cutoff was originally set at 3 cm [35], and it was then increased to 5 cm. With improved technological resources and the use of robotic resection which allows a precision surgery, larger tumors have been reported to be successfully removed using MIT [36].

The current line of evidence therefore seems to indicate that tumor dimension is not an absolute contraindication to MIT provided the basic principles of MIT are preserved (preservation of the capsule and complete resection), [37]. Indication to MIT largely depends on the local invasion of the tumor to the great vessels/pericardium rather than the dimension. Local invasion to the lung is usually easily managed with MIT using staplers.

In a very recent study based on the retrospective ITMIG database on 2514 patients receiving surgical resection for thymic tumors between 1991 and 2012, Burt and associates [38] investigated the determinants of R0 resection by MIT and OS. In their population, 18% of the patients (N = 461) received MIT resection and 82% (N = 2053) received a OS resection. The rate of complete resection did not significantly differ between the two groups. In a multivariate analysis, the surgical approach (MIT vs. OS) was not an independent determinant of R0 resection.

The body of evidence from the most recent literature (Table 2), therefore, indicates that for early stage thymic tumors (Masaoka Stage I/II), MIT are no inferior to OS in terms of postoperative complications, loco-regional recurrence rates, overall and recurrence-free survival. In addition, MIT are associated with a shorter length of stay, and reduced intraoperative blood loss [39–42]. The cosmetic results of MIT as compared to OS are unquestionable and should not be underestimated in a disease frequently affecting young female patients. However, although superior perioperative results have been proved by many published results, oncological equivalence of minimally invasive procedures to open surgery still needs to be proved by long-term follow-up data.

Among MIT, robotic resection (RATS) and the subxiphoid approach need additional comments. Resection of thymic tumors and thymectomy for MG have been among the first procedures performed using

robotic assistance in the early 2000's [43]. The 3D visualization, the precision surgery, the wristed instrument tips, the dexterity and tremor filtration, the superb view of the anterior mediastinal compartment which can be obtained using the robot have progressively made thymectomy the most appealing and attractive thoracic procedure to be performed by RATS. In a recent paper, Ruckert and associates [44] reported their experience in robotic thymectomy and compare it with the world experience. Most of the Institutions employed a 3-port access, with a similar preference for the side (left/right), while the authors prefer the left-sided approach assuming that the most challenging situations (difficult location of the left phrenic nerve, retro-left anonymous cervical thymus) are located on the left. The reported recurrence rate and the survival results (despite the short follow-up) of all the series are promising.

Some meta-analyses comparing RATS with VATS thymectomy and RATS vs. open surgery thymectomy have been recently published [45–47]. The first contribution [46] filtered 5 articles out of 478 initial studies who met the inclusion criteria for the analysis up to August 2016. A total of 450 patients were analysed (169 by RATS and 281 by VATS). The authors found no difference in the outcome, intra and postoperative complications and conversion rate between the two approaches. When adjusted for the docking time, there was no difference in the operative time between the two accesses. No cost analysis was undertaken. The second meta-analysis comparing RATS vs. open thymectomy [47] included 7 articles up to October 2016. A total of 489 patients were analysed, of which 215 RATS and 274 open thymectomies. No difference was found between the two approaches regarding the operation time. Patients receiving RATS thymectomy spent less time in hospital, had less postoperative complications and had less intraoperative blood loss. From the most recent literature, therefore, in selected patients (Stage I/II thymoma) RATS thymectomy seems to provide superior results as compared to open surgery, and similar results as compared to VATS thymectomy [48,49]. Unfortunately, the limited availability of the robotic equipment among Institutions and the still high costs of the robotic technology still represent a major limitation for the widespread use of the RATS. A cost reduction of the robotic resource is desirable in the next few years which may help increase the adoption of the technique in the thoracic community.

The most recently proposed MIT in thymic surgery is the subxiphoid approach [50]. With this approach, a 3-cm incision is made 1 cm under the xiphoid process and from this main port the instruments are inserted. The operation can be performed using video-assisted or robot-assisted equipment. According to the proponents of the technique, the subxiphoid approach, by inserting the camera in the midline of the patient, offers the advantages to provide a similar visual field as with median sternotomy, a better vision of both phrenic nerves and a secure visual field of the neck. Suda and colleagues [51] reported on the largest experience so far including 80 patients receiving thymectomy with a subxiphoid approach, of which 25 thymomas (all Stage I/II). Intraoperative blood loss was minimal, the length of hospital stay was around 4 days, and postoperative complication rate was 2%. Modifications of the subxiphoid technique include the addition of one or two intercostal ports and the sternal hook elevator [52]. Although promising, the subxiphoid approach is in its infancy. The short follow-up and the limited use of the technique across the Institutions so far do not allow to draw definite conclusions about the efficacy of this approach, which will need additional confirmations before its widespread use.

4. The role of lymphadenectomy in the surgical management of thymic malignancies

Removal of the loco-regional lymph nodes is a standard practice in every surgical procedure performed with oncological intent in all solid malignancies. It has unquestionably been demonstrated that in most tumors the lymphatic spread plays a crucial role in the diffusion of the disease. The TNM staging system underlines the importance of the lymphnodal assessment both in clinical and in the pathologic setting. Among the intrathoracic neoplasms, contrary to lung carcinoma where the role of lymphadenectomy has been found to be undisputable since the first TNM staging systems, in thymic tumors the lymphnodal assessment at the time of the surgical resection has long been underperformed. The Masaoka staging system which has been used for the thymic tumors so far included the N involvement in Stage IVb and made no distinction among the different nodal stations [13]. In view of the 8th edition of the TNM staging system of thymic tumors, ITMIG proposed a dedicated thymic nodal map [53] which classifies the loco-regional lymph nodes into anterior (N1) and deep (N2) regional nodes. The anterior nodes include the low anterior cervical, perithymic, prevascular, para-aortic and supradiaphragmatic nodes. The deep regional nodes are the lower jugular, supraclavicular, internal mammary, paratracheal, subaortic, subcarinal and pulmonary hilar nodes. N1 involvement is staged as IVa disease and N2 is staged as IVb disease.

The lymphatic involvement in thymic tumors is infrequent. Historically, a 2% prevalence has been demonstrated in thymomas, while the prevalence approaches 20% in thymic carcinomas/NETT [28], although the figures might be underestimated due to the fact that a systematic lymphadenectomy is very rarely performed by most Institutions during resection of thymic malignancies, there is no strong recommendation from the current clinical guidelines or standard teaching, and the reported rates of nodal involvement can be biased by data source or intentional nodal retrieval during surgery. A notable exception is Japan, where lymphadenectomy (using the Yamakawa-Masaoka nodal map) [54] has traditionally been part of the thymic resection.

The first important study reporting on the prognostic significance of lymphatic involvement in thymic tumors was performed by Kondo and Monden [55] using the Yamakawa-Masaoka nodal map. The authors found that survival rates were lower in N+ disease, and the N involvement was a significant prognostic factor in multivariable analysis in thymic carcinoma.

More recently, the prognostic impact of lymphatic involvement in thymic malignancies has been investigated by Hwang and associates [56], who retrospectively reviewed 131 thymic malignancies who underwent lymphnodal dissection during surgery according to the new TNM nodal map. N involvement was found in 13 patients (10%), of whom 6 N1 and 7 N2 (mostly paratracheal nodes). The mean number of dissected nodes was 10. The prevalence of N disease was far higher in thymic carcinoma (8/32, 25%) than in thymoma (5/99, 5%). The rate of N metastases was higher in high-grade thymomas (B2–B3), in larger tumors, and in high T status (Stage III or higher). Five-year freedom-from-recurrence rate was significantly worse in N1/N2 than in N0 (38.5% vs. 87.9%). The authors conclude that Stage higher than II and thymic carcinoma were predictive of nodal metastases.

Weksler and associates [57], using the SEER database from 1988 to 2009 on 442 patients receiving resection of thymic tumors and lymphadenectomy (at least 1 nodal station, median 2 stations) out of 2227 patients with thymoma reported a N prevalence of 13% (N = 59). Nodal involvement was more frequently seen in larger tumors and was significantly associated with a poorer prognosis.

A similar study from the same authors and the same SEER database focusing on thymic carcinomas (N = 176) and neuroendocrine thymic tumors (N = 53) where at least one lymphnode was harvested at the time of surgery (median 3 nodes) found N metastases in 40% of the patients (33% in thymic carcinoma and 62% in NETT) and the presence of N+ disease was an independent prognostic factor [58].

An important contribution to the issue has been published by Gu and associates [59] who enquired the ChART retrospective database from 1992 to 2014. Out of 2421 patients with thymic tumors treated in 18 Chinese Institutions the prevalence of N disease was surprisingly low (2.2%, 35 patients). It was 0.5% in thymoma, 8% in thymic carcinoma and 16% in NETT. The two SEER studies may not represent the general

picture of thymic tumors, due to the characteristics of the SEER registry and the inclusion criteria for analysis (more than 50% of the tumors were Masaoka Stage III or higher). On the other hand, the lower rate of N disease in the ChART series may result from the no intentional nodal harvesting during surgery.

Lymphnodal involvement is also correlated with the T stage. The practical recommendation of the authors is to perform a lymphnodal assessment in the form of lymphnodal dissection or sampling in selected patients at high-risk for N disease, namely thymic carcinoma/NETT and Stage III–IV patients.

The ESMO guidelines [29], based on the analysis of the available literature up to 2015, and the IASLC/ITMIG recommendations for the 8th edition of the TNM staging system suggest the routine removal of anterior mediastinal nodes and the low anterior cervical nodes (N1 stations) in all thymomas with invasion of the neighboring structures (> T2, Stage II or higher). The perithymic nodes are usually removed en-bloc with the specimen. Systematic sampling of the deep regional nodes is strongly encouraged in case of Stage III/IV thymomas. A systematic nodal dissection of all N1 and N2 regions are recommended in thymic carcinoma and NETT. Finally, any suspicious node on imaging or intraoperative visualization should be removed and sent for pathologic assessment.

In summary, the body of evidence (Table 3) suggests that the prevalence of lymphnodal involvement in thymic tumors is higher than what has been reported so far, and largely depends upon the willingness of the surgeon to perform a thorough systematic sampling/dissection of the nodal stations at surgery [60–62]. A higher prevalence is expected in higher stages thymomas and in non-thymoma histology (thymic carcinoma and NETT). The N+ status is an independent prognostic factor which adversely affect survival. The adoption since 2017 of a TNM staging system for thymic tumors makes it essential a change of attitude from the surgeons performing thymic resections, which are now strongly encouraged to routinely include lymphadenectomy in the resection of any invasive thymic tumor.

5. Surgery for early stage nonmyasthenic thymoma: thymomectomy and total thymectomy or simple thymomectomy?

Resection of thymic tumors has traditionally included removal of the tumor and the thymus gland. The rationale was that total thymectomy would reduce the chance of recurrence in the long-term follow-up. Recent guidelines [29,37,63] and large retrospective review series [64,65] recommend complete en-bloc resection of the tumor and the thymus gland (thymothymomectomy, TTM) in all resectable tumors. In recent years, however, some authors [66,67] questioned the need to remove the thymus gland in nonmyasthenic thymomas, suggesting that resection of the tumor (thymomectomy, TM) is enough from an oncological point of view in Stage I–II non-MG thymomas. In fact, there are no prospective studies evaluating the need to remove the thymus in case of early stage thymoma without Myasthenia Gravis. Proponents of the need to always resect the thymus along with the tumor emphasized the possibility of a postoperative MG [68,69], and the occurrence of multiple thymomas in the remaining gland [70]. On the other hand, the observation that in common practice most thymic registries include cases of thymomectomy alone [71], leaving the thymus behind, is in support of the fact that thymomectomy alone is a common practice in several Institutions worldwide. Not less importantly, the tremendous increase of the MIT in the surgical management of thymic tumors is associated with the tendency to offer a minimally invasive procedure both in terms of access and of the amount of resected tissue without violating the basic oncological principles. From the abovementioned considerations, therefore, it appears that the optimal resection in case of nonmyasthenic Stage I–II thymomas has not been fully elucidated yet.

Several papers on this issue have recently appeared in the literature.

Onuki and associates [72] studied 79 patients with Stage I–II thymoma undergoing thymomectomy + total thymectomy (TTM, N = 61) or simple thymomectomy (TM, N = 18). One case of postoperative MG was observed in the TM group. Disease-free survival was similar in the two groups.

Tseng and associates [67] analyzed a population of 95 patients with non-MG Stage I–II thymoma undergoing either thymomectomy + extended thymectomy (TTM, N = 42) by median sternotomy or thymomectomy alone (TM, N = 45) by VATS or thoracotomy. With a median follow-up time of 57 months, the authors did not find any difference in the two groups in the recurrence rate or in postoperative MG, with a lower perioperative complication rate in the TM group.

Nakagawa and associates [66] on a large monocentric series of 173 Stage I–II non-MG thymomas performed TM (N = 100) or TTM (N = 73) by either open access or VATS. Postoperative MG developed in 3 and 6 patients in the two groups (TM and TTM) respectively. There was no difference in recurrence rate, overall and disease-free survival in the two groups.

The same author [71], using the JART database, recently published the largest series so far comparing TM and TTM for the treatment of early stage thymoma. Out of a population of 1286 Stage I thymoma, resection of thymoma + partial thymectomy (TM) was performed in 289 patients, while resection of thymoma + total thymectomy (TTM) was performed in 997 patients. Due to the different patients' characteristics in the two groups, the authors performed their comparison analysis on a propensity-matched subgroup of 276 patients for each group. Postoperative complications were more frequent in the TTM

Table 3
The role of lymphadenectomy in the optimal surgical management of thymic malignancies. Sources, results and supporting comments.

Source	Results	Supporting comments
Historical literature	Lymphadenectomy is rarely performed in thymic tumors and N status is of little value in the Masaoka-Koga staging system	The rate of lymphnodal metastases is negligible in thymoma (< 2%), although higher in TC/NETT (20%)
Recent contributions	The introduction of a TNM staging system for thymic malignancies with a dedicated nodal map makes it necessary to perform a loco-regional lymphadenectomy. The new TNM classification emphasizes the importance of N disease.	The rate of lymphnodal metastases has been largely underestimated in the historical series. If a systematic LND is routinely performed, a not negligible prevalence of N disease can be found, even in thymomas
Guidelines	Removal of anterior nodes should be performed in all thymic tumors. Sampling of the deep regional nodes should be performed in Stage III–IV thymomas and in all TC/NETT. Any suspicious node (at preoperative or intraoperative evaluation) should be resected	
Comments	The thoracic surgeon needs to become familiar with the ITMIG thymic nodal map, which is different from the usual lung nodal map for NSCLC. The incorporation of the TNM classification of thymic malignancies in the 8th edition of the International TNM classification will require a paradigm shift in the thoracic community to incorporate regional lymphadenectomy in the resection of any thymic tumor.	

group, while a nonsignificant higher rate of local recurrence was observed in the TM group. Overall survival and disease-free survival were similar in the two groups.

A multicenter study based on the Korean Association for Research on the Thymoma (KART) database [73], using a propensity-matched cohort of 2 groups of 141 patients each with Stage I non-MG thymoma receiving either total thymectomy + resection of thymoma or limited thymectomy + resection of thymoma found no difference in overall or disease-free survival in the two groups. Similar to the JART study, patients receiving limited thymectomy had lower perioperative complications.

Very recently, a prospective study from JART [74] enrolled 36 patients receiving either partial or subtotal thymectomy associated to resection of Stage I–II thymoma in patients without autoimmune disease and after a median observation period of 63 months no recurrence was observed.

Fang and associates [75], using the ITMIG retrospective database recently performed a geographic study comparing surgical approach and the extent of resection in patients with early stage (Masaoka Stage I–II) non-thymomatous thymic tumors in Europe, North America and Asia. Median approaches (sternotomy/clamshell) were used more frequently in Europe (75%) and North America (76%) than in Asia (45%). Interestingly, they found that TM was performed far more frequently in Asia (31%) than in Europe (2.4%) or North America (5.4%). The 10-year recurrence rate, however, was similar among the three continents.

Despite the enthusiasm of the proponents of the limited thymectomy technique, however, the possibility of a potentially incomplete resection and consequently of an increased rate of loco-regional recurrence cannot be completely rule out when performing a limited thymectomy for Stage I–II thymoma, because the surgeon is asked to select a non-anatomical surgical margin. In this respect, a recent study from the Chinese Alliance for Research in Thymoma (ChART) [76] comparing thymomectomy alone vs, thymomectomy plus total thymectomy in Stage I–II thymoma with or without MG found a significantly higher local recurrence rate in patients with Masaoka Stage II who received thymomectomy alone (2.9% vs. 14.5%). The authors therefore conclude that based on their results, thymomectomy alone is a suboptimal procedure in early-stage thymomas and total thymectomy should therefore be performed along with tumor resection.

A major limitation of all the abovementioned studies is the low number of events (death and recurrence) and the relatively short follow-up, which makes it difficult to detect statistically significant differences and greatly reduce the statistical power of the studies.

Table 4 summarizes the results from the recent series investigating the efficacy of limited thymectomy vs. total thymectomy in patients with early stage non-MG thymomas.

In summary, from the analysis of the current literature (Table 5), in non-MG Stage I–II thymoma resection of the tumor without a total thymectomy is not infrequent (22% in the large JART database) despite the current recommendation from NCCN and ESMO guidelines. A longer follow-up and more confirmatory studies (possibly prospective) are needed before incorporating this procedure in future guidelines.

6. The role of pleural resection in the management of locally-advanced thymic tumors with pleural involvement

Pleural involvement is not infrequent in the natural progression of thymic tumors, and the surgeon is very often asked to decide the optimal surgical strategy in the presence of extensive invasion of the pleura [77].

Approximately 7–10% of the patients with thymic tumors present with a pleural involvement (Stage IVa disease) at the time of presentation [28,78]. In addition, the pleura represents the most frequent loco-regional site of recurrence after complete resection. Pleural involvement is usually in the form of one or more discrete or partially confluent pleural implants, up to a diffuse mesothelioma-like thickened pleura.

The rationale for surgery in patients with thymic tumors presenting with a Stage IVa pleural involvement is similar to what is expected in less advanced stages, that is a complete resection of the tumor [20]. Differently from patients with pleural carcinosis or Malignant Pleural Mesothelioma (MPM), patients with Stage IVa (pleural) thymic tumors are often young or middle-aged, with no major comorbidities. Also, the pattern of involvement is frequently represented by discrete pleural implants scattered among a macroscopically normal pleura [79,80]. Even in case of diffuse involvement, the diseased pleura can be dissected free from the underlying structures (endothoracic fascia, pericardium, diaphragm) easier than what is usually observed in MPM patients. Finally, given the relatively indolent nature of thymomas, long-term survivals can be expected in case of pleural recurrence or re-recurrence after pleural surgery.

Current guidelines [29,63] recommend that in case of pleural deposits at surgery, resection of pleural metastases is appropriate if a complete macroscopic resection is anticipated.

The surgical options in patients with Stage IVa (pleural) thymic tumors, either primary or recurrent, are: 1. Complete resections of all visible pleural implants; 2. Pleurectomy, partial or total or pleurectomy/decortication (P/D); 3. Extrapleural pneumonectomy (EPP). 4. Intraoperative hyperthermic intrathoracic chemotherapy (HITHOC).

Resection of all visible pleural implants is usually quite easy on the parietal pleura using electrocautery with a margin of free pleura. The number of pleural implants has been correlated with the prognosis [81]. Implants on the visceral pleura should be removed with cautery or with a lung wedge resection to minimize postoperative air leak.

In case of diffuse involvement of the pleura, a decision to perform a radical pleurectomy, P/D or even EPP needs to be made. Some historical series reported satisfactory long-term results using extended pleural resection in patients with Stage IVa pleural thymic tumors [82–84].

Table 4
Recent series comparing Thymomectomy + Total thymectomy (TTM) vs. Thymomectomy + partial thymectomy (TM).

References	No. patients	Stage (MK)	TTM/TM	Local recurrence rate (%) (TTM/TM)	Complication rate	Results
Tseng [67]	95	I-II	42[a]/53	4.5/1.9	Lower complication rate in TM group[a]	Similar results
Onuki [72]	79	I-II	61/18[c]	0/5	Not reported	Similar results
Nakagawa [66]	173	I-II	100/73	5/2	Not reported	Similar results
Nakagawa [71]	1286	I	276/276[b]	1.8/4	Lower complication rate in TM group	Marginally significant trend (p = 0.06) to a higher recurrence rate in TM group
Narm [73]	762	I-II	141/141[b]	4.1/3.7	Similar	Lower operative time and blood loss in the TM group
Gu [76]	1047	I-II	796/251	3.1/5.4	Not reported	Significantly higher recurrence rate in TM group/Stage II

[a] All TTM were performed through median sternotomy, while TM was performed either by VATS or open approach.
[b] Propensity-scored matched groups.
[c] 41% of TM and 1% of TTM were performed by VATS.

Table 5
Surgery for early stage non-Myasthenia Gravis (MG) thymoma: Thymomectomy and total thymectomy or simple thymomectomy? Sources, results and supporting comments.

Source	Results	Supporting comments
Historical literature	Resection of the tumor and total thymectomy (thymothymomectomy, TTM) is always indicated in Stage I–II thymoma also in non-MG patients	Risk of multiple thymomas Risk of postoperative MG Risk of local recurrence
Recent contributions	In selected Stage I–II non-MG patients with thymoma, resection of the tumor (thymomectomy, Limited thymectomy/TM) provides similar oncologic results with no increased postoperative MG episodes than TTM	The thymus plays a critical role even in adulthood and is worth being preserved when possible
Guidelines	TTM is the treatment of choice in all-stage resectable thymomas in patients with no MG	
Comments	A longer follow-up is needed to assess the oncologic value of leaving the thymus behind	It is difficult to preoperatively decide whether a tumor is encapsulated It is difficult to preset a tumor-free resection border in the thymus gland in Stage II tumors

Table 6
Recent series investigating the role of surgery in Thymic tumors with pleural involvement (Stage IVa).

References	N. patients	Initial tumor/recurrences	EPP	R0 rate	OS	Prognostic factors
Huang [84]	18	18/0	4	67%	78%	Multimodality therapy
Yano [80]	21	21/0	–	71%	73%	R0 resection Postoperative RT No. of implants
Lucchi [93]	20	0/20	–	100%	43%	No. Of implants
Ishikawa [85]	9	9/0	3	–	81%	Multimodality therapy
Okuda [89]	118	118/0	8	34%	86%	< 10 implants R0 resection
Murakawa [79]	13	7/6	2	100%	92%	Multimodality therapy
Moser [90]	152	107/45	40	71%	87%	Thymic carcinoma (negative) R0 resection

Table 7
The role of pleural resection in the management of locally-advanced thymic tumors with pleural involvement. Sources, results and supporting comments.

Source	Results	Supporting comments
Historical literature	Occasional reports of successful resection of individual pleural implants in initial or recurrent Stage IVa thymomas	Slow-growing tumors. Reasonable survival rates even in Stage IV disease.
Recent contributions	Possibility to perform more extended pleural resections, including pleurectomy, pleurectomy/decortication (P/D) and even Extrapleural pneumonectomy (EPP) with excellent survival rates and acceptable morbidity. Promising results with the use of intraoperative hyperthermic chemotherapy	Improved surgical techniques of P/D and EPP More centers performing thymic procedures worldwide
Guidelines	Any resectable thymic tumor should be removed, including tumors with pleural involvement, provided a complete resection might be anticipated	
Comments	The pattern of pleural diffusion and the slow-growing behavior of thymoma make it possible to obtain a complete resection even in case of diffuse pleural involvement. Thymic carcinoma/NETT with pleural involvement very unlikely can be totally resected and in these cases extended pleural resections are not indicated.	

Most series include both primary and recurrent tumors and major pleural resections are usually part of a multidisciplinary approach [85].

The use of intracavitary pleural treatments (HITHOC) during resection has been reported in selected patients with primary or recurrent thymic tumors with a long-term overall survival rates of 67%–89% [86]. Yellin and associates [87] reported their results on a population of 35 patients (17 primary, 14 recurrent, 4 thymic carcinoma); mortality was 2.5% at 90 days, morbidity was 11%. Overall survival and progression-free survival (at 10 years) were 73% and 43% for primary tumors and 56% and 18% for recurrent tumors; no patient with thymic carcinoma was alive at 5 years. Similar survival results (86% 5-year overall survival and median disease-free survival of 42 months) were obtained from a single-centre French study [88] on a population of 189 recurrent thymomas. The use of HITHOC seems therefore justifiable in Stage IVa primary or recurrent thymoma, but not in thymic carcinoma.

Whether surgery for Stage IVa pleural disease should be preceded by induction chemotherapy or radiotherapy is unclear. Almost all the published series are small-series, retrospective and very often evaluating both Stage III and Stage IVa patients.

Two recent collaborative studies have been published on surgical management of Stage IVa thymic tumors. Okuda and colleagues [89] retrospectively analysed the JART database on 118 patients with Stage IVa non-recurrent tumors from 1991 to 2010 receiving surgery. Extended pleural resection (EPP) was performed in 8 cases (70% 5-year survival rate), the remaining patients receiving resection of pleural implants. Five-year survival of all resected patients was 86%. Patients with less than 10 resected nodes had a better R0 rate and a better survival. No conclusions could be made from their data about the role of postoperative therapy.

Moser and associates [90] collected data of patients with thymic tumors and pleural involvement from 12 Institutions on behalf of the ESTS thymic working group. A total of 152 patients were analysed (107 primary surgery and 45 recurrent tumors). The type of surgical resection included EPP in 40 patients (26%), resection of pleural implants in 88 (58%) and total pleurectomy in 23 (15%). Complete resection rate was 71% for primary surgery and 91% for recurrent tumors. Almost 50% of the patients had a recurrence after pleural surgery (mostly locoregional). The median time to the first pleural recurrence from initial surgery was 55 months. Median time to second recurrence after pleural surgery was 46 months. The mean number of resected nodes were 7. Three- and 5-year survival rates were 91% 87% overall. Freedom-from-recurrence was 58% and 43% at 3 and 5 years. Thymic carcinoma had a

far worse prognosis than thymoma. At multivariable analysis, the completeness of resection was the most important independent prognostic factor. The type of resection depends on the volume and the distribution of the tumor, but even in case of extended pleural resection (EPP) a complete resection can provide excellent results.

Table 6 summarizes the results from the recent series investigating the surgical management of patients with thymic tumors with pleural involvement.

The possibility to offer non-surgical therapies in Stage IV thymic tumors is also an option and has been investigated in some studies. Hamaji and colleagues [77] queried the SEER database about patients with Stage IV thymic tumors (both Stage IVa and IVb). Out of 282 patients, 110 (39%) were managed surgically, and 172 non-surgically (of whom 40% with irradiation only). Five and 10-year overall survival were 67% and 35% for the surgically managed patients, and 26% and 19% for the non-surgically managed patients. Cancer-specific survivals were also better in the patients receiving surgical management than in patients who were treated without surgery (79% and 54% vs. 52% and 36% respectively at 5 and 10 years).

In summary, (Table 7), surgery (when feasible) seems to offer superior results over nonsurgical treatments in selected patients with thymic tumors with pleural involvement. Optimal surgical management relies on the possibility to obtain a complete resection. The choice of the extension of the surgical procedure (pleural implant resection, partial, total pleurectomy, P/D or EPP) has to be made on an individual basis, depending upon the number and distribution of the pleural deposits. Excellent results can be anticipated in thymoma, either for primary or recurrent tumors. Far worse results are expected in thymic carcinoma [91,92]. The role of adjuvant therapies is unclear based upon the current literature.

7. Conclusions

The role of surgery in the management of thymic tumors remains undisputable in all thymic tumors and in all stages. The international global effort which has recently involved the thoracic community worldwide, resulted in a critical discussion of many historical dogmas and in the adoption of the new available technological equipments. 1. For early stage thymic tumors, minimally invasive techniques of thymic resection (VATS, RATS) seem to be oncologically equivalent to open accesses and even superior with regards to postoperative length of hospital stay, intra and postoperative complication rate and cosmesis and are now the standard techniques in Stage I and II tumors. 2. The incorporation of thymic tumors in the 8th edition of the international TNM classification of thoracic malignancies requires that lymphadenectomy based on the proposed ITMIG/IASLC nodal map be an integral part of the surgical resection, according to the stage and histology of the tumor. 3.The role of limited thymectomy in case of non-MG Stage I–II thymomas remains to be confirmed until more mature data emerges. 4. Excellent results can be obtained with the use of major pleural resections (pleurectomy/decortication, extrapleural pneumonectomy) in selected patients with Stage IVa (pleural) thymomas, in a multidisciplinary setting.

The knowledge of these new trends in the surgical management of thymic tumors and the incorporation of these new concepts and techniques in the surgical armamentarium of the thoracic surgeons dealing with thymic malignancies will certainly be of help in the optimal management of these patients.

Conflict of interests

The authors declare that they have no conflict of interests.

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