Thymic Malignancy

More Hands Produce Stronger Flames

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We are pleased to announce that the "AME Research Time Medical Book Series" co-launched by AME Publishing Company, Central South University Press and DXY.cn will be published as scheduled.

Finishing my medical degree after 4 years and 3 months of study, I decided to quit going on to become a doctor only after 3 months of training. After that, I had been muddling through days and nights until I started engaging in medical academic publishing. Even 10 years after graduation, I had not totally lost the affection for being a doctor. Occasionally, that subconscious feeling would inadvertently arise from the bottom of my heart.

In April 2011, Mr. Tiantian Li, the founder of DXY.cn, and I had a business trip to Philadelphia, where we visited the Mütter Museum. As part of The College of Physicians of Philadelphia, the museum was founded in 1858 and has now become an exhibition hall of various diseases, injuries, deformities, as well as ancient medical instruments and the development of biology. It displays more than 20,000 pieces of items including pictures of wounded bodies at sites of battle, remains of conjoined twins, skeletons of dwarfs, and colons with pathological changes. They even exhibited several exclusive collections such as a soap-like female body and the skull of a two-headed child. This museum is widely known as "BIRTHPLACE OF AMERICAN MEDICINE". Entering an auditorium, we were introduced by the narrator that the inauguration ceremony of the Perelman School of Medicine at the University of Pennsylvania would take place there every year. I asked Mr. Li, "If it was at this auditorium that you had the inauguration ceremony, would you give up being a doctor?" "No," he answered.

In May 2013, we attended a meeting of British Medical Journal (BMJ) and afterwards a gala dinner was held to present awards to a number of outstanding medical teams. The event was hosted annually by the Editor-in-Chief of BMJ and a famous BBC host. Surprisingly, during the award presentation, the speeches made by BMJ never mentioned any high impact papers the teams had published in whichever prestigious journals over the past years. Instead, they laid emphasis on the contributions they had made on improving medical services in certain fields, alleviating the suffering of patients, and reducing the medical expenses.

Many friends of mine wondered what AME means.

AME is an acronym of "Academic Made Easy, Excellent and Enthusiastic". On September 3, 2014, I posted three pictures to social media feeds and asked my friends to select their favourite version of the AME promotional leaflet. Unexpectedly we obtained a perfect translation of "AME" from Dr. Yaxing Shen, Department of Thoracic Surgery, Zhongshan Hospital, Shanghai, who wrote: enjoy a grander sight by devoting to academia (in Chinese, it was adapted from the verse of a famous Chinese poem).

AME is a young company with a pure dream. Whilst having a clear focus on research, we have been adhering to the core value "Patients come first". On April 24, 2014, we developed a public account on WeChat (a popular Chinese social media) and named it "Research Time". With a passion for clinical work, scientific research and the stories of science, "Research Time" disseminates cutting-edge breakthroughs in scientific research, provides moment-to-moment coverage of academic activities and shares rarely known behind-the-scene stories. With global vision, together we keep abreast of the advances in clinical research; together we meet and join our hands at the Research Time. We are committed to continue developing the AME platform to aid in the continual forward development and dissemination of medical science.

It is said that how one tastes wine indicates one's personality. We would say how one reads gives a better insight to it. The "AME Research Time Medical Books Series" brings together clinical work, scientific research and humanism. Like making a fine dinner, we hope to cook the most delicate cuisine with all the great tastes and aromas that everyone will enjoy.

Stephen Wang
Founder & CEO,
AME Publishing Company

Thymic Epithelial Tumors (TETs) are rare neoplastic diseases, but the most common anterior mediastinal tumors in the adulthood. TETs are classified according to the World Health Organization (WHO) histopathological classification, which distinguishes thymomas from thymic carcinomas (tumors cathegory which also includes thymic neuroendocrine ones). Their rarity, along with the lack of randomized clinical trials (RCTs) make TETs' global management still questioned, and only few clinical recommendations currently exist.

The interest to the thymic disorders management has never been so strong as in the last few years. A huge number of articles about biology, associated parathymic syndromes, radiological tumor's appearance, surgery, induction/adjuvant medical therapy and radiotherapy have been published especially after 2014. These reflect of single Institution, multicenter experiences, or are the reults of retrospective societal databases. These datasets are commonly used to investigate the biological aggressiveness of the rare thymic tumours as well as their prognostic correlates.

Some recent examples of their usage and their effectiveness are the outcome of aggressive neoplasms (Thymic Carcinomas or Neuroendocrine Thymic tumors as well as their comparison), tumor's size as valuable predictor for complete resection and possible recurrence's development, the role of Myasthenia Gravis (MG) in thymomas outcome and, finally, the multimodality approach importance definitive demonstration while treating advanced lesions.

Last but not least, historically more than 15 different TETs' staging systems have been proposed and used, the most common of which were the Masaoka one and its update by Koga and Colleagues. Few years ago, under the International Association for the Study of Lung Cancer (IASLC) aegis, the need for a new TNM based staging system was evident, in accordance with other solid tumors. Therefore, merging the International Thymic Malignancy Interest Group (ITMIG), the European Society for Thoracic Surgeons (ESTS) and the Japanese Association for Research on the Thymus (JART) datasets, a retrospective analysis of the outcome of several thousand treated patients worldwide made the new TNM system final processing possible. Nowadays this represents the official staging system for thymic tumors.

The new prospective societal datasets development (ITMIG & ESTS, particularly) will furthermore improve our knowledge on some specific issues concerning TETs' treatment, and result are expected in few years. In particular, they will be focused on the optimal MG surgical management, the role of minimally-invasive procedures (VATS, robotic, transcervical or subxiphoid approaches), the role of lymphadenectomy, the correct indication for induction/adjuvant treatments in locally-aggressive lesions as well as the importance of personalised medicine, following the recent identification of molecular alterations occurring in the KIT, vascular endothelial growth factor receptors (VEGFRs) and mammalian target of rapamycin (mTOR) signalling pathways. This is the future.

This book is the result of the Authors' tremendous effort in collecting and making available all that was recently published on TET's diagnosis and management: they deserve a very major credit for putting this on.

Also AME Publishing Company, once again, demonstrated its extreme entrepreneurship, believing in the project and carefully curing it with a meticulous print apparel. The reading of this book should be suggested to all the researchers of thymic disorders and I'm sure this book will become a landmark text on this field.

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Preface for Thymic Malignancy: More Hands Produce Stronger Flames!

Thymic epithelial tumors (TET) are neoplasms that arise from the thymic gland usually in the prevascular mediastinum. They are considered malignant neoplasms as they can recur, metastasize and potentially lead to the death of the patient (1,2). However, many patients have a favorable outcome and eventually die of another cause. TET are rare with an incidence of 1.5 cases/million population/year. Because of their paucity and their usually favourable outcome, TET are difficult to study. While many single-institution studies of clinico-pathologic features have been published, these reports usually include a relative small number of cases. In addition, small case series to compare different treatment options are available, however, again, these studies in general lack power and are retrospective in nature. Prospective randomized clinical trials are extremely challenging and have not been performed on a large scale. However, such trials would be important as some TET behave in an aggressive manner and standardized treatment of these tumors is currently lacking.

The paucity of TET and their in general excellent prognosis requires "more hands to produce stronger flames". Joint global efforts are crucial to acquire a sufficient number of such cases for meaningful studies to advance our knowledge of the disease and its optimal treatment regimens. Within recent years, regional [Chinese Alliance for Research in Thymomas (ChART) (3), Japanese Association for Research of the Thymus (JART) (4), Surveillance, Epidemiology, and End Results (SEER) database (5)] and global [European Society of Thoracic Surgeon (ESTS) (6), International Thymic Malignancy Interest Group (ITMIG) (7)] organizations have been formed to bring physicians of various specialties including medical oncology, neurology, pathology, radiation oncology, radiology, and thoracic surgery, other health care personnel, patients and patient advocates from around the world together to study TET. Large regional and international databases comprised of patients with the disease are an important foundation of these studies. These databases are of retrospective and prospective nature and are used for the study of clinical features, pathologic subtypes and findings, surgical procedures, treatment strategies and outcomes as presented in many of the articles in this book. These databases will also potentially be advantageous to discern ethnic differences in the pathogenesis of the disease. Moreover, only these kind of global efforts and international collaboration will allow for future prospective randomized trials that might explore different treatment options and possibly personalized treatment.

To standardize treatment, global standardization of diagnosis and staging of TET are important. Therefore, major efforts have been undertaken within the last decade to enhance reproducibility of the pathologic subtyping of TETs and to develop a staging system that can be used for all subtypes of TET including thymoma, thymic carcinoma and thymic neuroendocrine tumors. As a result, the most recent WHO classification of TET was published in 2015 and pathologists are encouraged to use that for their diagnosis of TET and their subtypes (1,8) While over the years institutions have used the Masaoka staging (9) or the Masaoka-Koga staging (10) to stage thymomas and/or the TNM staging that was proposed by the WHO in 2004 (11) to stage thymic carcinomas, the International Association of the Study of Lung Cancer (IASLC) together with ITMIG proposed a staging for TET that now can be used for thymomas, thymic carcinomas and thymic neuroendocrine tumors (12) This proposed staging system was incorporated in the 8th AJCC/UICC TNM staging classification and is currently introduced or will be introduced shortly globally for staging of TET.

This book illustrates the remarkable results in the study of TET that have been accomplished through collaborative projects at regional and global level. Many of these projects were only possible thanks to established retrospective and prospective regional and international databases. These concerted efforts built a solid foundation for future projects such as the molecular study of TET and studies towards standardized and personal treatment of patients with these tumors amongst other projects. "More Hands Produce Stronger Flames!"

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Thymic tumors are a series of malignancies with different biological behaviors, clinical manifestation, and prognosis. Because of their unique nature and rarity, many issues remain to be explored so as to improve management outcomes. And there has never been any book specialized in the disease. Therefore, I congratulate AME on publishing this series of papers as a monograph, which is certainly unprecedented.

In recent years, two advances have contributed greatly to improved understanding of thymic tumors. The first is international and regional collaborations in joint studies for this relatively rare disease. Included in this compilation of related publications are the results from the Chinese Alliance for Research in Thymomas (ChART) retrospective studies that cover the most concerned questions in diagnosis and management of thymic malignancy (*Part I. General concepts and strategies in the management of thymic malignancies*). These include preoperative diagnosis, induction and adjuvant therapies, surgical procedures, and concomitant myasthenia. Although many of these still remain unsolved, it is a great step forward and help pave the way for future studies. And there is reason to believe that readers would benefit greatly from the comments on these studies by an international panel, many of them have been actively involved in the International Thymic Malignancy Interest Group (ITMIG).

The second and also a striking progress owes greatly to the advance in modern technology. Similar to the recent trend in lung and esophageal cancer surgery, minimally invasive approaches in thymic surgery has also attracted increasing attention and has contributed to improved outcome while maintaining similar oncological results. It is thus not surprising at all to notice that *Part II*, *Surgical therapies for thymic malignancies* of this book consists almost exclusively of topics on minimally invasive thymic surgery. A diversity of approaches is introduced here, including both left and right, subxiphoid VATS as well as robotic thymectomy. On top of these are introduction and perspectives on oncological principles and outcomes of minimally invasive surgery in management of thymic tumors. Hopefully this book would help disseminate the ideas of standardized management in thymic malignancy to many medical practitioners involved.

More hands build a higher flame. This book is not yet a comprehensive text that would solve all problems in the related area. Yet, it represents the state of the art in the management of thymic tumors and collected wisdom from colleagues in different specialties related to this interesting and important disease. The contents included here would be helpful for all medical professionals and researchers in the field and better inspire those interested to probe further for continuing improvement. We very much look forward to updating the contents and make it more educational in a future edition.

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Although tumors of the thymus gland are rare, they are not infrequently encountered by thoracic oncologic specialists. Thymic tumors have been managed for many decades using clinicians' anecdotal experience because their rarity has prohibited the performance of high quality clinical studies. Over the past decade, however, the landscape has begun to change for two major reasons. First, the development of formal research organizations dedicated to producing clinically applicable data for the everyday management of patients with thymic tumors has accelerated interest in these tumors. These organizations include the Chinese Alliance for Research in Thymomas (ChART), the Japanese Association for Research on the Thymus (JART) as well as the International Thymic Malignancy Interest Group (ITMIG). All of these organizations bring together physicians and researchers, working collaboratively, to try to answer clinically relevant questions regarding the management of patients with thymic tumors. Second, these organizations have dedicated resources and energy to develop multi-institutional databases (in the case of ITMIG, a multinational database) to serve as repositories of high quality patient data to be used for research purposes. Through this pooling of data and collaboration, research involving data from thousands of patients is now being performed with regularity, resulting in tangible benefits for patients.

This book represents a compilation of manuscripts that reflect recent contributions to the literature regarding thymic tumors. Several of these studies have resulted from analyses performed using the aforementioned large datasets compiled by investigators from all over the world, while others represent literature reviews by recognized experts in the field of thymic tumors, or single institutional experiences. Topics range from treatment strategies for complex cases to the technical aspects of cutting edge surgical techniques. Caregivers will find this collection of manuscripts an invaluable resource when involved in the management of patients with any type of thymic tumor, regardless of their specialty.

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As a summary of the rich experiences in the diagnosis and treatment of thymic tumors, the book *Thymic Malignancy* is now offered to the public with the joint efforts of Shanghai Chest Hospital (SCH) and AME Publishing Company. As the president of SCH, I appreciate the work done by the mediastinal tumor team and congratulate them on the interim results they have achieved.

Medicine has entered an era of constant updating of knowledge and extensive exchange of information. The concept of "Precision Medicine" further requires that clinicians not only should have a wide range of knowledge but also achieve high accuracies in the prevention, diagnosis, and treatment of a specific disease.

Thymic tumors are rare, with a prevalence of 0.393/100,000 in China. However, there are still many unknown areas in the diagnosis and treatment of thymic tumors. Specialized in thoracic tumors, SCH has accumulated a great deal of clinical data on thymic tumors. And we have been taking the lead in establishing the Chinese Alliance for Research in Thymomas (ChART) in an attempt to form a collaborative force of clinical studies for this rare disease. The data need to be further explored in a deeper and more precise way, while at the same time, data sources should be expanded, so as to pave the way for precision medicine. To this end, we have established a clinical research team focusing on mediastinal tumors (including thymic tumors) in the department of thoracic surgery, with an attempt to maximize the strengths of SCH in the clinical practice and scientific research on thymic tumors, establish standards and guidelines on the diagnosis and treatment of thymic tumors in different stages, and thus contribute to the improved thymic tumor management in China and abroad.

With the publication of this book, we sincerely hope the clinical research team on mediastinal tumors, in attempt to be one of the top teams worldwide, will follow the rules of modern medical sciences, focus their efforts on their goals, and strive for new breakthroughs in the diagnosis and treatment of thymic tumors.

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Table of Contents

General Concepts and Strategies in the Management of Thymic Malignancies

Surgical Therapies for Thymic Malignancies

Management of thymic tumors—consensus based on the Chinese Alliance for Research in Thymomas Multi-institutional retrospective studies

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Thymic tumors are relatively rare malignancies comparing to other solid tumors in the chest (1). Its incidence is estimated to be at 3.93 per 1,000,000, which is about 1/00 of lung cancer and 1/25 of esophageal cancer in China. And it appears to be higher than that reported from North America, which is only 2.14 per 1,000,000 according to the SEER database. However, in the SEER database, the incidence rate was much higher in Asians (3.74 per 1,000,000) than in Caucasians (1.89 per 1,000,000) and close to the data from China. This implicates that there might be some ethnical and generic difference in thymic tumors. In the meantime, both these two registrations record only 'malignant tumors' that are clinically advanced diseases. A large part of early stage, low grade lesions are considered 'benign tumors' and thus, not registered. Therefore, the actual incidence of thymic tumors is much under-estimated. With the increasing use of screening for other malignancies such as lung cancer, it can be expected that more early stage thymic tumors would be discovered.

In fact, all thymic tumors are now considered malignant (2). Distant metastasis has been witnessed even in Type A thymomas. And recurrence after complete removal of stage I disease is not unheard of. The delineation of 'malignant' or 'benign' thymomas is thus inappropriate and the term Thymic Malignancies, as proposed by the International Thymic Malignancy Interest Group (ITMIG) should be recommended. At the same time, the indolent nature of the disease is often manifested by prolonged survival even after disease progression in many thymoma patients. Therefore, a longer follow-up time (10 years) should be recommended

for thymic malignancies, with focus on both overall survival and recurrent status (3).

Because of its rarity and relatively indolent nature, it has been extremely difficult to carry out prospective randomized studies on a large scale so as to provide high level evidence for clinical practice. This would explain the long existing controversies concerning diagnosis and management of thymic tumors. The widely used Masaoka staging system was proposed more than 30 years ago, and was based on the results of less than a hundred cases from a single institution (4). Controversies regarding the World Health Organization histological classification have never stopped, although it is receiving more and more recognition (5). Currently available clinical guidelines are formed by expert opinions or single center retrospective studies. It is thus critically important to join force and initiate global or regional collaboration so as to change the scenario. Founded in 2010, ITMIG is an organization dedicated to research, education and support for patients with thymic malignancies, with the joint effort from hundreds of members worldwide. The Chinese Alliance for Research in Thymomas (ChART) was established in 2011, echoing the ITMIG global effort. With contribution from 18 tertiary referral centers in 14 provinces and cities, ChART has successfully built up the first national database for thymic malignancies, which now contains more than 2,500 cases of treated during 1994–2012. Clinic-pathological features, management modalities, and outcomes were retrospectively studied. And changes along with time were analyzed by comparing the results in the past two decades (1994–2003 *vs.* 2004–2012). The results are presented in this special issue of the Journal of Thoracic Diseases. It is based on the collective wisdom that the ChART consensus for management of thymic tumors is proposed here for reference in future clinical practice and researches.

A distinct feature in thymic tumors is a high prevalence of accompanying autoimmune diseases, especially myasthenia gravis (MG, 22.8% in the ChART database). Over 90% of the patients with MG had Type B thymoma components in their tumors. And concomitant MG symptoms often lead to detection of the tumors in an earlier stage, with two-thirds of them in stage I and II. Even in advanced stage (III and IV) tumors, patients with MG tend to have lower grade histology (thymomas instead of thymic carcinoma or carcinoids). These help explain a significantly better 10-year overall survival associated with MG. However, a better survival was found in non-MG patients with stage I tumors, indicating that the disease is still a negative prognostic factor (6).

Up till now, surgery remains the most often used treatment modality for thymic tumors, and still carries the most chance of cure (7). In the ChART retrospective database, only 5.5% of the patients received non-surgical treatment. And surgical resection alone was used more often in early stage lesions (stage I: 69.9%; II: 55.3%; III: 23.6%; IV: 21.5%) and in low grade tumors (thymoma versus thymic carcinoma 53.2% *vs.* 20.1%, $P<0.001$). Overall, results of surgical management of thymic tumors have improved significantly in the past two decades. This was first reflected in the ChART retrospective database as increased overall resection rate (82.1% *vs.* 88.1%), especially in thymic carcinomas (62% *vs.* 83.3%, $P<0.05$) and stage III thymomas (73.9% *vs.* 89.5%, $P<0.05$). Then there was also a significant increase in the use of minimally invasive approaches for thymic surgery, especially for early stage diseases. Video-assisted thoracoscopic surgery (VATS), including robotic surgery, accounted for one-fourth of the procedures in clinically stage I and II diseases in the later decade, and has increased to over 40% after 2010. The 5-year overall survival after VATS resection was similar to open thymectomy in pathological stage I and II tumors, implicating that VATS could provide comparable long-term outcome to traditional open surgery (8).

Appropriate extent of resection has been controversial in surgical management of thymic tumors. Both thymectomy and tumor resection only (partial thymectomy, or thymomectomy) have been widely used in China, with more thymomectomies seen in minimally invasive surgery for early stage lesions. Over two-thirds of the stage I and II patients received thymectomy in this series. Although there was no survival difference in general, overall survival tends to be higher in stage II diseases after thymectomy than after thymomectomy, with a significantly lower recurrence rate. And it is not at all surprising that for patients with MG, remission rate was also higher after thymectomy than after thymomectomy (9). These results suggest that thymectomy should be considered the standard procedure in surgical resection of thymic malignancies, even if the tumors were in early stages.

It should again be emphasized that complete resection is essential to prognosis of thymic tumors. Therefore, attention should be paid not only to staging but also to resectability during pretreatment workup. Although CT characters like tumor shape, contour, enhancement, with or without invasion of the adjacent structures (mediastinal

fat, mediastinal pleura, lung, pericardium, mediastinal vessels, phrenic nerve),and presence of pleural, pericardial effusion or intrapulmonary metastasis were all correlated with Masaoka-Koga staging, only absence of artery system invasion was predictive of complete resection of the primary lesion in multivariate analysis (10). This more or less echoes the ITMIG proposal for the upcoming new staging system (11), in that tumors invading the arterial system or intrapericardial vascular structures should be considered as T4 diseases and not amenable to upfront surgery.

Multimodality therapies have been used more frequently in thymic carcinomas than in thymomas. These included adjuvant radiation (58.9% *vs.* 38.3%, P<0.001), chemotherapy (37.2% *vs.* 8.6%, P<0.001), induction therapies (8.7% *vs.* 3.5%, P<0.001) in combination with surgery, and definitive chemo/radiotherapies for non-surgical patients. Increasing complete resection rate is essential to the improvement of outcomes in advanced stage diseases. Although less than 5% of the patients in this series received induction therapies, a 25% downstage and significant increase in complete resection rate associated with neo-adjuvant treatment was detected (12). For potentially unresectable tumors, resection rate and survival for locally advanced tumors downstaged by effective neoadjuvant treatment turned out to be non-inferior to those regarded resectable and thus went directly to surgery, both significantly better than tumors not responding to induction therapies. For unresectable diseases or medically inoperable patients, immerging results suggest that concurrent chemoradiation may be more effective than sequential chemoradiation or chemotherapy alone in disease control (13). It is also noteworthy that pretreatment biopsy for histological diagnosis has increased significantly from 11.8% to 18.6% (P=0.008) during the past 20 years. And for stage III and IVa tumors, radical resection rate was significantly higher after induction therapies followed by surgery than after upfront surgery. Overall survival in patients with their tumors downstaged by induction therapies appeared to be higher than those who received upfront surgery (14). Prognosis for tumors not responsive to neoadjuvant treatments, however, remained poor and was even worse than those receiving definitive chemoradiation**.** Clearly more attention should be paid to look into effective neo-adjuvant therapies in the future so as to improve the outcome of advanced stage thymic tumors.

In general, long-term outcome of management of thymic malignancy in China is similar to what has been reported in literature from all over the world. Follow-up results showed that 5- and 10-year overall survivals were 85.3% and 76.4% in this series. Only 17% of the tumors relapsed after surgical resection, with increased recurrence rate in more advanced stages (stage I: 3.1%, II: 7.3%; III: 30.7%; and IV: 48.5%) and higher grade histology (Type A/AB: 2.9%; B1–3: 14.9%; and C: 39.7%). Upon multivariate analysis, tumor stage, histology, and resection status were again revealed as independent prognostic factors, while MG or adjuvant therapies were not related to improved survival. This is in accordance with most reported results from large single center cohorts (15). During the 20-year study period, management outcome has improved significantly in China. This was mainly reflected in decreased overall recurrence (25.4% *vs.* 14.5%, P<0.05), especially in Type B thymomas and thymic carcinoma. Although no difference was detected in overall survival (82.7% *vs.* 85%, P=0.618), a trend toward increased survival was detected in thymic carcinomas, especially in stage III diseases (45.8% *vs.* 60.7%, P=0.077).

Along with the increase in surgery-only approach for thymic malignancy, adjuvant therapies were used less frequently after operation, especially in early stage and low grade tumors. Comparison with surgery alone, adjuvant radiation after complete resection failed to show any survival advantage in stage I–III tumors. In case of incomplete resection, however, adding radiation after surgery does help improve long-term prognosis (16). Similarly, no survival benefit was detected with adjuvant chemotherapy in stage III–IVa thymomas or thymic carcinoma (17). Considering the changes in management modality and outcome in the past two decades, survival for stage I and II tumors remained quite satisfactory even though less adjuvant radiation was applied, probably owing to a high complete resection rate in early stage lesions. With no obvious change in adjuvant therapies, the increased survival and decreased recurrence in stage III thymic carcinoma was mainly due to the increase in surgical resection rate. As for stage III thymomas, survival and recurrence rate remained unchanged, along with increased resection rate but less application of adjuvant radiation. All these suggest that postoperative radiation may be unnecessary in early stage tumors, as they are readily resectable and seldom recur after complete resection. Potential benefit from adjuvant radiation in stage III thymomas and thymic carcinomas still needs further evaluation.

To conclude, thymic malignancies are a series of relatively rare and indolent tumors, with distinctive clinic-pathological features. Based on the findings of this series of retrospective studies using the ChART database, the

following consensus could be reached to guide future research and practice.

(I) All thymic tumors are malignant, although most of them are relatively low grade in histology and clinical manifestation. Both over-treatment and under-treatment should be avoided in their management;

(II) Both tumor stage and histology should be considered in therapeutic decision making. Multi-disciplinary approach is mandatory in pre- and post-operative decision making;

(III) Curative resection should always be pursued and best result can be anticipated if the tumor could be removed completely. For this purpose, pretreatment evaluation using imaging study should focus not only on tumor staging, but also on respectability of the tumor.

(IV) For early stage tumors, surgery alone is enough and there is no evidence to support the use of adjuvant therapies after complete tumor resection;

(V) Minimally invasive surgery is safe and technically feasible and therefore, should be tried in early stage tumors. While immediate postoperative results may be superior to open approaches, more evidence is still in need to prove its long-term efficacy;

(VI) Although no definite conclusion could be made at present, total thymectomy should be recommended to ensure the completeness of resection and to reduce the risk of recurrence. And complete removal of anterior mediastinal fatty tissue together with the tumor offers better result in thymoma patients with concomitant myasthenia gravis;

(VII) Myasthenia gravis as a frequent co-morbidity in thymic malignancies is associated with better histology and may lead to early detection of the tumor. Increased resection rate and better survival may thus be anticipated, although this advantage is to some extent offset by the increased mortality from myasthenia per se in early stage tumors;

(VIII) For high grade tumors in advanced stage, improved outcome could only be achieved with multimodality approach, especially with precise preoperative staging, histological diagnosis, and effective induction to downstage the lesion so as to increase the chance of complete resection;

(IX) Routine application of adjuvant radiation and traditional chemotherapy agents has been unsatisfactory. Attention should be paid to select those patients at high risk of recurrence and thus may benefit from adjuvant therapies. Much effort is needed to explore more effective treatment modalities and new agents for thymic tumors;

(X) For unresectable diseases or medically inoperable patients, concurrent chemoradiation may offer better disease control and prolonged survival.

Up till now, many problems still remain unsolved concerning the management of thymic malignancies. Because of their rarity and relatively indolent nature, joint effort is crucial in clinical studies so as to gain a better understanding of the disease. The ChART retrospective database analysis, in line with the ITMIG global database projects, has set a good example for the study of rare tumors such as thymic diseases (3). Multi-institutional collaboration among different regions is definitely in need for organizing large scale clinical studies to solve currently existing problems and to pave the way for further improvement in clinical practice.

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None.

Footnote

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The impact of ChART on the science of thymic malignancies

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Thymic malignancies qualify as an orphan disease. Many hurdles stand in the way of scientific advancement for such rare diseases, including the difficulty in having an adequate and homogeneous population of patients to study, and the fact that grants and other support for research is mostly unavailable for rare diseases (1). It is clear that the only way to make progress is through grass roots efforts, collaboration, and an organizational infrastructure. This realization led to the formation of both the International Thymic Malignancy Interest Group (ITMIG) and the Chinese Alliance for Research in Thymomas (ChART).

From the outset, ITMIG has supported the development of regional thymic groups such as ChART (2). While ITMIG provides infrastructure for global collaboration, there are many advantages to having strong regional groups working on the same issues. We all have a lot to learn from one another. There may be regional differences in risk factors, susceptibility, management and outcomes (3). The ability to address questions both regionally as well as globally is ideal to develop a full understanding of thymic malignancies.

ChART has been a major contributor to the science in thymic malignancies. ChART has led a number of investigations, both of ChART data as well as global ITMIG data that are shedding new light on management. The size of the database assembled by ChART is a major component of the available global data. The scope of ChART activities is broad—ranging from retrospective and prospective data, to clinical trials, and to efforts to set reasonable standards such as in the article by Professor Fang in this issue. The impact of these activities is just beginning, and clearly will be substantial.

Most impressive is the quality of the ChART activities. ChART is a role model for regional organization, for assembling high quality data, for attention to the scientific process and for thoughtful development of infrastructure. All of this has been accomplished in the span of only a few years. It is a testament to the hard work, dedication, and attention to quality and science of the ChART members, and a great example of the contributions China is making to the global community in general.

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Footnote

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Management of thymic tumors: a European perspective

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Abstract: Thymic tumors are rare mediastinal tumors, which are considered as orphan diseases due to their low prevalence. The most recent histologic classification divides thymic tumors into thymomas, thymic carcinomas (TC) and neuroendocrine thymic tumors (NETT). Until recently, clinical research on thymic tumors has been primarily represented by single-institution experiences usually scattered over a long time period in order to accumulate a sufficient number of patients for clinical analysis. Europe has played a pivotal role in the advancement of the clinical research on thymus in the past years. In the last decade, there has been an increased interest in thymic malignancies in the scientific community. The European Society of Thoracic Surgeons (ESTS), the most representative society of general thoracic surgeons in the world, established a dedicated thymic working group in 2010 with the intent to provide a platform among ESTS members with a specific interest in thymic malignancies. The present review is intended to provide, through the description of the activity of the ESTS thymic working group and its published results, an overview of the European contribution to the thymic research. A brief overview of the state-of-the-art of clinical presentation, diagnosis, staging and histologic classification of thymic tumors is also provided, along with the most recent therapeutic advancements.

Keywords: Thymoma, thymic carcinoma; thymic tumors; staging; surgery

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Introduction

Thymic tumors are infrequent tumors, although they represent the most common adult tumors in the anterior mediastinal compartment. Thymic tumors represent a wide variety of tumors, and the the most recent histologic classification clearly classifies them in thymomas, thymic carcinomas (TC) and neuroendocrine thymic tumors (NETT). Although thymic tumors have traditionally been considered as orphan diseases, in the last few decades there has been an increased interest in thymic malignancies in the scientific community, and a number of thymic tumors working group and international thymic interest groups have been instituted all over the world. In Europe, the European Society of Thoracic Surgeons (ESTS) established a thymic working group in 2010 with the intent to provide a platform among ESTS member with a specific interest in thymic malignancies.

The present review illustrates the most recent results of the ESTS thymic working group, its collaboration with other major international thymic groups, and the future projects of the group.

Thymic tumors: demographics, clinical presentation and diagnosis

Thymic tumors are rare neoplasms with an overall incidence in the USA of 0.15 cases per 100,000 person-year (1). They are the most frequent anterior mediastinal tumors in adults; they can occur in all ages, with a demonstrated peak around 30-40 years of age in thymomas with Myasthenia Gravis (MG) and 60-70 years of age in those without MG (2). Men and women are affected with the same frequency according to most series. Thymic tumors are divided into thymomas, TC and NETT. About 30% of thymoma patients are asymptomatic, while about 60%-70% of patients

Table 1 Paraneoplastic syndromes associated with thymic tumors

Hematologic syndromes
Red cell aplasia
Pancytopenia
Multiple myeloma
Megakaryocytopenia
Hemolityc anemia
Neuromuscular disorders
Myasthenia Gravis
Eaton-Lambert syndrome
Myotonic dystrophy
Myositis
Neuromyotonia (Morvan's syndrome)
Stiff person syndrome
Limbic encephalopathy
Collagen diseases and autoimmune disorders
Systemic Lupus Erythematosus
Sjogren syndrome
Rheumatoid arthritis
Polymyositis
Myocarditis
Sarcoidosis
Scleroderma
Ulcerative colitis
Endocrine disorders
Addison's diseasae
Hashimoto's thyroiditis
Hyperparathyroidism
Immunodeficiency syndromes
Hyopogammaglobulinemia
T-cell deficiency syndrome
Dermatologic disorders
Pemphigus
Alopecia aerata
Chronic mucocutaneous candidiasis
Renal diseases
Nephrotic syndrome
Minimal change nephropathy
Bone disorders
Hypertrophyc osteoartropathy
Malignancies
Carcinomas (lung, colon, stomach, breast, thyroid)
Kaposi's sarcoma
Malignant lymphoma

with TC and NETT have symptoms at presentation. The most reported symptoms in any thymic tumor include local symptoms. Chest pain, cough, shortness of breath are present in both capsulated and invasive forms, while in case of invasive neoplasms, superior vena cava (SVC) syndrome, haemidiaphragm paralysis (phrenic nerve involvement) and hoarseness (recurrent laryngeal nerve infiltration) are frequently observed. Pleural effusion and chest pain are also observed in case of tumor pleural spread.

Thymic tumors are frequently associated with parathymic (paraneoplastic) diseases; *Table 1* illustrates the most frequent associated diseases. MG is, by far, the most commonly associated paraneoplastic disease in thymoma patients: most series report that 30% to 50% of thymoma patients have MG, while 10%-15% of MG patients present with a thymoma. Five percent of thymoma patients with MG have more than one paraneoplastic syndrome. Among non-MG paraneoplastic syndromes, Pure Red Cell Aplasia (PRCA) and Hypogammaglobulinemia (Good's syndrome) are the most frequently observed conditions, occurring in up to 5% of the patients (3).

Thymic carcinoma is rarely associated with MG, with a variable prevalence ranging from 0% to 30% depending upon the series. Very rarely, TCs have been found to be associated with polymyositis or dermatomyositis or erithrocytosis (4,5).

NETT are frequently associated with endocrinopathies (up to 30% of the cases), including Cushing's syndrome, multiple endocrine neoplasia type 1 (MEN-1 or Wermer syndrome, with tumors of the parathyroids, pancreatic islet cells, and pituitary gland), and growth hormone releasing hormone (GHRH) hyper-secretion with ectopic acromegaly. Other less frequent syndromes include prolactin secretion, MEN-2, peripheral neuropathy, Eaton-Lambert syndrome. Carcinoid syndrome and MG are exceptional in NETT (6).

Finally, thymoma patients have an increased (2-fold higher risk) risk to develop second malignancies.

Diagnosis of thymic tumors includes clinical examination, radiologic imaging and cyto-histologic biopsy in selected cases. Clinical examination may reveal signs and symptoms of associated parathymic syndromes or of local invasion (SVC syndrome). Computed tomography (CT) scan is considered the imaging modality of choice in the initial assessment as well as in the follow-up of patients with thymic malignancies (7-9). MRI is of little utility in diagnosis of thymic malignancies, except in case of suspected infiltration of the heart and great vessels (10). PET scan has been evaluated in its ability to differentiate

thymic hyperplasia from thymoma, low-risk *vs*. high-risk thymomas, and thymoma *vs*. thymic carcinoma, although it is still less frequently used as compared to its widespread utilization in other thoracic neoplasms.

Cyto-histological diagnosis is required, although less frequently than in the past. Refinements in imaging techniques resulted in an improved diagnostic yield, and the need for a mediastinal biopsy has dramatically decreased in the recent years. There is a general agreement, however, that biopsy should be reserved in case of undefined CT findings which may suggest lymphoma, or in case of unresectable tumours before induction chemotherapy or definite chemo-radiotherapy (11).

Staging and histologic classification

No official stage classification system for thymic malignancies has been defined by the Union Internationale Contre le Cancer (UICC) and the American Joint Commission on Cancer (AJCC) and several different systems have been proposed in the past (12). The most used staging system is the Masaoka staging classification, proposed in 1981 (13), further refined with little modifications in 1994 (14) (*Table 2*). The classification includes four stages based upon the local extent of the disease. N factor is of limited value in the Masaoka classification. A new TNM-based system is expected in 2017, through a collaborative effort between the International Thymic Malignancies Interest Group (ITMIG) and the International Association for the Study of Lung Cancer (IASLC).

Similar to staging, a number of different histological classifications of thymic tumors have been proposed in the past 50 years, and a considerable debate has occurred among pathologists which continues until now. After a long period of controversies, in 1999 the World Health Organization (WHO) (15) reached a consensus on histologic classification of thymomas based upon both morphology and the lymphocyte to epithelial cell ratio using letters and numbers and identifying 6 subtypes: type A (medullary); type AB (mixed); type B1 (organoid); type B2 (cortical); type B3 (well-differentiated thymic carcinoma), and type C (thymic carcinoma). The classification was updated in 2004 (16) (*Table 3*), and the most important modification was the inclusion of type C thymomas into a separate type of thymic tumors (thymic carcinoma), further subdivided into 11 subtypes including NETT. Despite this elegant histologic differentiation into different subtypes, the prognostic significance of histology in thymic tumors, with the exception of thymic carcinoma, has never been validated in large-scale studies.

Treatment of thymic tumors

A number of papers have been published in the literature in the past decades investigating possible prognostic factors in thymic tumors. A recent review analyzed prognostic factors for survival and for recurrence in thymic tumors exploring the most recent literature (17). The only validated prognostic factors for both survival and recurrence were the stage at presentation (Masaoka or Masaoka/Koga) and the completeness of resection. Gender and MG are consistently reported NOT to be significant predictors for either survival or recurrence. Histology according to WHO classification does not seem to be a validated prognostic factor, with the exception of thymic carcinoma. Other prognostic factors, including age, tumor size, other parathymic syndromes were inconsistently reported as significant prognostic factors.

Surgery

Surgical resection is the mainstay of treatment of thymoma, with a reported operative mortality of 2% and a complication rate of approximately 20% (18). Complete resection should be the primary goal and results depend on the localization and the size of the tumor. The ITMIG recommends en bloc resection including complete thymectomy and resection of the surrounding mediastinal fat because of the possibility of subtle macroscopically invisible invasion of the tumor. The 10-year survival rates are 90%, 70%, 55%, and 35% for stages I, II, III, and IVa thymoma, respectively The recurrence rate is 3%, 11%, 30% and 43% in resected stage I, II, III, and IVa thymoma, respectively. The disease free survival at 10 years is 94%, 88%, 56%, and 33% for stages I, II, III, and IVa, respectively (19).

Most centers recommend a sternotomy as the optimal incision for thymoma as it might not be possible to perform a complete thymectomy via thoracotomy (20). Transcervical approach has also been used for this purpose. Minimally invasive approaches including video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS) for early stage thymomas have been reported (21-23) and are gaining popularity in specialized centers. Especially RATS allows an excellent exposure and precision of resection in tumors of adequate size and location.

Table 2 Masaoka and Masaoka/Koga staging systems for thymic tumors

The Masaoka staging system-1981		
Stage		Description
I		Macroscopically encapsulated tumor without microscopic invasion of capsule
II		Macroscopic invasion into surrounding fatty tissue or mediastinal pleura or microscopic invasion into capsule
III		Macroscopic invasion into neighboring organs; i.e., pericardium, great vessels or lung
IV	a	Pleural or pericardial dissemination
	b	Lymphogenous or hematogenous metastasis
The Masaoka-Koga staging system-1994		
Tumor stage		Description
I		Grossly and microscopically completely encapsulated tumor
II	a	Microscopic transcapsular invasion
	b	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent but not breaking through mediastinal pleura or pericardium
III		Macroscopic invasion of neighboring organs (pericardium, great vessels or lung)
IV	a	Pleural or pericardial dissemination
	b	Lymphatic or hematogenous metastasis

Table 3 Histologic classification of thymic tumors (WHO, 2004)

Thymoma	• Type A, spindle cell; medullary
	• Type AB, mixed
	• Type B1, lymphocyte-rich; lymphocytic; predominantly cortical; organoid
	• Type B2 cortical
	• Type B3 epithelial; atypical; squamoid; well-differentiated thymic carcinoma
	Micronodular thymoma
	Metaplastic, sclerosing, microscopic thymoma
	Lipofibroadenoma
Thymic carcinoma	• Squamous cell, Epidermoid keratinizing
	• Epideromid non-keratinizing
	• Basaloid
	• Lymphoepithelioma-like
	• Mucoepidermoid Ca
	• Sarcomatoid
	• Clear cell
	• Mucoepidermoid
	• Papillary
	• Undifferentiated
	• Combined
Neuroendocrine tumors	• Well-differentiated neuroendocrine tumor/carcinomas, including typical and atypical carcinoids
	• Poorly-differentiated neuroendocrine carcinomas, including large and small cell neuroendocrine carcinoma

Radiotherapy (RT)

Thymic tumors have a tendency to local recurrence, and show moderate-high radiosensitivity profiles. This has always been considered a prerequisite for the adoption of RT in the whole treatment strategy. RT may be delivered before surgery, after surgery, and as exclusive treatment in patients not eligible to surgical intervention or for treatment of recurrent tumors. The delivered doses varies according to the clinical setting, ranging from 45 Gy as preoperative therapy, to 45-55 Gy as postoperative, to 60-66 Gy as exclusive treatment, with conventional fractionation (1.8-2.0 Gy/day) (24).

Postoperative RT is usually performed within 3 months from the surgical procedure, for a total dose of 50-54 Gy in 1.8-2.0 Gy fractions. In Masaoka Stage I, adjuvant RT has no role. In stage II, the largest series so far found either no differences with or without RT (25), or even a detrimental effect (26); In stage III, adjuvant RT has a well-established role among clinicians, although the evidence so far is low. The most recent trials failed to show any significant advantage (25,27,28).

Radical "curative" RT is customarily adopted in inoperable patients, or in patients deemed inoperable after induction chemotherapy. Combined chemo-radiation is usually delivered in a sequential manner to a total dose of 54-70 Gy. The response rate reaches 70%, with a 5-year survival projection of 70%-80%: these results are similar to those reported after surgery with incomplete resection (24,29).

Chemotherapy

Thymic tumors are generally chemosensitive, and thymomas are more sensitive to chemotherapy than TC. Chemotherapy strategies comprise chemotherapy used as initial treatment and as treatment in case of recurrence. Chemotherapy as initial treatment can be further divided in chemotherapy with curative intent (primary/preoperative/induction chemotherapy or postoperative chemotherapy) and chemotherapy with palliative intent. Exclusive (palliative) chemotherapy is administrated in patients medically or technically not suitable for surgical procedures or in patients with metastatic disease (30).

The major goal of primary chemotherapy is to downstage the tumor prior to surgery. A recent Cochrane analysis was performed (31) to evaluate the role of induction therapy in thymic tumors: 49 relevant randomized studies were identified; however none of them met the criteria allowed for a Cochrane analysis. Therefore all published guidelines to multi-modal treatment of thymic neoplasm remain expert opinions. On average, in patients with stage III-IV thymic neoplasms, primary chemotherapy achieves a response rate of 71% (29%-100%) and surgery results in a complete resection in 68% (22%-86%) (2). All used regimens are poly-chemotherapies.

In the majority of the cases post-operative therapy after resection of thymic tumors consists of RT or radio/chemotherapy. In contrast to lung cancer, since improved local control is the main focus of adjuvant therapy in thymic neoplasms, chemotherapy alone is rarely used in an adjuvant setting.

Finally, in case of metastatic spread or contraindications to local treatment with surgery or RT, exclusive chemotherapy with palliative intent is offered with reasonable results. In emergency situations like SVC syndrome or evident clinical symptoms, poly-chemotherapy is an option with a proven efficacy on QoL.

Combined radio/chemotherapy

The rationale to combine chemotherapy and radiation therapy is to augment cytotoxicity against remaining tumor cells by an additive effect of chemotherapy and radiation. Combined radio/chemotherapy can be used in the post-operative setting if a large unresectable tumor volume (R2) remains in the thorax. Furthermore radio-/chemotherapy is the definitive treatment for patients medically unfit or with a thymic neoplasm technically not resectable (32).

Targeted therapies

A recent interest has developed in the molecular and genomic analysis of thymic tumors for the evaluation of possible targeted therapies (33).

KIT is overexpressed in 2% of thymomas and in 79% of TC when analyzed by immunohistochemistry (34). There are activating mutations in exon 9, 11, 13 and 17. Imatinib is a small molecule multi-kinase inhibitor blocking KIT, Bcr-Abl, and PDGFR. However, the treatment with imatinib resulted only in short disease stabilization in phase II studies (35).

EGFR is overexpressed in 70% of thymomas and 53% of TC. Erlotinib and gefitinib are small molecule tyrosine kinase EFGR inhibitors. Unfortunately, no clear association has been described so far between specific mutations in the EGFR and activity of specific tyrosine kinase inhibitors.

Markers of angiogenesis have been investigated in

thymic neoplasms. VEGF-A serum levels were elevated in serum samples of patients with TC, and VEGF-R1 and R2 were expressed in the malignant thymic tissue. Although a theoretical application of anti-angiogenetic agents (sunitinib, sorafenib and antibodies binding VEGF-bevacizumab and aflibercept) is appealing, the published data indicate only a weak clinical efficacy (36,37).

Thymic tumors: the European contribution by ESTS

By definition, a rare and orphan disease is one that affects fewer than 200,000 individuals in the United States. Thymic tumors are classified as orphan diseases, due to their low prevalence. As a consequence, most of our knowledge on these tumors has been based so far from single-institution case series, usually spanned over a long time period to collect a sufficient number of cases to draw a statistically appropriate analysis. For this reason, advancements in management strategies have been slow so far. In addition, at least until recently, the lack of coordination among centres with sufficient experience resulted a major obstacle.

A dramatic improvement occurred in the past decade, when the most important thoracic societies addressed this issue by establishing dedicated thymic groups into their structure.

A major step forward in the scientific advancement of thymic tumors has been the creation, in 2010, of the ITMIG (www.itmig.org) (38), which was endorsed and supported by the most representatives medical and surgical societies around the globe. According to its constitution, ITMIG's mission is to promote the advancement of clinical and basic science related to thymic malignancies. It provides infrastructure for international cooperation, it maintains close collaboration with other related organizations and it facilitates the spread of knowledge about thymic neoplasms. ITMIG works in close cooperation with the most important thymic groups of the international medical societies including the ESTS, the European Association of Cardio-thoracic Surgeons (EACTS), the Japanese Association for Research of the Thymus (JART). It is a multidisciplinary organization, involving thoracic surgeons, radiation and medical oncologists, pathologists, pulmonologists, radiologists and basic science researchers. It includes more than 600 members from all continents.

Europe has a long-standing tradition in the research of thymic tumors, and many European Institutions from France and Italy have been leading centres over the past 30 years. A substantial number of papers have been published from European centres, which have constituted landmark manuscripts for the scientific community. Not surprisingly, therefore, the ESTS, which is the most representative general thoracic surgical society in Europe, started its thymic working group in 2010 with the intent to provide a common platform to its members interested in thymic tumors.

The thymic group first met at the ESTS annual meeting in Valladolid, Spain in 2010 where a list of 35 interested centres were identified and a survey was designed about the current management of thymic tumors among ESTS members. The results of the survey were published in 2011 (39).

At the next ESTS annual meeting in Marseille, France in 2011 the thymic group launched the ESTS thymic retrospective database project to collect data of patients submitted to surgical resection of thymic tumors among any interested ESTS centre. The dataset was designed in collaboration with ITMIG to have similar datafields for future common projects.

At the 2012 ESTS annual meeting in Essen, Germany, the preliminary results of the thymic retrospective database were presented, and a dedicated thymic section in the ESTS Registry was funded and provided using the official platform of the ESTS database.

Finally, at the 2013 ESTS annual meeting in Birmingham, UK, the ESTS prospective thymic database was officially launched into the thymic section of the ESTS Registry, where any ESTS member may upload his/her patients with thymic tumors prospectively.

As mentioned above, therefore, ESTS represents the leading European force in the study of thymic tumors, with an unprecedented collaborative effort among the participating institutions and an enthusiasm which will certainly stimulate new projects in the future.

The major products of this extraordinary collaborative effort have been three papers which have been published in the last three years, covering important aspects of the management of thymic tumors.

The ESTS survey on management of thymic tumors (39)

After its establishment in 2010, the first move of the ESTS thymic working group was to test the differences of management of thymic tumors in the ESTS community. Due to their rarity, there are no current guidelines or consensus statements about appropriate management of thymic tumors, and most of the current practice is based

upon personal series and expertise of the individual centres. For this reason, a survey was deemed a useful tool to investigate the state-of-the-art of the current practice.

A questionnaire was designed, which was circulated by email to all ESTS members. The questionnaire included 25 points organized in seven sections:

- Volume of activity of the participating center;
- Preoperative assessment;
- Histology and staging system employed;
- Details on surgical resection;
- Pre- and post-operative treatments for invasive thymic tumors;
- Management of recurrence, thymic carcinoma and Stage IVa thymic tumors;
- The organization and logistics of the thymic activity of the centre.

Overall, 44 centres replied and their answers were used for the results. Although ESTS is primarily a European thoracic society, it is open to any centre from any country all over the world who has interest in general thoracic surgery. Out of the 44 responders, 33 were from Europe, 7 from USA/Canada/South America, 4 from Asia.

The results of the study showed that there are some areas of agreement about different aspects in the diagnosis and management of thymic tumors, although there still are many "grey" areas of controversy which need to be elucidated by large-scale collaborative studies.

In particular, the study found that there is a substantial agreement on the following issues: (I) the pivotal role of CT scan in the preoperative diagnosis of thymic tumors. Last generation CT scans allow a well-definite morphological imaging of the thymic tumor, the possible invasion of the surroundings organs, and a precise differential diagnosis with other anterior mediastinal tumors, thus avoiding routine cyto-histologic confirmation; (II) as a consequence of the former, routine cyto-histologic diagnosis before surgical resection is not performed by the vast majority of the interviewed centres, unless differential diagnosis remains difficult or induction therapy is required; (III) the Masaoka staging system (although with a still considerable confusion with the updated Masaoka-Koga system) and the 2004 WHO histologic classification are used by the vast majority of the centres; (IV) the importance of a complete resection for good long-term results. Most centres correctly indicated complete resection as a major prognostic factor, although some concern still exists by some centres about resection of great vessels (innominate vein, SVC) and reconstruction, as well as the resection of the phrenic nerve in MG patients. The message of the survey was that resection/reconstruction of the great vessels is indicated for the venous conduits (innominate vein, SVC), and unilateral resection of the phrenic nerve can be accomplished, even in MG patients, while bilateral phrenic nerve resection and resection of the arterial conduits are to be avoided in most cases; (V) the surgical approach to recurrence. Most centres also indicated that a proper selection of patients candidates to surgical resection of the recurrence is mandatory, although recurrence resection is indicated whenever possible; (VI) the importance to have a dedicated pathologist for thymic tumors, along with a dedicated thymic tumor board including dedicated medical and radiation oncologists.

On the other hand, the survey clearly indicated that there is still a considerable debate about the following issues: (I) the role of PET scan for the preoperative assessment. Only half of the interviewed centres declared to routinely use PET scan, although most institutions use it on a selecetive basis with the following indications: (i) to detect a potentially invasive thymoma; (ii) in case of suspected pleural dissemination (Stage IVa); and (iii) for the assessment of response after induction therapy. The results of the survey seem to confirm some studies recently published on this topic (40,41); (II) the administration of postoperative therapies after resection of invasive (Stage II-III) thymomas. This is possibly the most controversial issue in the management of thymic tumors, which has been addressed also in the other two papers based on the ESTS retrospective database. In the survey, 60% of the interviewed centres indicated that they use postoperative RT even in Stage II thymoma, although on a selective basis (high-risk WHO histology-B2/B3; high-risk free resection margins). As for Stage III thymomas, the survey confirmed the standard practice to administer postoperative RT after resection (60%), either complete or not. Postoperative chemotherapy alone is seldom performed (7%), although postoperative radio-chemotherapy was indicated by some centers. Induction therapy is, on the other hand, a consolidated treatment modality in the scientific community, and 75% of the centres stated that they use it in case of perceived unresectable tumors; (III) treatment modality for thymic carcinoma. The general feeling from the centres was that thymic carcinoma should be treated in a multidisciplinary setting, and this prompted the ESTS thymic group to analysed thymic carcinoma separately in the ESTS retrospective database; (IV) the role of extended surgery in the treatment of thymoma extending to the pleura (Stage IVa). Although 40% of the centres replied that

they may consider extrapleural pneumonectomy in these patients, the majority of the institutions seems reluctant to embark in this extensive surgery in this subset of patients.

Finally, the study addressed the question whether high-volume (>10 thymic resections/year, N=18) institutions have different diagnostic and treatment management as compared to low-volume (<10 thymic resections/year, N=26) centres. Interestingly, the approach to thymic tumors was quite similar in the two groups, indicating that a high-quality standard of management can be obtained irrespective of the number of performed resections.

Despite the limitations of the study, which are common to any survey, the major value of the ESTS survey was to provide a large, multiinstitutional, clear overview of the clinical practice in the management of thymic tumors, ranging from top-quality excellence centres to regional community hospitals all interested in the treatment of these rare tumors.

Overall results of the ESTS thymic retrospective database (42)

The ESTS thymic retrospective database was launched in 2011 and included data on patients submitted to surgery for thymic tumors from 1990 to 2010. The preliminary results were shown in 2012 and the final paper was published in 2014. The manuscript investigated possible prognostic factors for all thymic tumors on a cohort of 2,151 patients from 35 institutions. Overall survival (OS) and disease-free survival (DFS) were used as outcome measures, along with the cumulative incidence of recurrence (CIR).

The analysis was conducted examining the following points:

- Analysis of predictors of incomplete resection;
- Analysis of predictors of OS and DFS;
- Analysis of predictors of recurrence;
- Subgroup analysis on the role of adjuvant (postoperative) therapy.

Analysis of predictors of incomplete resection indicated that the probability to perform an incomplete resection increased in male patients (*vs.* female), in absence of MG, in larger tumors, and in high-risk thymomas (B2/B3), thymic carcinoma and NETT.

Predictors of OS and DFS were similar. Mortality increased with age, with Masaoka stage, and in incomplete resection. The ESTS study did not indicate WHO histology as a significant prognostic factor.

Predictors of recurrence were investigated after complete resection. CIR was 5%, 8% and 12% at 3, 5 and 10 years respectively. The probability of a recurrence increased with non-MG status, in larger tumors and in advanced stages.

Finally, the subgroup analysis on the role of adjuvant therapy following a complete resection of the thymic tumor indicated (using a Cox model adjusted for propensity score) that an overall beneficial effect of adjuvant therapy on OS occurred in the cohort, without major differences in other subgroups.

The ESTS cohort study is the largest collaborative retrospective study on thymic tumors published so far, and this certainly represents a major value. As any other multi-institutional retrospective study it suffers from an inhomogeneous geographical distribution, different volume activity of the participating centres, the lack of a central review of the pathology reports, etc. Nonetheless, while awaiting for the results from prospective studies, it still represents an important reference in the field of thymic tumors.

Results of the ESTS thymic retrospective database on the patients with thymic carcinoma

The third contribution of the ESTS thymic group is the subgroup analysis of patients with thymic carcinoma from the ESTS thymic retrospective database, which was presented at the ASCO meeting in June 2013 in Chicago, and which is in press in JTO. The patient population included 229 TC out of 2,265 patients with thymic tumors from 36 institutions. As in the study on the overall population, primary endpoints were OS, DFS and CIR.

Survival analysis was performed according with different covariates, and analysis of predictors for OS, DFS and recurrence was undertaken.

As for the ESTS cohort study of prognostic factors on the overall population of thymic tumors, this study represents so far the largest series of patients with thymic carcinoma submitted to surgical resection ever published.

Conclusions

We can therefore conclude that a dramatic improvement in our knowledge on the diagnosis and management of thymic tumors has occurred in the last few years (43,44). Europe is a leading force in the development of the collaborative international effort which has taken place in the most recent year. The ESTS thymic group played a major role in this effort. ESTS is actively working with the Japanese Association for Research in Thymus (JART), ITMIG and IASLC in the development of the next 8th edition of the

TNM of thoracic malignancies, expected in 2017, where a new TNM-based staging system for thymic tumors will be proposed, based upon the extraordinary data collection from the three most important datasets ever collected (ITMIG, JART and ESTS). Further projects are under way in the ESTS thymic group, including the prospective collection of thymic data using the ESTS Registry, and the exploration for a possible tissue bank of thymic tumors for genomic and molecular analysis with possible therapeutic implications. All these projects can be pursued only with the dedicated enthusiasm of the people involved in the ESTS thymic group, along with all the representatives of the institutions from Europe, USA/Canada, and Asia who sent their data for the patient collection, and who actively participate in the activity of the group.

The results of this amazing European-based international cooperation led by ESTS will soon be available, resulting in a major improvement in the outcome of a patient population which until now has suffered from the difficulties common to many orphan diseases.

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Prof. Frank Detterbeck: more attention should be paid to subgroup in the study of rare disease

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The 6th Annual International Thymic Malignancy Interest Group (ITMIG) Meeting in Shanghai on Oct 23–25 came to a close with a resounding success. It was marked by exciting sessions, scientific progress and further development of relationships and collaborations among clinicians, researchers and industry partners.

During the conference, Prof. Frank Detterbeck, the former President and the committee member of ITMIG, has given an innovative lecture on outlier analysis, leading us to think out of box and find novel ways to advance in a rare disease.

Journal of Visualized Surgery was honored to invite Prof. Detterbeck for a brief interview to further share his opinion on the controversial issues presented during the meeting (*Figures 1*,*2*).

The full report and abstracts for the conference has been published as a supplement issue in *Journal of Thoracic Disease*: http://www.jthoracdis.com/issue/view/158.

Figure 1 Prof. Detterbeck with *Journal of Visualized Surgery* (*JOVS*) editor.

Figure 2 Interview with Prof. Detterbeck (1). Available online: http://www.asvide.com/articles/764

Introduction

Frank Detterbeck, MD, FACS, FCCP is a Professor of Surgery and Chief of Thoracic Surgery at Yale University and Associate Director of the Yale Cancer Center. He earned a BS in Cell Biology at the University of Michigan, and an MD degree from Northwestern University. After completing general surgery training at the Virginia Mason Clinic in Seattle, he pursued a cardiothoracic fellowship and a fellowship in thoracic transplantation at the University of North Carolina at Chapel Hill. He rose to the rank of professor of surgery at the University of North Carolina during a long tenure there before being recruited to Yale University in 2005. The major focus of his career has been on thoracic oncology. In particular, he has promoted evidence-based care and multidisciplinary teamwork. He has written extensively on these and other topics, with over 150 papers and book chapters. He holds leadership positions in many of the major professional societies associated with thoracic surgery and has given invited lectures on a wide variety of topics at many institutions and international meetings.

Interview question

- What is the take home message from your Innovative Lecture on Outlier Analysis?
- What do you think of the efficacy of subtotal and total thymectomy?

- How is the updated IASLC (proposal) and WHO tumor classification going to influence the upcoming study of thymic surgery?
- In terms of thymic surgery, which is your preferred procedure: open, video-assisted thoracoscopic surgery (VATS) or robotic surgery?
- How would you comment on the recent development of thymic surgery in China?

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Footnote

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

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Prof. Robert Korst: PORT in completely resected thymoma—more observation is needed

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The 6th Annual International Thymic Malignancy Interest Group (ITMIG) Meeting in Shanghai on Oct 23–25 came to a close with a resounding success. It was marked by exciting sessions, scientific progress and further development of relationships and collaborations among clinicians, researchers and industry partners.

In the conference, Prof. Robert Korst has given a speech on "Post Operative Radiation Therapy in Completely Resected Thymoma". *Journal of Visualized Surgery* was honored to conduct an interview with Prof. Korst to further share the recent advancement of thymic tumor research (*Figures 1,2*).

The full report and abstracts for the conference has been published as a supplement issue in *Journal of Thoracic Disease*: http://www.jthoracdis.com/issue/view/158.

Figure 1 Prof. Robert Korst with *Journal of Visualized Surgery* (*JOVS*) editor.

Figure 2 Interview with Prof. Robert Korst (1).
Available online: http://www.asvide.com/articles/757

Introduction

Prof. Korst is board certified in surgery and thoracic surgery, and he received his medical degree from the University of Connecticut School of Medicine in 1989. He completed a general surgery internship at Hartford Hospital, Ct., in 1990. Midway through his residency at the University of Connecticut Integrated Program in General Surgery, Farmington, Ct., Dr. Korst went to the National Institutes of Health's Heart, Lung, and Blood Institute in 1992 as a research fellow in genetics. Before coming to Valley, Dr. Korst was a member of the departments of Cardiothoracic Surgery and Genetic Medicine at New York-Presbyterian Hospital/Weill Cornell Medical Center.

Interview questions

- From your presentation about efficacy of Post Operative Radiation Therapy in Completely Resected Thymoma, what is the key message you would like to convey to the audience?
- How would you comment on the recent development of thymic tumor research?
- What is your expectation for future international collaboration in thymic tumor research?
- What is your impression for the ITMIG 2015 annual conference?

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Prognostic stratification of thymic epithelial tumors based on both Masaoka-Koga stage and WHO classification systems

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Background: The aims of this study were to stratify the risk of recurrence based on the Masaoka-Koga stage and World Health Organization (WHO) classification systems after R0-resection for thymic epithelial tumors (TETs).

Methods: A retrospective analysis was conducted on 479 patients who underwent surgery between Jan 1994 and Feb 2014 for TETs. The study group comprised 251 males and 228 females, with a median age of 52 years (range, 15–84 years).

Results: Of the 479 patients, 406 (84.8%) patients underwent R0-resection. Recurrence after R0-resection occurred in 32 patients during a median follow-up of 53 months (range, 2–227 months). A multivariate analysis revealed that the preoperative treatment including chemotherapy (P=0.036), Masaoka-Koga stage (P=0.011) and the WHO classification (P=0.001) were predictors for recurrence after R0-resection. Patients were stratified into four risk groups using a potential model incorporating both the Masaoka-Koga stage and WHO classifications. Group 1 comprised WHO types A/AB/B1 in stage I/II; Group 2 comprised WHO type A/AB/B1 in stage III or WHO type B2/B3 in stage I/II or WHO type C in stage I; Group 3 comprised Type B2/B3/C in stage III, or WHO type C in stage II/III; and Group 4 comprised WHO type B2/B3/C in stage IV. The 5-year freedom-from-recurrence (FFR) rates were 99.4% for group 1, 84.7% for group 2, 63.7% for group 3, and less than 44.4% for group 4 (P<0.001). In group 3, the rate of locoregional recurrence of patients treated with postoperative radiation therapy was lower than patients treated without postoperative radiation therapy (P=0.032).

Conclusions: A risk model incorporating both Masaoka-Koga stage and WHO classification systems may provide multi-faceted information about recurrence and adjuvant treatment after R0-resection of TETs.

Keywords: Thymoma; thymic carcinoma; surgery; recurrence

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Introduction

The Masaoka staging system and the World Health Organization (WHO) classification system are widely used to stage and to classify thymic epithelial tumors (TETs) including thymomas and thymic carcinomas, although the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG) proposed new TNM classification or TETs for forthcoming (8th) edition of the TNM classification of malignant tumors (1-3).

The Masaoka staging system, published in 1981, staged

tumors on the basis of their anatomical extent (4). In 1994, Koga *et al*. suggested a modification of this system (5). The ITMIG opted to use the Masaoka-Koga system until a scientifically validated system is defined and remains the most widely used system currently (6,7). The WHO's histologic typing system of tumors of the thymus, published in 1999, classifies TETs as type A, AB, B1, B2, B3, or C on the basis of the morphology of their epithelial cells and the ratio of lymphocytes to epithelial cells. The WHO classification system has been widely adopted because it enables simple comparisons of clinicopathological studies (8). It has previously been suggested that the Masaoka stage and the WHO histological subtype may be independent factors for the prognosis of TETs (4,8-16), however, the potential advantages of using a combination of these two classification systems is still unclear. Therefore, the aims of this study were to evaluate prognostic factors after complete resection for TETs and to stratify the risk of recurrence after R0-resection based on the Masaoka-Koga stage and WHO classification systems.

Methods

Patients

A retrospective analysis of 479 patients who underwent surgical resection for TETs at Asan Medical Center between Jan 1994 and Feb 2014 was conducted. Patients with tumors that could not be classified according to the WHO system, those with thymic neuroendocrine carcinomas and those who underwent biopsy alone were excluded from this study. This study was approved by our institutional Ethics Committee/Review Board, which waived the requirement for informed patient consent because of the retrospective nature of this study.

Classification of thymic epithelial tumors (TETs)

TETs were histologically categorized according to the WHO classification system (17). Routine histological sections were stained with hematoxylin and eosin and examined by a pathologist. A second experienced pathologist then reviewed the histological classification and made the final decision on the histological type. The Masaoka-Koga stage was determined after review of the surgical and pathological reports. For patients who received preoperative chemotherapy, their staging was determined based on the post chemotherapy status.

Surgical treatment

The mainstay of treatment of TETs was surgery. The surgical procedures included tumor excision (including the partial thymus), total thymectomy, and extended thymectomy, which were achieved via transsternal thoracic surgery, video-assisted thoracic surgery (VATS), or robotic surgery. For each approach, the basic principles of total thymectomy included en bloc resection of the gland (including the cervical poles and adjacent mediastinal fat), protection of the phrenic nerves, and prevention of intrapleural dissemination whenever possible. For patients with myasthenia gravis (MG), extended thymectomy under a full median sternotomy was most commonly performed. Systematic mediastinal lymph node dissection was not routinely performed at our institution, although lymph node dissection was performed in cases of metastasis on preoperative evaluations. Of the 479 patients enrolled, 187 (39.0%) patients underwent lymph node sampling or dissection during surgery.

Preoperative and postoperative treatments and surveillance

Preoperative chemotherapy (with or without radiation therapy) was administered to patients with advanced disease, such as non-resectable stage III or disseminated stage IV tumors. In patients whose tumors became resectable after preoperative treatment, curative-intent surgery was performed. Postoperative radiation therapy was recommended for patients with stage II or III disease and was not considered appropriate for patients who underwent complete resection for stage I disease. Of the 479 patients, 46 patients (9.6%) received preoperative chemotherapy or radiation therapy and 219 patients (45.7%) received postoperative radiation therapy with or without chemotherapy.

Recently, our institution's radiation oncologists are recommending postoperative radiation therapy for patients with WHO-classified type B2, or B3 or type C tumors, even in the setting of R0-resection. The actual rates of patients who received postoperative radiation therapy with/without chemotherapy were 12.1% in type A (4/33), 28.6% in Type AB (30/105), 30.6% in type B1 (37/121), 50.0% in type B2 (41/82), 72.5% in type B3 (45/62), and 65.8% in type C (50/76).

Postoperative surveillance included routine annual computed tomography (CT) scans (performed with contrast) of the thorax for five years after surgical resection,

followed by annual chest radiographs. In cases of resected stage III and IVa disease, WHO-classified type B3 or C, incomplete resection, or other high risk tumors, bi-annual CT scans were performed for three years after surgical resection. In cases of suspected recurrence on CT scans, patients were suggested to undergo positron emission tomography-computed tomography (PET-CT) to confirm the extent of recurrent disease.

Determination of the efficacy of thymic epithelial tumors (TETs) treatment

The efficacy of treatment of TETs was determined by measuring the rates of postoperative survival and tumor recurrence. Overall survival is easy to measure and is hence the most commonly used end point; however, it is not an ideal metric because many patients with thymoma die of unrelated causes and patients can survive for many years with recurrent disease (18). The ITMIG proposed that the rate of recurrence of tumors is the most appropriate measure of the efficacy of treatment of thymic malignancies (19). Here, the overall survival (OS) rate was used in all patients and the freedom-from-recurrence (FFR) rate was used as a measure of successful complete resection, and the definition of recurrence after R0-resection was based on the ITMIG proposed criteria (19).

Statistical analyses

Categorical variables were compared using Chi-squared or Fisher's exact tests. Continuous variables are expressed as the median ± range. Kaplan-Meier curves were used to delineate the overall survival rate, the FFR rate, and the progression-free-rate. Log-rank tests were used to compare the between-group differences in these rates. For multivariable analyses, Cox-proportional hazards models were used to determine the risk factors for recurrence or death. Variables with $P \leq 0.10$ in univariate analyses were candidates for the multivariable Cox models. Multivariable analyses involved a backward elimination technique. All statistical analyses were performed using SPSS version 18.0 software (SPSS Inc., Chicago, Ill, USA). P value less than 0.05 was considered statistically significant.

Results

Patient and tumor characteristics

The baseline characteristics of the 479 patients are summarized in *Table 1*. The study group comprised 251 males and 228 females, with a median age of 52 years (range, 15–84 years). The most frequent histologic subtypes were B1 (25.3%), followed by type AB (21.9%), and B2 (17.1%) thymomas. A total of 93 patients (19.4%) were diagnosed with MG; the prevalence rates of MG were 0% in type A (0/33), 17.1% in type AB (18/105), 20.7% in type B1 (25/121), 32.9% in type B2 (27/82), 37.1% in type B3 (23/62), and 0% in type C (0/76).

Median maximal tumor size was 6.0 cm (range, 0–20.0 cm). 406 (85.7%) of the surgical procedures were considered R0-resections. The rates of R0-resection were 95.8% in stage I, 85.3% in stage II, 60.2% in stage III, and 40.0% in stage IV. Of the 187 patients who underwent lymph node dissection or sampling (more than 1 retrieved lymph node), lymph node metastasis was confirmed in 16 patients (8.6%).

Analysis of prognostic variables

Overall survival analysis in all patients

The median follow-up duration of the 479 patients was 55 months (range, 2–227 months). Sixty seven patients died during the study period. Overall survival in this series was 90.1% at 5 years and 79.1% at 10 years. When classified according to the Masaoka-Koga system, the 5-year OS rates were 93.7%, 89.2%, 82.7%, and 82.5% for stage I, II, III, and IV patients, respectively ($P<0.001$). In univariate analyses, age ($P<0.001$), completeness of resection ($P=0.019$), Masaoka-Koga stage ($P<0.001$), and maximal diameter of tumor ($P=0.009$) were significant predictors. In multivariate regression analyses revealed that age ($P<0.001$), Masaoka-Koga stage ($P<0.001$) correlated significantly with overall survival (*Table 2*).

Freedom-from recurrence analysis in patients who underwent R0-resection

Four hundred six patients underwent R0-resection; 32 patients (7.9%) of these patients recurred at a median of 24 months (range, 3–108 months). The sites of recurrence were the pleura in 14 patients, the lung in 7 patients, the anterior mediastinum in 3 patients, the bone in 2 patients, and multiple sites in 6 patients. Recurrences were classified as local recurrence in 3 patients, regional recurrence in 14 patients, distant recurrence in 11 patients, and mixed types (local with regional in 1, local with distant in 1, and regional with distant in 2) in 4 patients.

Freedom-from recurrence in these series was 88.0% at 5 years and 82.3% at 10 years. When classified according

Table 1 Baseline characteristics of the 479 patients who underwent surgical resection for thymic epithelial tumors

Variables	Number of patients (n=479)
Age in years (median, range)	52 [15–84]
Sex (male:female)	251:228 (52.4%:47.6%)
Association with MG, n (%)	93 (19.4)
Preoperative treatment, n (%)	
None	433 (90.4)
CTx	44 (9.2)
RTx	2 (0.4)
Surgical extent, n (%)	
Thymectomy/excision	376 (78.5)
Extended thymectomy	103 (21.5)
Surgical approaches, n (%)	
Transsternal	340 (71.0)
VATS or robotic	139 (29.0)
LN sampling or dissection, n (%)	
None	292 (61.0)
Yes	187 (39.0)
Number of retrieved LN (median, range)	4 [1–30]
LN metastasis, n (%)	
None	171 (91.4)
Yes	16 (8.6)
Type of resection, n (%)	
R0-resection	406 (84.8)
R1-resection	64 (13.4)
R2-resection	9 (1.9)
Maximal tumor size in cm (median, range)	6.0 (0–20.0)
Masaoka-Koga stage, n (%)	
Stage I	262 (54.7)
Stage IIa	76 (15.9)
Stage IIb	33 (6.9)
Stage III	93 (19.4)
Stage IVa	7 (1.5)
Stage IVb	8 (1.7)
WHO classification, n (%)	
A	33 (6.9)
AB	105 (21.9)
B1	121 (25.3)
B2	82 (17.1)
B3	62 (12.9)
C	76 (15.9)
Postoperative treatment, n (%)	
None	260 (54.3)
CTx	204 (42.6)
RTx	12 (2.5)
CRTx	3 (0.6)

MG, myasthenia gravis; CTx, chemotherapy; RTx, radiation therapy; CRTx, chemoradiation therapy; VATS, video-assisted thoracoscopic surgery; LN, lymph node; WHO, World Health Organization.

to the Masaoka-Koga system, the 5-year-FFR rates were 95.1% for stage I, 86.0% for stage II, and 69.4% for stage III. Two-year-FFR of stage IV was 44.4% (*Figure 1A*). When classified according to the WHO system, the 5-year-FFR rates were 100%, 98.7%, 95.8%, 87.6%, 72.6%, and 65.2% for types A, AB, B1, B2, B3, and C patients, respectively (*Figure 1B*). In univariate analyses, preoperative treatments (P<0.001), Masaoka-Koga stage (P<0.001), WHO classification (P<0.001), and postoperative treatments (P=0.002) were significant predictors of FFR. In multivariate analyses, preoperative treatments (P=0.016), Masaoka-Koga stage (P=0.008), WHO classification (P=0.001) were significant prognostic variables to predict recurrence after R0-resection (*Table 3*).

Prognostic stratification based on a potential risk model incorporating both Masaoka-Koga stage and WHO classification systems

A cross-comparison of the WHO classifications and Masaoka-Koga stages of the 406 patients who underwent complete resection for TETs is shown in *Figure 2A*. A multivariate analysis of prognostic factors for recurrence subdivided the 406 patients into 12 subpopulations based on the basis of combinations of Masaoka-Koga stage and WHO histological classifications (the subtypes were grouped into three categories; type A or AB or B1, type B2 or B3, and type C).

According to results of the 5-year-FFR rate of the each subpopulation (*Figure 2A*), the subpopulation comprising type A/AB/B1 in stage I or stage II was labeled as 'Group 1'. And the subpopulations comprising type B2/B3/C in stage I, or type B2/B3 in stage II, or type A/AB/B1 in stage III were labeled as 'Group 2'. And the subpopulations comprising type C in stage II/III, or type B2/B3 in stage III were labeled

Table 2 Predictors of postoperative overall survival on 479 patients who underwent surgical resection for thymic epithelial tumors

Variables	Overall survival					
	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.043	1.023–1.064	<0.001	1.047	1.026–1.069	<0.001
Sex						
Female	1			–	–	–
Male	1.530	0.936–2.502	0.090			
Presence of MG						
No	1					
Yes	0.886	0.503–1.559	0.674			
Preoperative treatment						
None	1					
CTx or RTx	1.253	0.537–2.923	0.602			
Surgical approach			0.063	–	–	–
Transsternal	1					
VATS or robotic	0.448	0.192–1.043				
Surgical extent			0.084	–	–	–
Excision/thymecomy	1					
Extended thymectomy	0.581	0.314–1.076				
Resection status			0.019	–	–	–
R0-resection	1					
R1-resection	2.154	1.237–3.749	0.007			
R2-resection	2.108	0.511–8.705	0.303			
Masaoka-Koga stage			<0.001			<0.001
Stage I	1			1		
Stage II	1.389	0.734–2.628	0.313	1.454	0.768–2.751	0.250
Stage III	2.216	1.235–3.974	0.008	1.998	1.112–3.591	0.021
Stage IV	6.847	2.789–16.812	0.000	9.761	3.889–24.501	<0.001
Maximal tumor diameter	1.107	1.026–1.195	0.009	–	–	–
WHO classification			0.326			
Type A or AB or B1	1					
Type B2 or B3	1.073	0.630–1.828	0.794			
Type C	1.681	0.845–3.346	0.139			
Postoperative treatment			0.204			
None	1					
Radiation	1.011	0.614–1.666	0.964			
Chemotherapy	3.615	1.096–11.924	0.035			

OR, odds ratio; CI, confidence interval; MG, myasthenia gravis; CTx, chemotherapy; RTx, radiation therapy; CRTx, chemoradiation therapy; VATS, video-assisted thoracoscopic surgery; WHO, World Health Organization.

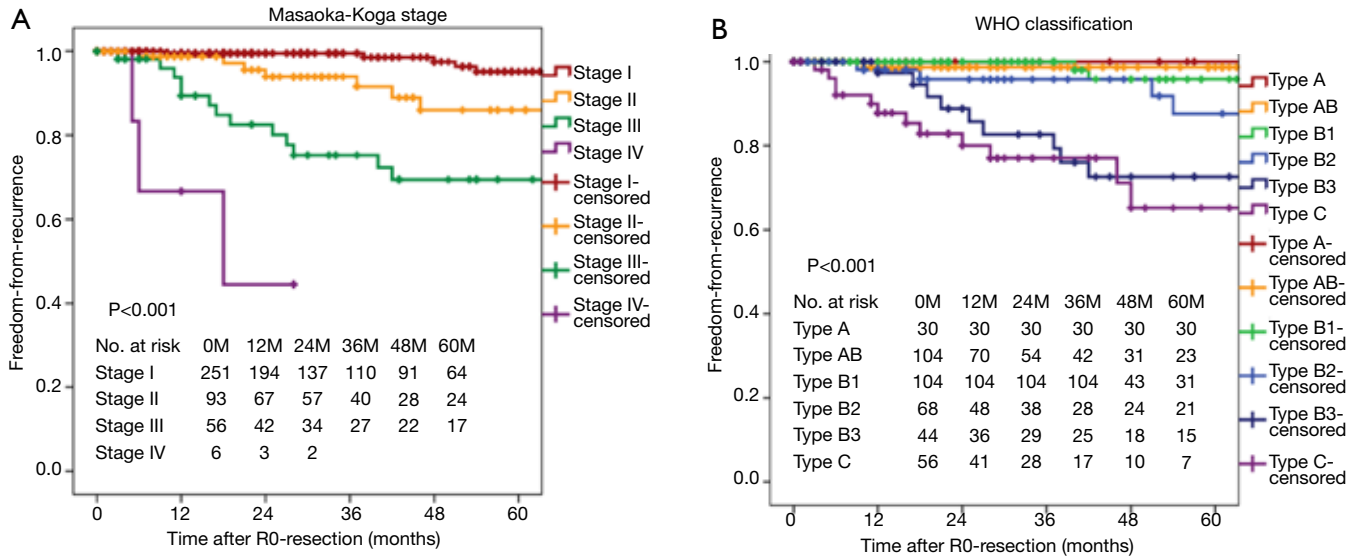

Figure 1 Freedom-from-recurrence curves of patients stratified by the Masaoka-Koga stage (A) and by the WHO histological classification (B).

as 'Group 3'. And the subpopulations comprising type B2/B3/C in stage IV were labeled as 'Group 4' (*Figure 2B*).

The 5-year FFR rates were 99.4% for group 1, 84.7% for group 2, 63.7% for group 3, and less than 44.4% for group 4 (P<0.001, *Figure 2C*). In a multivariate regression adjusting for preoperative treatments and maximal tumor size, risk groups were significant factors predicting recurrence after R0-resection (data not shown).

The effect of postoperative radiation therapy on the recurrence after R0-resection

The rates of patients who received postoperative radiation therapy were 19.3% in group 1 (43/223), 53.3% in group 2 (64/120), 82.5% in group 3 (47/57), and 16.7% in group 4 (1/6). All types of recurrence occurred in 3 out of 223 patients in group 1, 9 out of 120 patients in group 2, and 17 out of 57 patients in group 3, and 3 out of 6 patients in group 4. In group 1, 2, and 3, the rates of all type of recurrence were not different between in patients treated with postoperative radiation therapy and in those treated without postoperative radiation therapy).

Locoregional recurrences occurred in 2 patients in group 1, 7 patients in group 2, and 7 patients in group 3. In group 1 or group 2, the rates of locoregional recurrence of patients treated with postoperative radiation therapy was not significantly different from patients treated without postoperative radiation therapy (P=0.414 for group 1, P=0.151 for group 2, *Figure 3A,B*). On the contrary, in group 3, the rate of locoregional recurrence of patients treated with postoperative radiation therapy was lower than patients treated without postoperative radiation therapy (P=0.032, *Figure 3C*).

Discussion

The tumor-nodes-metastasis (TNM) classification system has been used to stage malignant tumors of multiple organs; however, there is currently no authorized TNM system for TETs, although IASLC/ITMIG is currently proposed evidence-based TNM-based stage classification system of TETs for 8th edition of the stage classification manuals (20). We fully recognize that it is necessary to apply and to validate a newly proposed system, however, it is difficult to apply this system to our clinicopathologic data, because of the lack of detailed data for lymph node status. Therefore, we decided to stratify the prognosis of TETs based on the currently using systems including Masaoka-Koga stage and WHO classifications of TETs.

Masaoka-Koga stage and WHO histological classification are important variables for disease recurrence after R0-resection. In this study, Kaplan-Meier curves demonstrated a clear distinction between the recurrence rates after complete resection in Masaoka-Koga stage I and stage II patients, which supports Masaoka's original opinion that these patients should be individually grouped (21). However, in accordance with previous studies (10,11,22-24), the multivariate analysis did not identify any significant prognostic differences between stage I and II patients.

Table 3 Predictors of postoperative recurrence on 406 patients who underwent complete resection (R0 resection) for thymic epithelial tumors

Variables	Freedom-from recurrence					
	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age	0.984	0.957–1.011	0.243			
Sex						
Female	1					
Male	1.473	0.727–2.984	0.282			
Presence of MG						
No	1					
Yes	0.951	0.410–2.205	0.906			
Preoperative treatment						
None	1			1		
CTx or RTx	6.297	2.881–13.761	<0.001	3.803	1.232–7.715	0.016
Surgical approach						
Transsternal	1					
VATS/Robotic	0.461	0.161–1.319	0.149			
Surgical extent						
Excision/thymectomy	1					
Extended thymectomy	1.150	0.552–2.396	0.708			
Masaoka-Koga stage			<0.001			0.008
Stage I	1			1		
Stage II	3.426	1.186–9.897	0.023	2.669	0.906–7.868	0.075
Stage III	10.227	3.966–26.368	<0.001	4.775	1.793–12.713	0.002
Stage IV	46.013	11.058–191.474	<0.001	9.269	1.888–45.510	0.006
WHO classification			<0.001			0.001
Type A or AB or B1	1			1		
Type B2 or B3	5.445	1.960–15.124	0.001	3.700	1.303–10.505	0.014
Type C	14.093	4.999–39.734	<0.001	8.089	2.740–23.884	<0.001
Maximal tumor diameter	1.109	0.990–1.241	0.074	1.107	0.988–1.241	0.080
Postoperative treatment			0.002			
None	1			–	–	–
Radiation	2.726	1.240–5.991	0.013	–	–	–
Chemotherapy	12.570	3.381–46.728	<0.001	–	–	–

OR, odds ratio; CI, confidence interval; MG, myasthenia gravis; CTx, chemotherapy; RTx, radiation therapy; CRTx, chemoradiation therapy; VATS, video-assisted thoracoscopic surgery; WHO, World Health Organization.

Controversies regarding proposals to combine stages I and II will need to be resolved by additional large cohort studies with long-term follow-up periods.

Consistent with recent reports (10,11,22,24), the WHO histological classification was also a prognostic factor for TET recurrence in this study. Although the official WHO classification subdivides TETs into three major categories (A, B, and C), the Kaplan-Meier curves presented here enabled division of these tumors into different three categories on the basis of their recurrence rate: type A or

A

5Y-FFR		WHO classification		
		Type A/AB/B1	Type B2/B3	Type C
MK stage	Stage I	99.3%	86.8%	83.3%
	Stage II	100.0%	84.6%	50.6%
	Stage III	81.8%	65.2%	64.2%
	Stage IV		2Y-35.4%	2Y-25.0%

B

Risk group stratification		WHO classification		
		Type A/AB/B1	Type B2/B3	Type C
MK stage	Stage I	Group 1	Group 2	Group 2
	Stage II	Group 1	Group 2	Group 3
	Stage III	Group 2	Group 3	Group 3
	Stage IV		Group 4	Group 4

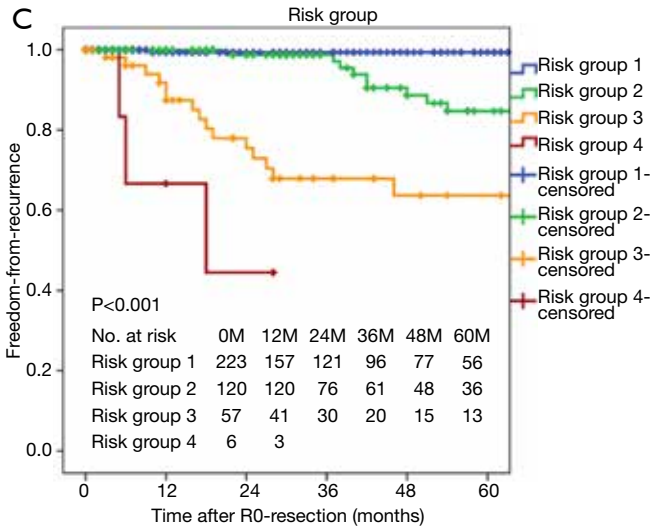

Figure 2 The risk group model classifying the risk of recurrence of thymic epithelial tumors after complete resection. The model incorporate both the Masaoka-Koga stage and WHO histological classification systems, which were grouped into four categories as indicated. The 406 patients who underwent complete resection for TETs were initially classified into nine subgroups. (A) The freedom-from-recurrence rates of patients in the nine initial subgroups at the 5-year time point; (B) the proposed grouping system to assess the risk of recurrence after complete resection; (C) freedom-from-recurrence curves stratified by recurrence risk groups. 5Y-FFR, 5-year-freedom-from-recurrence rate.

AB or B1, type B2 or B3, and thymic carcinomas. Regarding type B1 thymoma, among the 104 patients proved type B1 thymoma after complete resection in this study, only 4 patients (3.8%) experiences recurrence after R0-resection; One of these 4 patient underwent extended thymectomy at the age of 61 for type B1 thymoma with regional lymph node metastasis (four of nine lymph nodes) and received adjuvant radiation therapy. Recurrent pleural seeding (regional recurrence) was identified in the left pleural cavity 40 months after the initial operation and chemotherapy was administered. The patient died 93 months after surgical resection (at the age of 69) due to pneumonia. Consequently, it seems that B1 thymomas follow a favorable clinical course; even at stage IV they may not be fatal due to the very slow progression of the disease. These results are consistent with those of previous study, which reported that WHO type A and AB thymomas are considered benign and type B1 thymomas have a very low malignant potential, although local recurrence or late metastasis may occur rarely (25). On the contrary, type B2 or type B3 thymomas had a greater degree of malignancy, which is consistent with a previous report that showed a clear association between malignancy and type B2 or B3 thymomas and thymic carcinomas (26).

This study demonstrates that a potential risk model incorporating both the Masaoka-Koga stage and WHO classification systems can be used to stratify the recurrence risk after R0-resection for TETs. This concept is in close agreement with those of other clinicians or researchers who tried to establish a simplified tool for the stratification of patients with TETs and to propose rationale for adjuvant therapies (27-30). This study tried to assess the effect of postoperative radiation therapy in group 1, 2, and 3. Because it is obvious that systemic chemotherapy is needed in group 4. Our results demonstrated that the postoperative radiation therapy could not reduce overall recurrence in risk group 1, 2, and 3. However, the postoperative radiation therapy could reduce the locoregional recurrence in group 3, although it is not effective in group 1 and 2. The goal of postoperative radiation therapy is to reduce not distant recurrences but the locoregional recurrence, because the radiation field was localized in anterior mediastinum. These results suggest that postoperative radiation therapy might be necessary to reduce the rate of locoregional recurrence in group 3, but it might not be needed in group 1 and 2.

This study has important limitations stemming from its limited number of events (such as death or recurrence) and a retrospective analysis of observational data from a

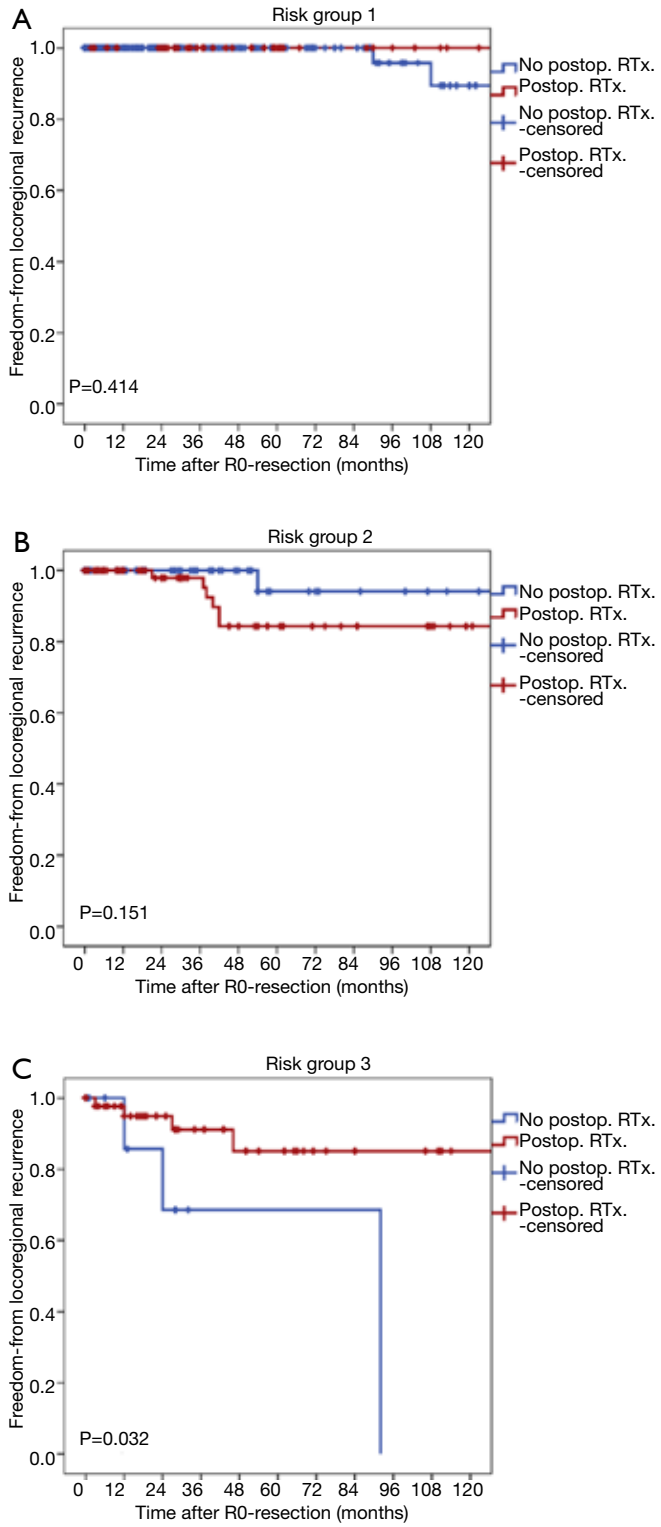

Figure 3 Freedom-from-locoregional recurrence curves stratified by the postoperative radiation therapy in each risk groups. (A) Risk group 1; (B) risk group 2; (C) risk group 3. RTx, postoperative radiation therapy.

single institution. The major shortcoming of the study is the approaches to reclassify the patients required the use of somewhat biased and potentially inappropriate statistical methods and the lack of a confirmatory subgroup of patients. Our results should be considered preliminary until confirmed in an independent validation cohort. Nevertheless, we have reported the retrospective outcomes of our cohort, because the risk grouping method based on a combination of the Masaoka-Koga and WHO classification systems takes into account the tumor extent and histology after complete resection of TETs and may aid the formulation of hypotheses required to develop future studies.

In conclusion, the Masaoka-Koga stage and WHO histological classifications were independent predictors of recurrence after R0-resection of TETs. A potential risk stratification model incorporating both classification systems may provide multi-faceted information about recurrence and adjuvant treatment after R0-resection of TETs.

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Footnote

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

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CT staging and preoperative assessment of resectability for thymic epithelial tumors

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Background: The aim of this study was to determine the computed tomography (CT) features potentially helpful for accurate staging and predicting resectability of thymic epithelial tumors (TET).

Methods: One hundred and thirty-eight consecutive TET patients undergoing surgical resection from April 2010 to November 2011 were prospectively entered into a database. All patients were staged according to the Masaoka-Koga staging system. The relationship between CT features with tumor staging and complete resection was reviewed after surgery.

Results: Surgico-pathological staging was stage I in 63, stage II in 32, stage III in 32, and stage IV in 11 patients. Preoperative CT staging was highly consistent with postoperative surgico-pathological staging (Kappa =0.525). Tumor shape, contour, enhancement, with or without invasion of the adjacent structures (mediastinal fat, mediastinal pleura, lung, pericardium, mediastinal vessels, phrenic nerve), and presence of pleural, pericardial effusionor intrapulmonary metastasis were correlated with Masaoka-Koga staging ($P<0.05$). However, tumor size, internal density or presence of calcification was not associated with staging ($P>0.05$). Tumor size, presence of calcification and mediastinal lymph node enlargement were not correlated with complete tumor resection ($P>0.05$). Tumor shape, contour, internal density, enhancement pattern, and invasion of adjacent structures were related to complete resection of the primary tumor in univariate analysis ($P<0.05$). However, upon multivariate logistic regression, only absence of artery systems invasion was predictive of complete resection ($P<0.05$).

Conclusions: Clinical staging of TET could be accurately evaluated with CT features including tumor shape, contour, enhancement pattern, with or without invasion of adjacent structures, and presence of pleural, pericardial effusion or intrapulmonary metastasis. Absence of arterial system invasion on CT was the only predictive feature for predicting complete resection of TET.

Keywords: Thymic epithelial tumor (TET); computer tomography (CT); tumor stage; complete resection

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Introduction

Thymic epithelial tumor (TET) is the most common primary neoplasm of the anterior mediastinum (1). Tumor stage and completeness of resection have been shown to be the most important prognostic factors for TET (2-4). Treatment of TET may involve surgery, radiation, chemotherapy, or combined modalities, determined by the stage and resectability of the tumor. Until now, computed tomography (CT) is the most commonly used imaging tool for preoperative assessment of TET (5). However, there have been only a few published reports describing the CT characteristics of TET with reference to Masaoka-Koga staging (6-9). There has been only one previous retrospective study examining the relationship between CT appearance and the resectability of TET, in which tumor characteristics on CT scan and surgical findings were retrospectively evaluated. In addition, patients who had neoadjuvant therapy were also included in the study, which might have influenced its result (10). The aim of this study was to determine the CT features potentially helpful for accurate staging and predicting resectability of TET through prospective clinical study.

Materials and methods

This study was approved by the Institutional Review Board of the Shanghai Chest Hospital. From April 2010 to November 2011, 145 consecutive TET patients as surgical candidates were prospectively included. Seven of these, who received preoperative chemotherapy or/and radiotherapy, were excluded. CT images were obtained in all patients by PHILIPS Brilliance 64-sclice scanners with a volumetric spiral acquisition in baseline conditions and intravenous administration of iodinated contrast material given at 3 mL/s. Scan field was from the lung apex to the middle portion of both kidneys (slice thickness 5-mm with 1-mm multiplanar reformation). Multiplanar reformation images were assessed for lesion shape, size, margins with both a mediastinal window (width 400 HU, centre 40 HU) and a lung window (width 1,450 HU, centre –520 HU). Clinical staging and resectability were evaluated and recorded by a radiologist (Yan Shen) and a thoracic surgeon (Zhitao Gu) prospectively before surgery. Masaoka-Koga staging system was used to define the clinical and pathological stage (3), whereas the 2004 World Health Organization (WHO) classification was used for histological classification. Resection margins were marked right after the tumor was removed, according to the proposal by the International Thymic Malignancy Interest Group (ITMIG) (11). The completeness of resection was verified during operation and confirmed by histological examination after surgery. Resection status was defined as complete (R0) if resection margins were microscopically negative and incomplete in case of microscopically (R1) or grossly (R2) positive margin.

The staging CT scans were reviewed by two chest radiologists (Yan Shen and Jianding Ye) who were unaware of the clinical information. Differences in their findings were resolved by consensus. The CT characteristics of each tumor were prospectively recorded. These included tumor size in three perpendicular diameters, shape, contour, internal density, enhancement pattern (homogeneous/heterogeneous enhanced density), calcification, infiltration of mediastinal fat, whether tumor abutted of adjacent anatomical structures (mediastinal pleura, lung, pericardium, phrenic nerves, great vessels), pleural and/or pericardial effusion, lymph node enlargement (short-axis diameter >10 mm), and pleural or pulmonary nodules. The contour was considered smooth if there were no spiculations, lobulations, or poorly defined borders. A tumor was considered lobulated if one or more lobulations were identified; lobulations were defined as convex tumor contours with adjacent notches between tumor lobules. Tumor internal density or enhanced pattern was described as homogeneous if the lesion was of uniform attenuation and as heterogeneous if there were areas of mixed attenuation within it before or after enhancement.

The CT standards for TET developed by the ITMIG were used to define part of the CT characteristics (12). The CT findings of tumor size, shape (*Figure 1*), contour (*Figure 1*), internal density, enhancement pattern (*Figure 2*), calcification, infiltration of surrounding structures (*Figures 3*,*4*), presence of pleural effusion, mediastinal lymph node enlargement, pleural or lung nodule were observed in our study.

Statistical analysis was performed with the SPSS 16.0 (SPSS for Windows). Patients were subdivided into four stage groups according to the Masaoka-Koga classification after surgical resection. Statistical differences in the prevalence of each CT finding for the different groups were analyzed using the Pearson chi-squared test for the discrete variables, or for small samples with the Fisher test. Differences between the numerical variables in the groups were analyzed using the One-Way ANOVA. The diagnostic value of CT compared to Masaoka-koga stages

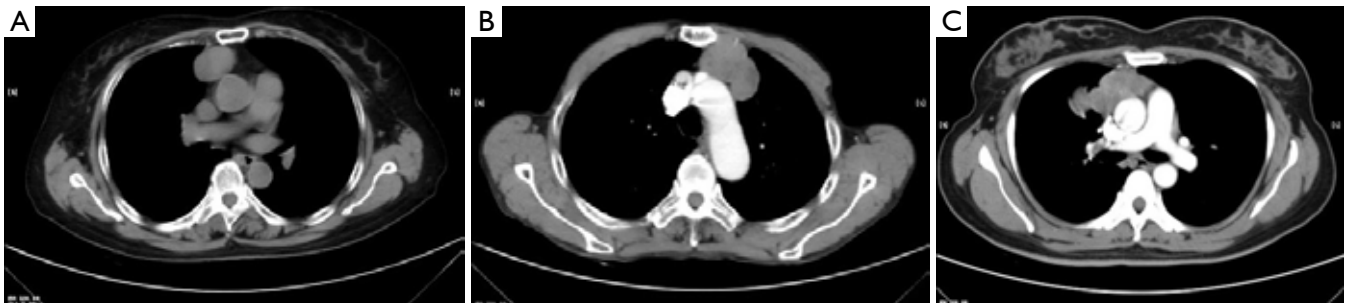

Figure 1 A tumor contour is considered smooth in the absence of spiculation, partial smooth or unsmooth; as well as, tumor shape is considered round, lobulated and irregular. (A) Round shape with smooth counter; (B) lobulated shape with partial smooth counter; (C) irregular shape with unsmooth counter.

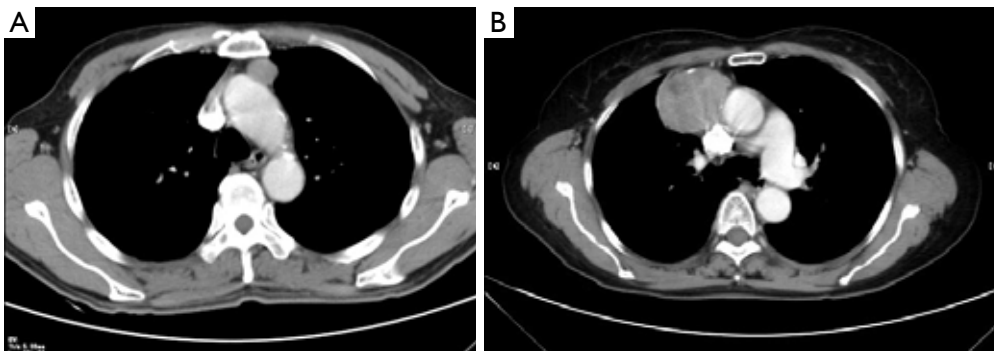

Figure 2 A tumor attenuation is considered homogeneous or heterogeneous. (A) Enhanced CT of a homogeneous tumor; (B) enhanced CT of a heterogeneous tumor.

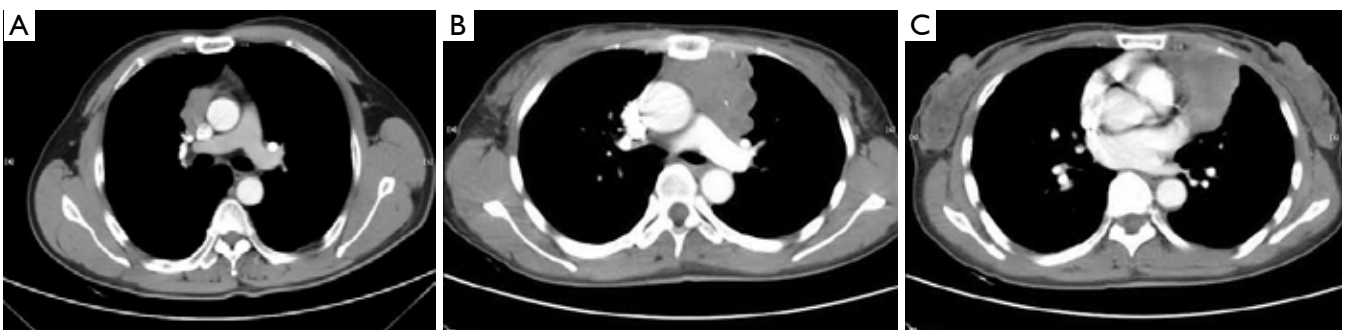

Figure 3 Tumor invasion of surrounding structures, as mediastinal pleura, lung or pericardium is showed on CT. (A) If the tumor exhibited a lobulated interface of the tumor with the adjacent mediastinum pleura, it was characterized as pleura invasion; (B) when the tumor abutted ≥50% of the lung and there was an irregular interface of the tumor with the adjacent lung, involvement of the lung was considered present; (C) pericardium invasion was suggested if the tumor abutted ≥50% of the pericardium, and there was thickening of the pericardium.

was expressed in terms of sensitivity, specificity, positive predictive value and negative predictive value. Data were analyzed by Kappa statistics to measure the agreement between CT and pathologic examination. Kappa values of 0.00–0.40 represent slight agreement, 0.40–0.75 represent fair agreement, and 0.75–1.00 represent almost perfect agreement. A multivariate logistic regression analysis was used to estimate the relationship between CT characteristics and primary tumor resectability. In all cases, a P value <0.05 was interpreted as statistically significant.

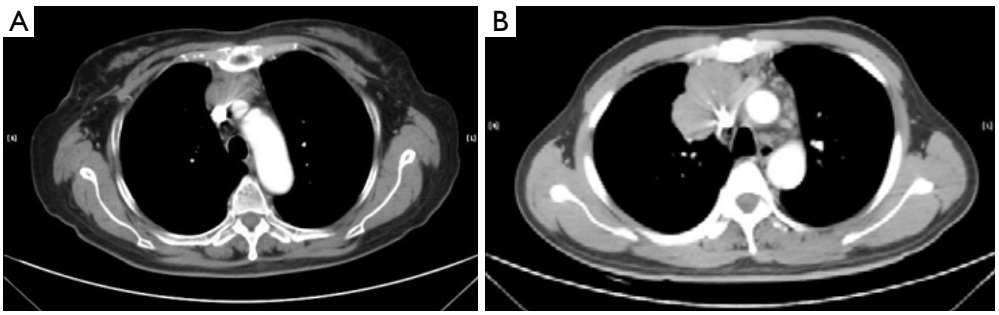

Figure 4 Tumor invasion of vessels is showed on CT. (A) When the tumor abutted ≥50% of the vascular circumference with loss of the fat plane and the vascular wall is rough, involvement of the vessel was considered present; (B) when the vascular lumen was directly penetrated by the tumor, involvement of the vessel was also considered present.

Results

A total of 138 patients (68 females, 70 males) with a mean age of 54.1 years (range, 17–77 years) were prospectively entered into the database. Histological analysis revealed 105 thymomas (nine of type A, 37 of type AB, 15 of type B1, 23 of type B2, 16 of type B3, three of micronodular thymoma, two of metaplastic thymoma), six thymic carcinoids, and 27 thymic carcinomas. Surgico-pathological staging was stage I in 63, stage II in 32, stage III in 32, and stage IV in 11 patients. The WHO classification of the tumors was significantly related to Masaoka-Koga staging (P<0.05) (*Table 1*).

Correlation between the CT characteristics and Masaoka-Koga staging are summarized in *Table 2*. Tumor size, shape, contour, enhancement pattern, with or without invasion of the adjacent structures (mediastinal fat, mediastinal pleura, lung, pericardium, mediastinal vessels, phrenic nerve), and presence of pleural, pericardial effusion or intrapulmonary metastasis were correlated with Masaoka-Koga staging (P<0.05). On the other hand, tumor internal density or presence of calcification was not related to staging (P>0.05). In addition, tumor sizes had statistical differences among Masaoka-Koga stages (P<0.05), but did not show a positive correlation, with the mean diameter of stage I lesions even larger than those of stage II and stage IV tumors.

Accuracy of the CT staging (sensitivity, specificity, positive predictive value and negative predictive value) and its Kappa value, as compared with postoperative histological findings, is shown in *Table 3*. Preoperative CT staging was fairly consistent with postoperative surgico-pathological staging (Kappa =0.525, P<0.05) (*Tables 4,5*).

Complete resection rate of primary tumor was 92% (127/138) in this series. Correlation analysis showed that tumor size, presence of calcification and mediastinal lymph node enlargement did not correlate with complete resection of primary tumor (P>0.05). Tumor shape, contour, homogeneity, enhancement pattern, invasion of adjacent structures were related to complete resection in univariate analysis (P<0.05) (*Table 6*). However, when invasion only involved mediastinal pleural (n=20), lung (n=13) or pericardium (n=2) on preoperative CT scan, complete resection was achieved in all patients. Resection was palliative in all three patients suspected of sternum invasion. But all three patients had concomitant artery invasion. Phrenic nerve invasion was identified in 13 patients. Of these, seven patients underwent palliative surgery. Five patients had concomitant artery invasion, one patient with myasthenia gravis, and one patient had pericardium, upper lobe of right lung invasion, and pleura implantation. Great vessels invasion was suspected in 21 patients. In the 14 patients suspected of invasion into the venous system only (superior vena cava and/or left or right inominate veins), 12 had complete resection. One patient had VATS exploration and biopsy only because of detection of pleural implantation. Only one patient underwent debulking of a tumor invading extensively into the superior vena cava, both left and right innominate veins, as well as the right phrenic nerve. On the other hand, complete resection was not possible in all seven tumors suspected of both venous and arterial systems invasion. Upon multivariate logistic regression, only absence of arterial system invasion was predictive of complete resection [odds radio (OR) =3.77; 95% confidence interval (CI): 4.34–433.36; P=0.001].

Discussion

CT is currently considered the preferred imaging modality

Table 1 Correlationship between WHO histologic classification and Masaoka-Koga staging (P<0.05)

WHO type	Masaoka-Koga staging				Subtotal
	I (n=63)	II (n=32)	III (n=32)	IV (n=11)	
Thymoma	59	28	13	5	105
A	5	3	1	0	9
AB	27	10	0	0	37
B1	8	4	3	0	15
B2	10	7	4	2	23
B3	5	3	5	3	16
Micronodular thymoma	3	0	0	0	3
Metaplastic thymoma	1	1	0	0	2
Thymic carcinoid	2	1	2	1	6
Thymic carcinoma	2	3	17	5	27

Table 2 Patient characteristics and CT findings in TETs

Patient characteristics and CT findings	Masaoka-Koga clinical stage				P value
	I (n=63)	II (n=32)	III (n=32)	IV (n=11)	
Gender (male/female)	31/32	14/18	18/14	7/4	NS*
Myasthenia gravis (yes/no)	10/53	5/27	3/29	0/11	NS*
Age (mean value, years)	53.2	58.6	52.6	50.9	NS**
Size (mean value, cm)					
X-axis diameter	5.5	4.5	6.6	5.1	0.005**
Y-axis diameter	3.8	3	4.4	3	0.004**
Z-axis diameter	6.4	4.7	7.1	5.9	0.005**
Shape (round/lobulated/irregular)	29/29/5	10/16/16	4/7/21	2/3/6	0.000*
Contour (smooth/partial smooth/unsmooth)	31/31/1	6/24/2	0/21/11	1/6/4	0.000*
Internal density (homogeneous/heterogeneous)	33/30	16/16	9/23	3/8	NS*
Enhancement pattern (homogeneous/heterogeneous)	15/48	8/24	1/31	3/8	0.041*
Calcification (yes/no)	12/51	8/24	8/24	3/8	NS*
Infiltration of surrounding fat (yes/no)	29/34	29/3	29/3	11/0	0.000*
Invasion of mediastinal pleura (yes/no)	24/39	15/17	29/3	9/2	0.000*
Invasion of lung (yes/no)	7/56	1/31	22/10	7/4	0.000*
Invasion of pericardium (yes/no)	4/59	2/30	22/10	5/6	0.000*
Invasion of great vessels (yes/no)	4/59	0/32	15/17	6/5	0.000*
Invasion of phrenic nerve or elevated hemidiaphragm (yes/no)	1/62	1/31	11/21	3/8	0.000*
Presence pleural effusion (yes/no)	2/61	1/31	2/30	3/8	0.000*
Mediastinal lymph node enlargement (yes/no)	0/63	0/32	1/31	1/10	NS*
Pleura and/or pulmonary nodule (yes/no)	0/63	0/32	0/32	5/6	0.000*

NS, not significant; *, P values were calculated using the chi-square test or the Fisher exact test for categorical variables; **, P values were calculated using the Mann-Whitney U test for continuous variables; CT, computed tomography; TET, thymic epithelial tumor.

Table 3 Accuracy of CT diagnosis

CT features	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa value
Infiltration of surrounding fat	92.5% (62/67)	49.3% (35/71)	63.3% (62/98)	87.5% (35/40)	70.3% (97/138)	0.413
Invasion of mediastinal pleura	94.1% (32/34)	56.7% (59/104)	41.6% (32/77)	96.7% (59/61)	65.9% (91/138)	0.357
Invasion of the lung	92.0% (23/25)	76.2% (99/113)	62.2% (23/37)	98.0% (99/101)	88.4% (122/138)	0.671
Invasion of pericardium	69.0% (20/29)	88.1% (96/109)	60.6% (20/33)	91.4% (96/105)	84.1% (116/138)	0.543
Invasion of the great vessels	85.7% (18/21)	97.3% (110/117)	72.0% (18/25)	97.3% (110/113)	92.8% (128/138)	0.74
Invasion of the phrenic nerve	76.9% (10/13)	95.2% (119/125)	62.5% (10/16)	97.5% (119/122)	93.5% (129/138)	0.654
Presence of pleural effusion	50.0% (3/6)	95.7% (127/132)	37.5% (3/8)	97.7% (127/130)	94.2% (130/138)	0.138
Pleura and/or pulmonary metastases	62.5% (5/8)	100% (130/130)	100% (5/5)	0 (0/130)	97.8% (135/138)	None
Mediastinal lymph node enlargement	20.0% (1/5)	99.2% (132/133)	50.0% (1/2)	97.1% (132/136)	96.4% (134/138)	0.271

Table 4 Consistency between CT staging and postoperative Masaoka-Koga staging

Preoperative evaluation	Masaoka-Koga postoperative staging				Subtotal
	I (n=63)	II (n=32)	III (n=32)	IV (n=11)	
I	27	1	0	0	28
II	23	28	3	2	56
III	13	3	29	2	47
IV	0	0	0	7	7

Table 5 Accuracy of CT diagnosis (Masaoka-Koga stage)

CT stage	Sensitivity	Specificity	PPV	NPV	Accuracy
Stage I	42.9% (27/63)	98.7% (74/75)	96.4% (27/28)	67.3% (74/110)	73.2% (101/138)
Stage II	87.5% (28/32)	73.6% (78/106)	50% (28/56)	95.1% (78/82)	76.8% (106/138)
Stage III	90.6% (29/32)	83% (88/106)	61.7% (29/47)	96.7% (88/91)	84.8% (117/138)
Stage IV	63.6% (7/11)	100% (127/127)	100% (7/7)	96.9% (127/131)	97.1% (134/138)

PPV, positive predictive value; NPV, negative predictive value.

for the initial assessment and follow-up for patients with TET. There have been only a few studies comparing CT appearance of TET with Masaoka or Masaoka-Koga staging (*Table* 7) (6-9). Tomiyama *et al.* and Priola *et al.* attempted to separate stage I disease from stage II-IV (7,8). Marom *et al.* assessed whether CT could distinguish stage I/II disease from stage III/IV (6). In Qu's study, relationships between preoperative CT staging and postoperative Masaoka staging was investigated (9). However, all the above studies were retrospective in nature. Besides, all of them focused on CT staging only and none has mentioned respectability of the tumor. In the present study, all patient data were recorded and their CT images studied prospectively. What is more, not only the accuracy of staging but also prediction of complete resection was studied based on preoperative CT scan using a large size sample.

As is shown in *Table* 7, tumor size was related to Masaoka-Koga staging in all previous studies. However, no ideal cutoff value has ever been established. Marom *et al.* reported primary tumor with radiologic tumor size ≥7 cm was more likely to have stage III or IV disease (6). Contrary to the previous findings, we failed to detect a positive correlation between tumor size and stage. In the current study, 16 (51.6%) of 31 tumors more than 7 cm were in stage I/II, while 28 (26.2%) of 107 tumors less than 7 cm were in stage III/IV. Furthermore, mean diameter of

Table 6 Patient characteristics and CT features at diagnosis of the complete resection of primary tumor

CT features	Complete resection (n=127)	Incomplete resection (n=11)	P value
Gender (male/female)	62/65	8/3	NS*
Myasthenia gravis (yes/no)	17/110	1/10	NS*
Age (mean value, years)	54	55	NS**
Size (mean value, cm)			
X-axis diameter	5.4	6.5	NS**
Y-axis diameter	3.7	3.8	NS**
Z-axis diameter	6.1	6.6	NS**
Shape (round/lobulated/irregular)	45/52/30	0/3/8	0.001*
Contour (smooth/partial smooth/unsmooth)	38/77/12	0/5/6	0.000*
Internal density (homogeneous/heterogeneous)	60/67	1/10	0.023*
Enhancement pattern (homogeneous/heterogeneous)	36/91	0/11	0.031*
Calcification (yes/no)	28/99	3/8	NS*
Infiltration of surrounding fat (yes/no)	87/40	11/0	0.033*
Invasion of mediastinal pleura (yes/no)	67/60	10/1	0.023*
Invasion of lung (yes/no)	29/98	8/3	0.001*
Invasion of pericardium (yes/no)	23/104	10/1	0.000*
Invasion of venous system (yes/no)	13/114	10/1	0.000*
Invasion of arterial system (yes/no)	3/124	9/2	0.000*
Invasion of phrenic nerve or elevated hemidiaphragm (yes/no)	9/118	7/4	0.000*
Invasion of sternum (yes/no)	0/127	3/8	0.000*
Mediastinal lymph node enlargement (yes/no)	1/126	1/10	NS*

NS, not significant; *, P values were calculated using the chi-square test or the Fisher exact test for categorical variables; **, P values were calculated using the One-Way ANOVA for continuous variables.

Table 7 Comparison of CT findings with previously literatures

CT findings	Reference (y, n)				
	Tomiyama (7) (N=50)	Priola (8) (N=58)	Marom (6) (N=99)	Qu (9) (N=129)	Present study (N=138)
Size	S	S	S	S	S
Shape and (or) counter	S	S	S	S	S
Capsule	S	S	NM	S	NM
Internal density	S	S	S	S	NS
Enhancement pattern	S	S	NM	NM	S
Calcification	S	S	S	NM	NS
Mediastinal fat obliteration	NS	NS	NS	NM	NM
Infiltration of surrounding fat	NM	NM	S	NM	S
Invasion of great vessels	NS	NS	S	NM	S
Invasion of other mediastinal structures	NS	NM	S	S	S
Pleura effusion	NM	NS	NS	NM	S
Mediastinal lymph node enlargement	NM	NS	NM	NS	NS
Pleura and/or pulmonary nodule	NM	NM	S	NM	S

S, P<0.05 for staging; NM, not measured; NS, not significant.

stage I tumors was larger than those in stage II and stage IV. Therefore, it seems that tumor size is of limited value in differentiating Masaoka-Koga stages.

The previous studies showed that heterogeneous density of the tumor in CT plain scan was suggestive of stage II/III/IV thymoma (7,8). In our study, although heterogeneous density was more frequently seen in stage III (23/32, 71.9%) and IV (8/11, 72.7%) than in stage I (30/63, 47.6%) and II (16/32, 50%), it was not significantly related to Masaoka-Koga staging. On the contrary, pattern of enhancement was significantly associated with Masaoka-Koga staging in our study, with heterogeneous enhancement after the administration of contrast medium suggesting a higher tumor stage. Therefore, enhancement pattern may be more helpful than internal density in CT plain scan for accurate staging, and contrast-enhanced chest CT should be recommended if not contraindicated.

Calcification is a common finding in TET, reported to be 10%–41% in previous studies (6-8). In Tomiyama's and Priola's studies, calcification was more frequently seen in patients with stage II/III/IV thymoma than in patients with stage I thymoma (7,8). In the current study, calcification was seen in 22.5% patients, but there was no significant difference between stage II/III/IV (19/75, 25.3%) and stage I tumors (12/63, 19%). Our result is in consistency with Harris's review on 32 papers about calcification in thymic tumors in different stages (13). They also reported that calcification type, location, size or other characteristics of calcifications were not relative factors for clinical and radiologic diagnosis of thymoma (13).

In Tomiyama's study, CT appeared to be a poor predictor of invasion into surrounding structures (7). Priola *et al.* also found it impossible to distinguish between simple adhesion and invasion of mediastinal structures based on CT features (8). However, Marom *et al.* considered suspicion of infiltration into mediastinal fat or other mediastinal structures on CT was associated with higher Masaoka stage (6). The result of the current study is in consistency with that of Marom's. In the meantime, specificity for CT judgment of mediastinal fat invasion and sensitivity for mediastinal lymph node metastasis or pleural dissemination appeared to be low, leading to lower sensitivity for diagnosis of stage I and IV tumors.

Complete resection has been widely recognized as one of the most important prognostic factors for thymic tumors (2,14). For locally advanced tumors that are potentially unresectable, effective induction therapy may help improve survival and reduce local recurrence by increasing the rate of complete resection (15,16). It seems reasonable to consider induction therapy whenever preoperative assessment indicates that complete resection may not be feasible. Therefore in addition to accurate staging, it is even more important to distinguish between tumors that might benefit from induction therapy and those could proceed directly to surgery. Hayes SA reported that the preoperative CT characteristics of a lobulated tumor contour, invasion of adjacent vessel or lung, thoracic lymphadenopathy, and pleural nodularity were correlated with incomplete surgical resection on univariate analysis (10). In the current study, the accuracies of CT diagnosis of invasion of the lung (88.4%), of the pericardium (84.1%), of the phrenic nerve (93.5%), of the pleural/pulmonary metastases (97.8%), of the mediastinal lymph node enlargement (96.4%) suggests that CT scan is highly valuable in predicting the feasibility of complete resection. And the results of CT staging had a good consistency with surgical-pathological findings (kappa value =0.74). Owing to the relatively indolent nature of thymic tumors and potential long term survival, surgical resection is still an acceptable practice even in stage IV tumors with pleural spreading or lymph node involvement. Therefore in current study, we studied only the respectability of primary tumors. And we found that when primary tumor invaded only mediastinal pleural, lung or pericardium on preoperative CT scan, complete resection could be achieved more readily than tumors invading phrenic nerve, sternum or great vessels. In addition, we noticed that when phrenic nerve or sternum was involved, it was often associated with great vessels invasion. Upon multivariate logistic regression, only absence of mediastinal vessel invasion, the arterial system to be more specific, was predictive of complete resection ($P<0.05$). In the current study, the sensitivity of CT was 85.7% (18/21) and specificity was 97.3% (110/117) for assessing the presence of great vessel invasion, with an accuracy of 92.8%.

In Hayes SA's study on relationship of CT features with resectability of TET, only degree of abutment of adjacent vessel and pleural nodularity were independent predictors of incomplete resection on multivariate analysis. The retrospective nature of the study made it impossible to rule out potential inaccuracy in surgico-pathological staging (10). Besides, 49 patients with neoadjuvant chemotherapy were also included in that study. And it is sometimes difficult, if not impossible, to differentiate between fibrosis after treatment with actual tumor invasion on imaging study. All imaging and resection status evaluation were prospectively carried out in the current study, and only patients without pretreatment were included, making it possible to improve

the accuracy of the study. In both studies, absence of invasion into surrounding fat, mediastinal pleura, and lung was associated with complete resection. Our results were also in accordance with Hayes's finding that the degree of abutment of adjacent vessels was significantly associated with an incomplete surgical resection. In addition to these, we also found that enhancement pattern, invasion of surrounding tissues such as pericardium, phrenic nerve, sternum were statistically significant between complete and incomplete resection, which were not mentioned in Hayes' study. More importantly, we found that when primary tumor only invaded venous systems, it could often be removed completely, while on the contrary when arterial systems were involved, it often indicated that the tumor would not be completely resected. These findings underscore the importance of identifying arterial systems invasion in preoperative workup before deciding on surgery upfront.

Limitation of our study include the number of patients in stage III/IV was small, especially when seven cases were excluded for induction therapy. Patients were not operated by one team and the surgeon's experience might have affected the outcome for complete resection. Pleural metastasis was not included for evaluation of resectability of the primary lesion. Because of the difference in the structure and flexibility of arterial and venous wall, the evaluation standard for arterial and venous invasion might be different. As only arterial but not venous invasion is associated with complete resection, future study should focus on these differences so as to increase the accuracy in predicting resectability.

Conclusions

Our study shows that clinical staging of TET could be accurately evaluated via CT features including tumor shape, contour, enhancement pattern, with or without invasion of adjacent structures, and presence of pleural, pericardial dissemination or intrapulmonary metastasis. Absence of arterial system invasion on CT is the only predictive feature for complete resection of TET. These CT findings can predict the feasibility of complete resection of the primary tumor and help identifying patients who may benefit from neoadjuvant chemotherapy or nonsurgical management, ultimately guiding treatment decisions.

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Footnote

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

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Only when all contribute their firewood can they build up a big fire

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Imaging plays a crucial role in the identification, staging and follow-up of patients diagnosed with a thymic epithelial tumor (TET). Staging and complete resection (1-3) have consistently shown to be associated with improved survival in patients with TETs. It is because of this that patients with local spread of disease or even pleural spread of disease receive neoadjuvant therapy, either chemotherapy alone or in combination with radiation therapy prior to resection, in an attempt to decrease tumor burden and decrease microscopic spread to enable a complete resection. However, final staging is performed after resection, after pathology inspection. Thus the identification of tumor spread relies solely on imaging, primarily on computed tomography (CT) scanning. For this, CT has to be accurate: not over stage patients and expose them to damaging therapy and not under stage them, potentially leading to incomplete resection with worse survival.

As an orphan disease, the numbers of studies assessing the accuracy of imaging in staging patients with TET or in assessing their resectability are few (4-13). The study of Shen *et al*. (14) adds light to the data available. It is the largest imaging study conducted so far and first prospective one. It brings with it interesting data which one could not study in other centers: patients with advanced disease proceeding to surgery without neoadjuvant therapy. Because patients in Dr. Shen's study routinely did not receive neoadjuvant therapy, even for advanced disease, the correlation between imaging findings to surgery were robust and straight forward. However, like other studies on CT's ability to stage TETs or predict resectability, Dr. Shen's study suffers from the same drawback of thymic studies we have seen in the past: single institution studies and did not assess the reproducibility of categories assigned. Some of the variables for assessing tumors can be subjective and result in great inter or even intra-observer variability. This especially applies to those dichotomous tumor characteristics such as assigning tumors a heterogeneity category, assigning a contour, establishing infiltration of surrounding fat or invasion into abutting structures. We hope that in the future, routine computer aided evaluation such as recently seen with texture analysis (15) will alleviate some of this interobserver variability. Of all imaging features, intuitively, perhaps size is the most reproducible one. Unfortunately, size was not found in Dr. Shen's study to enable stage differentiation. In many other cancers, size is a component in T staging. Multiple studies in the past trying to correlate size with survival or staging of TETs produced variable and contradictory results (1-3,7-9,11,16,17). This is perhaps of no surprise, as tumor size did not impact overall survival nor could it predict complete resection among the 5,796 patients studied from International Thymic Malignancy Interest Group's (ITMIG's) database to formulate the new Tumor Node Metastasis (TNM) staging system (18,19).

Prior to assessing CT's ability to correlate to Masaoka-Koga pathologic staging in TETs' one should question this gold standard. The staging of TET has been lagging decades behind that of more common malignancies such as lung cancer. The bodies responsible for defining stage classification, the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control

(UICC) have not declared a staging system for TET. Until recently, there were at least 15 different stage classifications created for these diseases, all based on single institution studies of less than 100 patients. Perhaps the most widely known were the Masaoka (20) and the Masaoka-Koga (21) staging systems, both suffer from similar ambiguities. Well known from clinical practice and all imaging studies, the differentiation of Masaoka-Koga stage I to stage II, or even the differentiation between stage IIa and IIb is almost impossible, all requiring the identification of the microscopic relationship with a tumor capsule (14). It is because of this that some imaging studies grouped stage I and II together, as both require no neoadjuvant therapy and thus this preoperative differentiation was thought to be of lesser importance (7). However, this differentiation proved difficult at pathology as well as not all tumors have a capsule. It is ambiguities like this with the older staging systems, as well as other vague definitions, that prompted the ITMIG to join hands with the International Association for the Study of Lung Cancer (IASLC) and formulate a robust evidence based new staging system.

For the formation of the first large scale staging process, ITMIG provided the collaboration of worldwide experts in TET which together formed a retrospective database of over 10,000 patients submitted from 105 institutions from North and South America, Europe, and Korea as well as from the Chinese Alliance for Research in Thymoma which was then supplemented by additional cases from the Japanese Association for Research in the Thymus (JART) and additional cases from the European Society of Thoracic Surgeons. Statistical analysis was funded by IASLC and performed by the Cancer Research and Biostatistics organization. This collaboration resulted in a leap forward with a new TNM classification for TETs and ended the contradicting ambiguities of prior staging systems. It is now known that the task which was found as impossible with imaging, differentiating completely encapsulated tumors from those which involve the adjacent fat is of no importance as patients have similar survival and thus they were all grouped into one stage. This new staging system, like Dr. Shen's study, found that tumor size has no role in a staging system as it does not predict survival. Most of all, what this new robust staging system has proven is, that even when dealing with an orphan disease, progress is possible, if we join hands together as with unity we can achieve a much needed goal, previously thought to be impossible.

We should refrain from resting on one's laurels as there is still much work to do. Although impressive, the ITMIG retrospective database did not gather with it any imaging studies. With the new 8th edition TNM staging system together with ITMIG's ongoing prospective database, we now have a window of opportunity to join hands and prospectively collect and submit staging TET imaging studies to a central repository to solve all remaining questions about imaging. Some of these questions which remain open are: How accurate is imaging in differentiating the different T categories from each other? What lymph node size best predicts lymph node involvement in TETs? How accurate are we in identifying pleural metastatic disease? Can computerized texture analysis of the primary tumor predict survival or staging? Can computer-aided detection identify metastatic lesions missed by the human eye? It is our hope that this work and collaboration continues so that we can move forward and improve our patients' lives as the Chinese proverb wisely says: "*Only when all contribute their firewood can they build up a big fire*".

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Footnote

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

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Comparison of the Masaoka-Koga staging and the International Association for the Study of Lung Cancer/the International Thymic Malignancies Interest Group proposal for the TNM staging systems based on the Chinese Alliance for Research in Thymomas retrospective database

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Background: To compare the predictive effect of the Masaoka-Koga staging system and the International Association for the Study of Lung Cancer (IASLC)/the International Thymic Malignancies Interest Group (ITMIG) proposal for the new TNM staging on prognosis of thymic malignancies using the Chinese Alliance for Research in Thymomas (ChART) retrospective database.

Methods: From 1992 to 2012, 2,370 patients in ChART database were retrospectively reviewed. Of these, 1,198 patients with complete information on TNM stage, Masaoka-Koga stage, and survival were used for analysis. Cumulative incidence of recurrence (CIR) was assessed in R0 patients. Overall survival (OS) was evaluated both in an R0 resected cohort, as well as in all patients (any R status). CIR and OS were first analyzed according to the Masaoka-Koga staging system. Then, they were compared using the new TNM staging proposal.

Results: Based on Masaoka-Koga staging system, significant difference was detected in CIR among all

stages. However, no survival difference was revealed between stage I and II, or between stage II and III. Stage IV carried the highest risk of recurrence and worst survival. According to the new TNM staging proposal, CIR in T1a was significantly lower comparing to all other T categories (P<0.05) and there was a significant difference in OS between T1a and T1b (P=0.004). T4 had the worst OS comparing to all other T categories. CIR and OS were significantly worse in N (+) than in N0 patients. Significant difference in CIR and OS was detected between M0 and M1b, but not between M0 and M1a. OS was almost always statistically different when comparison was made between stages I–IIIa and stages IIIb–IVb. However, no statistical difference could be detected among stages IIIb to IVb.

Conclusions: Compared with Masaoka-Koga staging, the IASLC/ITMIG TNM staging proposal not only describes the extent of tumor invasion but also provides information on lymphatic involvement and tumor dissemination. Further study using prospectively recorded information on the proposed TNM categories would be helpful to better grouping thymic tumors for predicting prognosis and guiding clinical management.

Keywords: Thymoma; staging; prognostic grouping

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Introduction

Up till now, not a single staging system for thymic malignancy has ever been universally adopted. Neither has an official stage classification ever been defined by the Union for International Cancer Control (UICC). The Masaoka staging system, further modified by Koga *et al.*, is most widely used (1,2). Although this staging system appeared to be closely related to prognosis for thymic malignancies in many studies (3), it was based on merely 91 patients treated over 30 years ago at a single institution. And comparing to the staging of most other malignancies, the Masaoka-Koga system is sketchy and does not separate the prognostic impact of lymphatic or hematologic dissemination from direct tumor invasion using TNM components as a common practice. Thus a universally acceptable staging system based on big updated data, preferably using the TNM classifications, is desirable to direct future practice and research (4). In collaboration with the International Thymic Malignancies Interest Group (ITMIG) and the International Association for the Study of Lung Cancer (IASLC), a Thymic Domain of the Staging and Prognostic Factors Committee has recently proposed a new TNM stage classification system (5). We hereby use the Chinese Alliance for Research in Thymomas (ChART) retrospective database to compare these two staging systems.

Materials and methods

Two-thousand three hundred and seventy patients treated at 18 tertiary centers in China during 1992 to 2012 were retrospectively recorded in the ChART database and were reviewed for the purpose of the study. Of these, 1,172 patients were excluded (due to missing information for the new TNM staging proposal in 627, missing Masaoka-Koga stage data in 2, and missing survival data in 543), leaving 1,198 patients for final analysis. Only de-identified data were used for this staging study and informed consent was waived by IRB. Cumulative incidence of recurrence (CIR) was assessed only in R0 patients. Overall survival (OS) was evaluated both in an R0 resected cohort, as well as in all patients (any R status). Results of recurrence and OS were first assessed according to the Masaoka-Koga staging system. And then, they were reevaluated using the new TNM staging proposal for comparison.

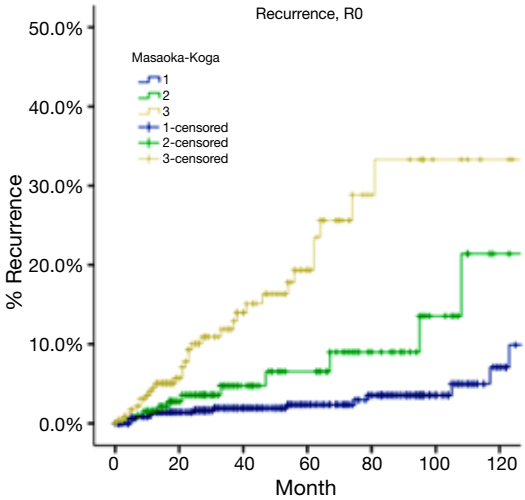
Statistical analysis was undertaken using the SPSS 18.0 software. Survival curves were estimated using the Kaplan-Meier method, and the significance of differences was assessed with Log-rank test. The CIR, which accounts for the presence of the competing, was used to estimate recurrence. Cox regression models were used to obtain hazard ratios for OS and recurrence adjusted for diagnosis. A two-sided P value less than 0.05 was considered to be statistically significant.

Table 1 Total proportion of recurrences or deaths of R0 patients base on Masaoka-Koga staging system

Masaoka-Koga	Recurrences		Deaths	
	%	N	%	N
I	3	17/600	1	8/616
II	6	12/197	2	4/197
III	13	31/242	4	9/251
Total	6	60/1,039	2	21/1,064

Table 2 Total proportion of recurrences or deaths of R any patients base on Masaoka-Koga staging system

Masaoka-Koga	Recurrences		Deaths	
	%	N	%	N
I	3	17/602	1	8/618
II	7	14/200	3	5/200
III	16	49/308	5	16/319
IVa	35	8/23	4	1/23
IVb	32	12/38	24	9/38
Total	9	100/1,171	3	39/1,198



Log rank	II	III
I	0.005	0.000
II		0.007

Figure 1 Kaplan-Meier survival curves: cumulative recurrence rate of patients with R0 resection in different stage by the Masaoka-Koga staging (log-rank). R0, complete resection.

Table 3 Differences between Masaoka-Koga categories

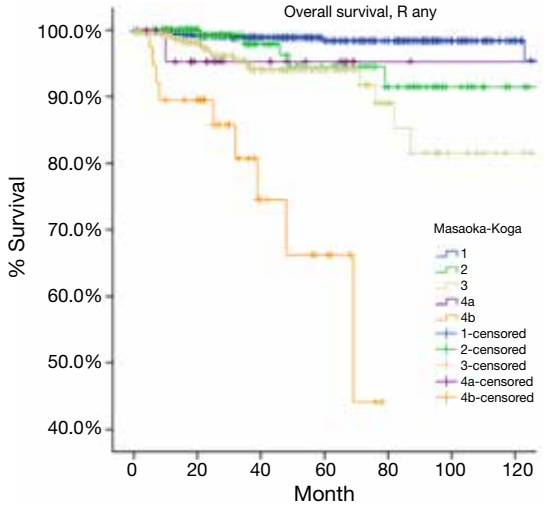
HR *vs.* adjacent Masaoka-Koga staging category	CIR, R0 (67/1,060)*		OS, R0 (23/1,085)*		OS, any R (39/1,198)*	
	HR	P	HR	P	HR	P
II *vs.* I	2.762	0.008	1.932	0.284	2.422	0.122
III *vs.* II	2.428	0.009	1.904	0.286	2.265	0.113
IV *vs.* III	—	—	—	—	3.506	0.002
IVb *vs.* IVa	—	—	—	—	6.482	0.078

Hazard ratios and statistical differences (χ^2) by Cox proportional hazards regression models, adjusted by diagnosis. *, number of events/total number of patients in entire data set for the particular analysis. HR, hazard ratio; CIR, cumulative incidence of recurrence; R0, complete resection; OS, overall survival.

Results

Based on Masaoka-Koga staging system, pathological staging was stage I in 618, stage II in 200, stage III in 319, stage IVa in 23 and stage IVb in 38 patients. Recurrence rate (*Table 1*) in patients with R0 resection increased with progression of tumor stage, while OS (*Table 2*) in patients with R any resection decreased. CIR in patients with R0 resection was shown in *Figure 1* and *Table 3*. Differences in CIR between stage I and stage II or III were statistically significant (P=0.005, P=0.000; respectively), as well as that between stage II and III (P=0.007). OS of patients with any R resection was shown in *Figure 2* and *Table 3*. Statistical significance was detected in differences of OS between stage I and stage III (P=0.000), and between stage IVb and all other stage categories (P<0.05); whereas differences between stage II and stage I or stage III were not significant (P=0.111, P=0.103; respectively).

According to the new TNM staging proposal, pathological staging was stage I in 886, stage II in 48, stage III in 205, stage IVa in 38 and stage IVb in 21 patients. Again recurrence rate in patients with R0 resection increased with progression of tumor stage (*Table 4*), while



Log rank	II	III	IVa	IVb
I	0.111	0.000	0.194	0.000
II		0.103	0.642	0.000
III			0.864	0.000
IVa				0.043

Figure 2 Kaplan-Meier survival curves: OS of patients with any R resection in different stage by the Masaoka-Koga staging (log-rank). OS, overall survival.

Table 4 Total proportion of recurrences or deaths of R0 patients, based on the IASLC/ITMIG TNM staging proposal

Stage	Recurrences		Deaths	
	%	N	%	N
I	4	32/858	2	14/874
T1aN0M0	4	28/792	1	11/808
T1bN0M0	6	4/66	5	3/66
II	14	6/43	2	1/44
IIIa	16	22/134	4	6/142
Total	6	60/1,035	2	21/1,060

R0, complete resection; IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.

OS in patients with R any resection decreased (*Table 5*). For T categories, CIR in TxN0M0 R0 patients with T1a was significantly lower compared to patients with other T stages (P<0.05). Especially noticeable was the significant difference in CIR between T1a and T1b tumors (P=0.021). However, differences in CIR between T1b and T2 or T3 were not significant (P=0.315, P=0.215; respectively), neither was the difference between T2 and T3 (P=0.963, *Figure 3*). For

Table 5 Total proportion of recurrences or deaths of R any patients base on the IASLC/ITMIG TNM staging proposal

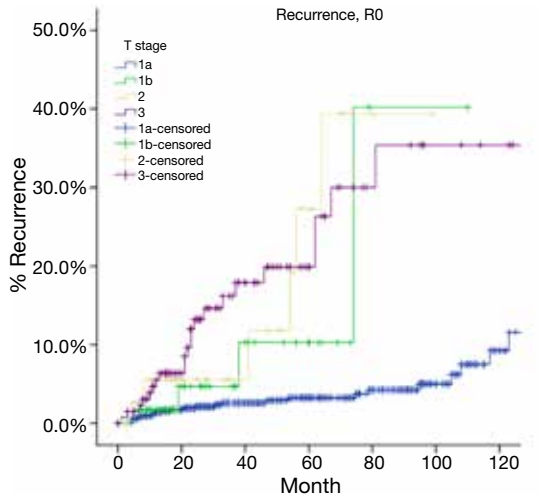
Stage	Recurrences		Deaths	
	%	N	%	N
I	4	36/870	2	17/886
T1aN0M0	4	30/798	1	12/814
T1bN0M0	8	6/72	7	5/72
II	13	6/47	2	1/48
III	19	38/195	5	11/205
IIIa	18	32/178	4	7/188
IIIb	35	6/17	24	4/17
IVa	39	15/38	13	5/38
TxN1M0	43	6/14	29	4/14
TxN0M1a	36	8/22	5	1/22
TxN1M1a	50	1/2	0	0/2
IVb	24	5/21	24	5/21
TxN2M0,1a	33	2/6	33	2/6
TxN0–2M1b	20	3/15	20	3/15
Total	9	100/1,171	3	39/1,198

IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.

OS in TxN0M0 R0 patients, T1a was significantly better than that of T1b (P=0.004), whereas no statistical difference was detected between T1b and T2 or T3 (P=0.428, P=0.481; respectively, *Figure 4*). For OS in TxN0M0 R any patients, T4 was significantly worse compared with all other T categories (P<0.05, *Figure 5*). Upon COX analysis, difference in OS was statistically significant between patients with T1a and T1b tumors (P=0.000), as well as that between T3 and T4 (P=0.001); whereas no statistical difference was detected between T2 and T3 (P=0.72, *Table 6*).

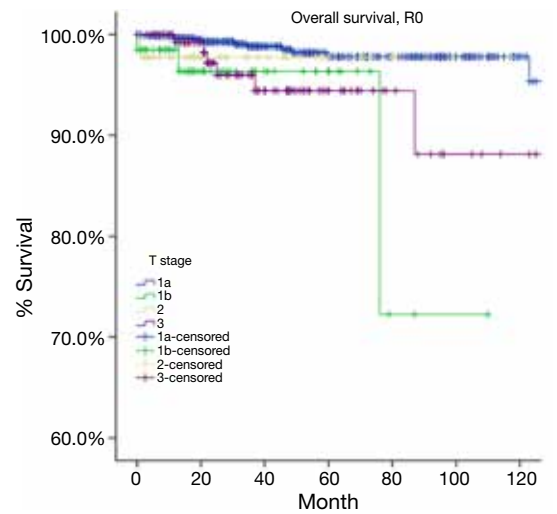
For N categories, CIR in R0 patients was shown in *Figure 6* and OS in R any patients was shown in *Figure 7*. CIR and OS in N negative patients were both better than those of N positive patients (P<0.05), whereas no statistical difference was detected between N1 and N2 (P>0.05). Upon COX analysis, N positive was a significant risk factor for increased CIR in patients with R0 resection and also a significant risk factor for worse OS in patients with any R (*Table 7*).

For M categories, CIR or disease progression in R any M negative patients was significantly lower than that in



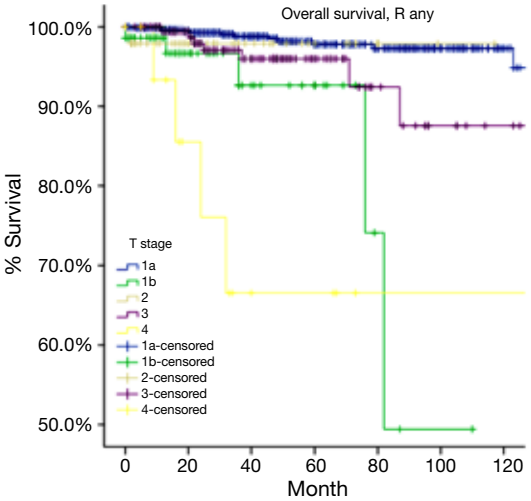
Log rank	T1b	T2	T3
T1a	0.021	0.000	0.000
T1b		0.315	0.215
T2			0.963

Figure 3 Kaplan-Meier survival curves: Cumulative recurrence rate of TxN0M0 patients with R0 resection in different T stage by the IASLC/ITMIG TNM staging proposal (log-rank). R0, complete resection; IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.



Log rank	T1b	T2	T3
T1a	0.004	0.435	0.009
T1b		0.428	0.481
T2			0.725

Figure 4 Kaplan-Meier survival curves: overall survival of TxN0M0 patients with R0 resection in different T stage by the IASLC/ITMIG TNM staging proposal (log-rank). R0, complete resection; IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.



Log rank	T1b	T2	T3	T4
T1a	0.000	0.517	0.019	0.000
T1b		0.194	0.049	0.079
T2			0.718	0.006
T3				0.000

Figure 5 Kaplan-Meier survival curves: OS of TxN0M0 patients with R any resection in different T stage by the IASLC/ITMIG TNM staging proposal (log-rank). OS, overall survival; IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.

patients with M positive diseases (P<0.05), whereas no statistical difference was detected between M1a and M1b (P=0.263, *Figure 8*). OS in M0 was significantly better than M1b (P=0.000) in R any patients. However, no difference was detected between M0 and M1a (P=0.682) or between M1a and M1b (P=0.109) (*Figure 9*).

Based on the proposed new TNM staging, CIR in R0 patients with stage I disease was significantly lower than stage II or stage IIIa (P=0.000, P=0.000; respectively), with no statistical difference detected between stage II and stage IIIa (P=0.963). OS in R any patients with stage I and stage II diseases was similar (P=0.694), as well between patients with stage II and stage IIIa (P=0.718). OS in R any patients with stage IIIa was significantly better than in those with stage IIIb tumors (P=0.000). For OS in R any patients, stage IVb was worst among all categories. Moreover, there was no statistical difference detected in OS between stage IIIb and stage IVa (P=0.312), or between stage IVa with stage IVb (P=0.315) (*Table 8*, *Figure 10*).

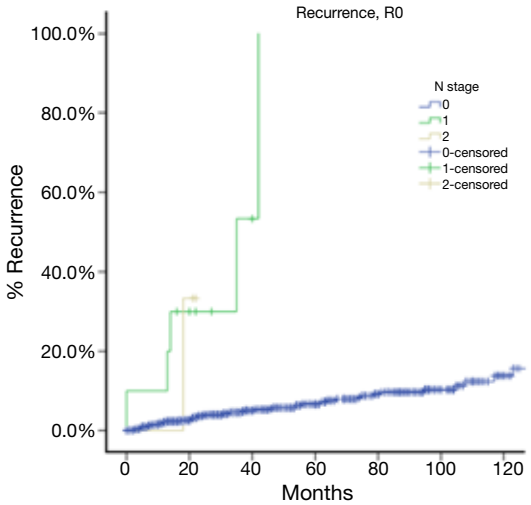
Discussion

Almost a dozen of different staging systems have been

Table 6 Differences between T categories (IASLC/ITMIG TNM staging proposal)

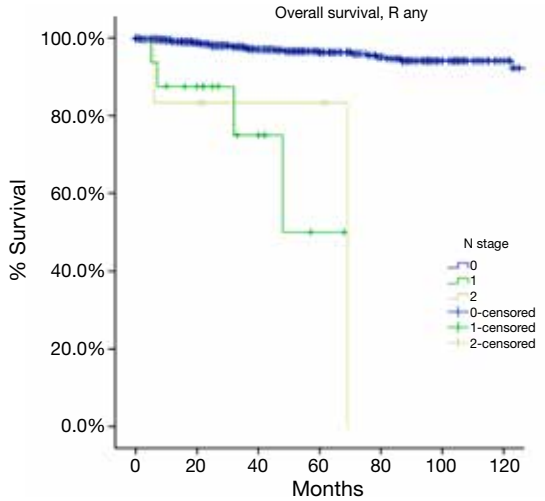
HR *vs.* adjacent T category	CIR, R0 (60/1,039)*		OS, R0 (21/1,064)*		OS, any R (29/1,139)*	
	HR	P	HR	P	HR	P
T1b *vs.* T1a	3.299	0.029	5.574	0.010	8.624	0.000
T2 *vs.* T1b	1.898	0.323	0.410	0.443	0.266	0.227
T3 *vs.* T1b	1.941	0.225	0.607	0.485	0.330	0.061
T2 *vs.* T1	6.299	0.000	1.837	0.558	1.497	0.696
T3 *vs.* T2	1.022	0.963	1.461	0.726	1.469	0.720
T4 *vs.* T3	—	—	—	—	8.088	0.001

Hazard ratios and statistical differences (χ^2) by Cox proportional hazards regression models, adjusted by diagnosis. *, number of events/total number of patients in entire data set for the particular analysis. IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group; HR, hazard ratio; CIR, cumulative incidence of recurrence; R0, complete resection; OS, overall survival.



Log rank	1	2
0	0.000	0.003
1		0.922

Figure 6 Kaplan-Meier survival curves: cumulative recurrence rate of patients with R0 resection in different N stage by the IASLC/ITMIG TNM staging proposal (log-rank). IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.



Log rank	1	2
0	0.000	0.000
1		0.553

Figure 7 Kaplan-Meier survival curves: OS of patients with R any resection in different N stage by the IASLC/ITMIG TNM staging proposal (log-rank). OS, overall survival; IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.

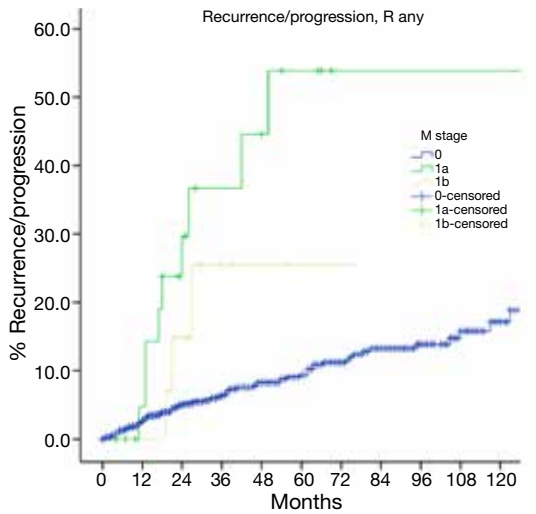
proposed for thymic malignancies (6-17). But few have adopted the TNM approach as in most other solid tumors. The IASLC/ITMIG proposal for the new UICC staging of thymic malignancy is mostly based on the widely used Masaoka-Koga system, but using the TNM components instead. As can be seen from *Table 9*, stages I–IIIb in this new staging system are classified primarily by the T component, which are corresponding to stages I–III in the Masaoka-Koga system. Stages IVa and IVb are determined by the presence of N1 or M1a disease for IVa and N2 or M1b disease for IVb (5), while in the Masaoka-Koga staging system all lymphatic metastasis were classified as stage IVb.

Our results showed that although there were significant differences in CIR among Masaoka-Koga stage I to III tumors, OS remained similar between stage I and II (*Tables 1-3*, *Figures 1,2*). These suggest that combining Masaoka-

Table 7 Differences between N categories (IASLC/ITMIG TNM staging proposal)

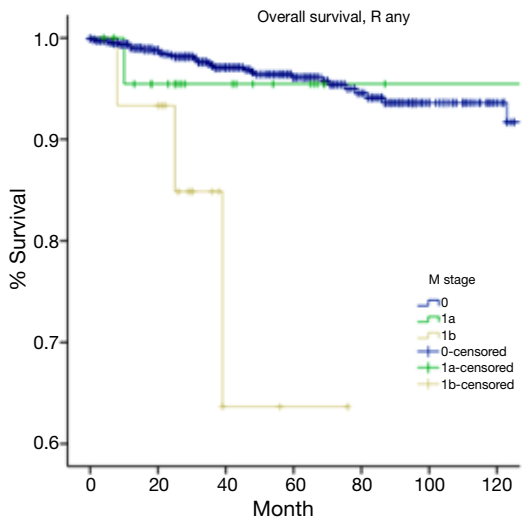
HR *vs.* adjacent N category	CIR, R0 (67/1,060)*		OS, R0 (23/1,085)*		OS, any R (39/1,198)*	
	HR	P	HR	P	HR	P
N1 *vs.* N0	15.66	0.000	6.817	0.062	13.034	0.000
N2 *vs.* N0	10.99	0.018	0.050	0.876	14.074	0.000
N2 *vs.* N1	0.893	0.922	0.033	0.737	0.515	0.559
N1 + N2 *vs.* N0	14.77	0.000	4.968	0.119	8.617	0.000

Hazard ratios and statistical differences (χ^2) by Cox proportional hazards regression models, adjusted by diagnosis. *, number of events/total number of patients in entire data set for the particular analysis. IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group; HR, hazard ratio; CIR, cumulative incidence of recurrence; R0, complete resection; OS, overall survival.



Log rank	M1a	M1b
M0	0.000	0.030
M1a		0.263

Figure 8 Kaplan-Meier survival curves: cumulative recurrence/progression rate of patients with R any resection in different M stage by the IASLC/ITMIG TNM staging proposal (log-rank). IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.



Log rank	M1a	M1b
M0	0.682	0.000
M1a		0.109

Figure 9 Kaplan-Meier survival curves: OS of patients with R any resection in different M stage by the 8th edition TNM staging (log-rank). OS, overall survival.

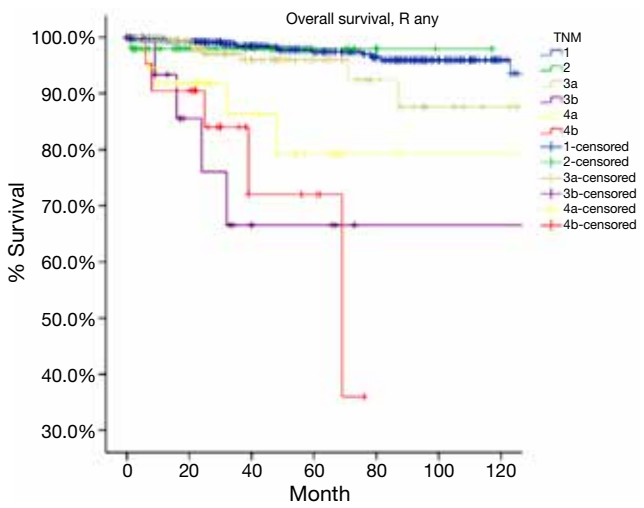
Koga stage I and II together to become T1a (stage I) as in the ITMIG proposed system may be warranted (18). Still, the difference between recurrence rates in tumors with or without invasion into the capsule or mediastinal fat (Masaoka-Koga stage I and II) leaves the question whether they should be further subdivided in the future, as recurrence is also an important measure in less aggressive tumors (19).

Tumors invading the mediastinal pleura were classified as stage II in the Masaoka and stage III in the Masaoka-Koga systems. They are now included into stage I because no consistent difference in outcomes (recurrence or survival) were detected during the IASLC/ITMIG staging project. Division into T1a and T1b was preserved because there was a slight difference in CIR in patients from Japan submitted by the Japanese Association for Research in the Thymus. Hopefully this could leave a window open for further testing. However, in the present study, there was a significant difference in both CIR and OS between T1aN0M0 and T1bN0M0 patients (*Tables 4-6*, *Figures 3-5*)

Table 8 Differences between the IASLC/ITMIG TNM staging proposal categories

HR *vs.* adjacent TNM staging category	CIR, R0 (67/1,060)*		OS, R0 (23/1,085)*		OS, any R (39/1,198)*	
	HR	P	HR	P	HR	P
II *vs.* I	0.159	0.000	0.544	0.558	1.497	0.696
IIIa *vs.* I	5.235	0.000	2.926	0.028	2.207	0.080
IIIb *vs.* I	—	—	—	—	16.665	0.000
IVa *vs.* I	—	—	—	—	8.806	0.000
IVb *vs.* I	—	—	—	—	17.847	0.000
IIIa *vs.* II	1.022	0.963	1.461	0.726	1.469	0.720
IIIb *vs.* II	—	—	—	—	11.282	0.030
IVa *vs.* II	—	—	—	—	5.787	0.109
IVb *vs.* II	—	—	—	—	12.108	0.024
IIIb *vs.* IIIa	—	—	—	—	8.088	0.001
IVa *vs.* IIIa	—	—	—	—	4.209	0.015
IVb *vs.* IIIa	—	—	—	—	8.616	0.000
IVa *vs.* IIIb	—	—	—	—	0.515	0.323
IVb *vs.* IIIb	—	—	—	—	0.920	0.901
IVb *vs.* IVa	—	—	—	—	1.872	0.322

Hazard ratios and statistical differences (χ^2) by Cox proportional hazards regression models, adjusted by diagnosis. *, number of events/total number of patients in entire data set for the particular analysis. IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group; CIR, cumulative incidence of recurrence; OS, overall survival; R0, complete resection; HR, hazard ratio.



Log rank	II	IIIa	IIIb	IVa	IVb
I	0.694	0.072	0.000	0.000	0.000
II		0.718	0.006	0.069	0.004
IIIa			0.000	0.008	0.000
IIIb				0.312	0.901
IVa					0.315

Figure 10 Kaplan-Meier survival curves: the overall survival of patients with any R resection in different stage by the 8th edition TNM staging (log-rank).

from the ChART database. Pleural invasion theoretically increase the chance of pleural cavity dissemination, which is the most common type of recurrence in thymic tumors. Given the difficulty in identifying pleural invasion in pathology, it is thus critically important to mark out mediastinal pleura in surgical specimens and prospectively record invasion status for future investigation.

Stage III in the Masaoka-Koga system is highly heterogeneous. Tumors invading mediastinal pleura (T1b), pericardium (T2), or any other structures (T3–4) are all included in a single category. In the current study, we failed to find any survival difference between Masaoka-Koga stage II and III, although CIRs were significantly different (*Tables 1-3*, *Figures 1,2*). Intuitively, limited invasion into readily resectable structures and those vital organs not readily resectable would carry different prognostic impact. In ChART patients we did not detect any significant difference in OS or CIR among T1b to T3 (stage I to IIIa in the IASLC/ITMIG proposal) diseases, although all were distinct from T1a tumors (*Tables 4-6*, *Figures 3-5*). The separation of recurrence or survival curves between T1 and T2 or T3 could be contributed to the better outcome in T1a diseases. Only in T4 tumors (stage IIIb) did survival and recurrence results became significantly worse. And we

Table 9 The relationship between the IASLC/ITMIG TNM proposal staging categories and Masaoka-Koga staging system

The 8th edition TNM stage	TNM	Definition (involvement of)	Masaoka-Koga
Stage I	T1aN0M0	Encapsulated or unencapsulated, with or without extension into mediastinal fat	Stage I and II
	T1bN0M0	Extension into mediastinal pleura	Stage III (partial-pleura)
Stage II	T2N0M0	Pericardium	Stage III (partial-pericardium)
Stage IIIa	T3N0M0	Lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels	Stage III (partial-completeness of resection)
Stage IIIb	T4N0M0	Aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus	Stage III (partial-incompleteness of resection)
Stage IVa	TxN1M0	Anterior (perithymic) nodes	Stage IVb
	TxN0M1a	Separate pleural or pericardial nodule(s)	Stage IVa
	TxN1M1a	Anterior (perithymic) nodes, Separate pleural or pericardial nodule(s)	Stage IVb
Stage IVb	TxN2M0	Deep intrathoracic or cervical nodes	Stage IVb
	TxN2M1a	Deep intrathoracic or cervical nodes, Separate pleural or pericardial nodule(s)	Stage IVb
	TxNxM1b	Pulmonary intraparenchymal nodule or distant organ metastasis	Stage IVb

IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.

failed to find any significant difference between stage I and stage II or IIIa according to the IASLC/ITMIG proposal (*Table 8*, *Figure 10*). This echoes with numerous previous studies revealing radical resection as an independent prognostic factor for thymic malignancies (20), as complete tumor removal can readily be achieved in T1 to T3 tumors. Since systemic dissemination is not commonly encountered in this low grade tumor, prognosis may be similar as long as the lesions could be completely resected. Considering that the TNM system is an anatomical classification, differentiating extent of tumor invasion according to the T categories of the IASLC/ITMIG proposal is warranted. However, prognostic grouping should still be based on long-term outcome of the patients. Thus except for stage IIIb (T4), further analysis is necessary to validate the current stage grouping in the IASLC/ITMIG proposal for the new staging system.

Among all the staging proposals for thymic malignancy, only four have used the TNM approach (11,12,15,21). In all others lymphatic involvement was simply considered as a sign of late stage disease. In the IASLC/ITMIG proposal lymph node metastasis was still classified as stage IV. But ITMIG has also proposed a new mediastinum lymph node map (21). This helped to separate the N status into N0 to N1–2 in the proposed new staging (22). However, no significant difference was detected between N1 and N2 diseases in either OS or CIR. Nor was the current study able to reveal any statistical significance between these two nodal statuses, as there were few patients with N (+) diseases and even fewer events in survival or recurrence analysis (*Table* 7), although there was indeed a significantly increased CIR (*Figure 6*) and worse OS (*Figure* 7) in node positive patients as compared to node negative patients. Lymph node dissection has seldom been considered as a necessary part of surgery for thymic tumors. An accurate estimation of true incidence or extent of lymphatic involvement would be impossible if systemic nodal dissection or sampling is missing. Only with future studies based on such information could the prognostic impact of lymphatic involvement be correctly addressed.

M categories in the IASLC/ITMIG proposal was divided into M1a (pleural dissemination) and M1b (distant organ metastasis) (22). And they were grouped as stage IVa and IVb, respectively, similar to the stage IVa and IVb classification in the Masaoka-Koga system. However, there was only a visual separation of the survival curves between

M1a and M1b during the staging process. In the current study, we did not find a statistical significance in CIR or OS between these two categories, either. Both M1 categories had worse prognosis than M0 patients (*Figures 8*,*9*). However, it is interesting to notice that while the M1a group had a significantly higher CIR than the M0 group (*Figure 8*), its OS was not significantly different from the latter (*Figure 9*). This may again be attributed to the few events noticed in survival analysis. For tumors with an indolent nature as thymic malignancy, long-term survival could still be expected even if local regional spread like pleural dissemination is present. On the other hand, distant organ metastasis represents a true adverse prognostic factor. Both CIR and OS in the M1b group were significantly worse than the M0 group.

As for prognostic grouping, we found that OS was almost always statistically different when comparison was made between stages I–IIIa and stages IIIb–IVb (*Table 8*, *Figure 10*). The differences were of borderline significance in comparison between stage I and IIIa (P=0.072), and between stage II and IVa (P=0.069). However, no statistical difference could be detected among stages IIIb to IVb. Although CIR were significantly lower in stage I as compared to stages II or IIIa, no statistical difference was revealed in OS among the three stages.

Overall, the ISLAC/ITMIG proposal of a new staging for thymic tumors was a major step forward in this relatively rare disease. It was the first time that careful analysis was carried out based on a large multicenter data with worldwide collaboration. The TNM components were adopted to describe tumor invasion as well as dissemination. The inability to discriminate survival difference in advanced stage disease is mostly owing to the nature of a surgically dominated database, and the unique behavior of the disease itself in slow progress and long-term survival. Using the ChART database which is also surgically dominated, we failed to demonstrate prognostic differences between N1 and 2 or M1a and 1b categories, except for a clear difference between N0 and N (+) or M0 and M1b diseases. In T components, T1a and T4 clearly stand for the two extremes of prognosis, while T1b through T3 show no statistical difference in recurrence or OS. This in itself reflects precisely the critical importance of complete resection in the management of thymic tumors. The new staging proposal provides a useful tool for future studies for better prognostic groupings. Careful recording the TNM components separately in each case and in a prospective manner would help revealing their prognostic significance which may not be able to attain with retrospective studies.

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Footnote

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The International Association for the Study of Lung Cancer/the International Thymic Malignancies Interest Group proposal for the TNM staging systems for thymic epithelial tumors and large-scale retrospective data

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Provenance: This is an invited Editorial commissioned by the Guest Editor Wentao Fang (Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

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Thymic epithelial tumors are rare tumors. However, they are the most common tumor of the anterior mediastinum (1). A lot of studies analyzed retrospective clinical data of patients with thymoma from single-institute (2). Recently some studies analyzed large-scale retrospective clinical data (more than 1,000 patients) of thymic epithelial tumors including thymoma and thymic carcinoma from multiple institutes (3-5). The studies in Japan analyzed 1,320 patients with thymic epithelial tumors treated surgically from 115 institutes during the period from 1990 through 1994 and 2,835 patients with thymic epithelial tumors treated surgically during the period from 1991 through 2010 (3,4). The study by the European Society of Thoracic Surgeons (ESTS) database analyzed 2,151 patients with thymic epithelial tumors treated surgically from 35 institutions during the period from 1990 to 2010 (5). Large-scale retrospective data can clarify the biology and the therapy for thymic epithelial tumors. In this article "*Comparison of the Masaoka-Koga staging and the International Association for the Study of Lung Cancer/the International Thymic Malignancies Interest Group proposal for the TNM staging systems based on the Chinese Alliance for Research in Thymomas retrospective database*" by Liang *et al*., the Chinese Alliance for Research in Thymomas (ChART) collected the retrospective data of 2,370 patients treated at 18 hospitals in China during 1992 to 2012. Of these, 1,198 patient data were used to compare Masaoka-Koga staging and the International Association for the Study of Lung Cancer (IASLC)/the International Thymic Malignancies Interest Group (ITMIG) proposal for the TNM staging systems. As there are few reports which judged the validity of the IASLC/ITMIG proposal for the TNM staging systems using large-scale data now, report of Liang *et al*. has an excellent value.

The clinical staging system for thymoma was first introduced by Bergh and associates in 1978 (6), later modified by Wilkins and Castleman (7), and confirmed by Masaoka and associates in 1981 (8). The Masaoka classification is now the most widely accepted and is an excellent predictor of the prognosis of thymoma (2,3). However, several articles have pointed out some problems and have suggested that an update of the system is desirable (9). To correct them, the ITMIG proposed the Masaoka-Koga stage classification system (10). The Masaoka system refers more vaguely to capsular invasion-definition between stage I and II. The Masaoka-Koga system defined stage I as "grossly and microscopically completely encapsulated tumors including tumors with invasion into but not through the capsule" and stage IIA as "tumor with microscopic transcapsular invasion", and stage III included tumors with microscopic involvement of mediastinal pleura.

However, many studies do not provide appreciable prognostic separation between stages I and II in the Masaoka or Masaoka-Koga system (11,12), as Liang *et al*. showed that differences in cumulative incidence of recurrence (CIR) between stage I and stage II were statistically significant, and that no statistical significance was detected in differences of overall survival (OS) between stage I and stage II. In the Masaoka or Masaoka-Koga system, the presence of local invasion (T factor) is strongly emphasized in comparison with lymphogenous and hematogenous metastasis (N and M factors) because of the rarity of lymphogenous and hematogenous metastasis in thymoma. However, it is necessary to determine how N or M factors influence prognosis to establish a TNM system classification of thymic epithelial tumors, including thymic cancer and carcinoid (13).

Now there is no an official-stage classification system for thymic malignancies. In 2009, both the ITMIG and the IASLC recognized the need for a consistent stage classification system for thymic epithelial tumors. A Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) was established collaboratively by IASLC and ITMIG. IASLC led discussions and received approval from AJCC and UICC to develop proposals for stage classification of thymic malignancies that would help define thymic stage classification in the 8th edition of the stage classification manuals. ITMIG assembled a retrospective global database of 10,808 patients with thymic malignancies from 105 sites worldwide, carried out statistical analysis and proposed the TNM classification for thymic epithelial tumors (14).

T1 includes tumors that were classified as stage I or II in the Masoaka or Masaoka-Koga stage classification systems, because there is no significant difference of recurrence and OS between stage I and II in the Masoaka or Masaoka-Koga stage classification systems. However, there is a slight difference in CIR in patients from Japan submitted by the JART. The TD-SPFC decided, to gain more prospective data for further testing, to subcategorize T1 into T1a (no mediastinal pleural involvement) and T1b (involvement of the mediastinal pleura) (12). Liang *et al*. showed that there was a significant difference in CIR between T1a and T1b tumors, which confirmed the result of JART data. T2 (the pericardium invasion) cases resulted in a worse rate of recurrence and survival in patients than T1 cases. Recurrence in T2 cases was lower than that in T3 cases, although there was no significant difference of OS between T2 cases and T3 cases (12). Liang *et al*. showed that there was no significant difference in CIR and OS between T2 and T3 cases. Some investigators think that as stage III thymoma is highly heterogenous in terms of the involved organs, the classification should divide the subgroups according to prognosis (15). The TD-SPFC analyzed CIR and OS of stage III cases in terms of involvement of each single structure (pericardium, lung, great vessels, etc.), the number of different structures involved and possible combinations. However, there were no apparent differences (12). There was a trend to worse OS between T4 cases and T3 cases (there was no significant difference) because the number of patients available for analysis with T4 involvement was limited (12). Liang *et al*. showed that there was significant difference in OS between T3 cases and T4 cases.

In terms of N factor, the JART has conducted the best analysis of the incidence and location of node metastases from thymic malignancies. Lymph node metastases were seen in 2% of thymomas, 27% of thymic carcinomas, and these node metastases were seen most often in anterior mediastinal lymph nodes N1 (89% of thymoma, 69% of thymic carcinomas) (16). Liang *et al*. showed that there was a significant difference in OS between N0 cases and N1–2 cases. However, the results of Liang *et al*. (comparing N0 cases with N1–2 cases) cannot estimate a prognostic feature of N factor. The TD-SPFC demonstrated that the recurrence and survival outcomes of patients with N1 involvement are similar to those of patients with M1a involvement, and that the outcomes of patients with N2 and M1b involvement (or both) are similar. The N1 and M1a cases were grouped into the stage group IVA and the N2 and M1b cases into stage group IVB (17).

Since now some organs like ITMIG collect large-scale retrospective and prospective data for thymic epithelial tumors with multi-institutes, analyze them and judged the validity of the IASLC/ITMIG proposal for the TNM staging systems like the report of Liang *et al*. The repeat of this process will make an excellent TNM classification for thymic epithelial tumors.

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Footnote

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The enlightenments from ITMIG Consensus on WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting

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Abstract: The World Health Organization (WHO) histological classification of the thymoma and thymic carcinoma (TC) has been criticized for poor interobserver reproducibility or inconsistencies in the routine pathological diagnosis. The International Thymic Malignancy Interest Group (ITMIG) panel achieved an agreement to maintain the widely accepted WHO framework but to refine historic definitions and histological criteria, and further introduce some new terms with the aim to improve interobserver reproducibility. This review addresses the enlightenments we can get from the ITMIG consensus on the WHO histological classification of the thymoma and TC, which may be helpful for most pathologists.

Keywords: Thymic epithelial tumor (TET); histology; reporting

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Introduction

The World Health Organization (WHO) classification is the most widely used histological classification of thymomas and thymic carcinomas (TCs). However, the WHO classification has been criticized for poor interobserver reproducibility or inconsistencies in the routine diagnosis (1-3), when encountering some certain cases: (I) thymomas with features intermediate between prototypic subtypes (borderland cases); (II) tumors with atypia, high mitotic activity, and necrosis; (III) tumors showing more than one histological pattern. To address these issues at an interdisciplinary conference organized by the International Thymic Malignancy Interest Group (ITMIG) in New York, in March 2011, the participants including 18 pathologists, two surgeons, and one oncologist reviewed prototypic and difficult-to-classify thymic epithelial tumors (TETs) and achieved the consensus to refine histological criteria for better management. The article about the consensus statement was published on *Journal of Thoracic Oncology*, in May 2014 (4).

The ITMIG panel achieved an agreement to maintain the widely accepted WHO framework but to improve historic definitions and introduce some new terms with the aim to improve interobserver reproducibility:

(I) The WHO classification has been criticized for imprecise descriptions of A and AB thymoma and for calling them benign (5-7). At the consensus workshop there was agreement that A and AB thymomas are tumors of low malignant potential. The data of Chinese Alliance for Research in Thymomas (ChART), 1,930 cases of TETs from 10 hospitals from 1994 to 2012, showed that 10-year overall survival of type A and AB thymomas (accounted for 4.4% and 22.8%), were 92.4%

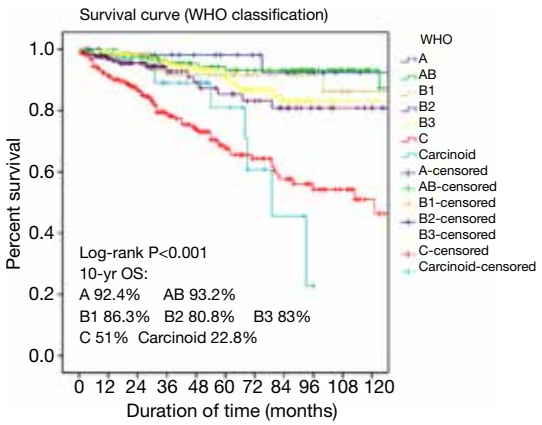

Figure 1 The 10-year overall survival of 1,930 cases of TETs from 10 hospitals from 1994 to 2012.

and 93.2% respectively (*Figure 1*);

(II) Taking into account that thymomas with heterogeneous histological features composed of different subtypes are very common, there was consensus that the term "combined thymoma" should be abandoned. Instead, the diagnosis in such tumors should follow an approach analogous to Gleason scoring listing all subtypes starting with the predominant component; minor components should be reported with 10% increments. Of note, AB thymoma is a distinct entity for which the 10% rule does not apply. For scientific and statistical purposes, thymoma components of 0% to 10% can be neglected, and the given tumor classified according to the dominant component. If thymic tumors comprising a carcinoma component should be different from the reporting of thymomas: such tumors should in the first place be labeled as carcinomas with listing of the proportion, differentiation, and grade, followed by the list of the thymoma components;

(III) In the WHO classification the imprecise definition of AB thymomas was "organotypic thymic epithelial neoplasms composed of a mixture of lymphocyte-poor type A thymoma component and a more lymphocyte-rich type B-like component analogous to B1 or B2 thymomas" (8). Now the potentially confusing term "B-like area" is replaced by "lymphocyte-rich" component in AB thymomas, and the criticized statement given in the WHO classification that lymphocyte-rich areas in AB thymomas harbor polygonal tumor cells is replaced: tumor cells in such areas are typically spindly or oval;

(IV) The new concept of atypical type A thymoma was posed in the consensus statement. Agreed criteria of "atypia" were increased mitotic activity (4 or more per 10 high power field) and "true" (coagulative) tumor necrosis (in contrast to ischemic or biopsy-induced necrosis). Other criteria, such as hypercellularity, enlarged hyperchromatic nuclei, large nucleoli, increased Ki67 index, and extent of atypical areas, were difficult to quantify or could not be agreed upon. Actually some of type A thymomas indeed showed overt invasiveness and metastasis (5,6), there was agreement that the type A thymoma family includes a small subset of aggressive tumors. Nevertheless, further subdivision of type A thymoma into different entities in analogy to the B1, B2, and B3 paradigm appears to premature before reliable data available (9).

The panel members agreed on the description of major (indispensable) and minor (typical) diagnostic criteria by tables, instead of the "narrative style" of the WHO classification. As supplement, "galleries of figures" illustrated different-to-classify tumors at the "borderlands" between prototypic cases. On account of the interest in borderland cases with differential diagnostic value, 72 cases were selected for review at the consensus workshop, only 58 could finally be fully evaluated due to time restrictions. The differential diagnosis on these borderland cases mainly focused on type A and AB thymoma, type B1 and B2 thymoma, type B3 thymoma and TC.

Differential diagnosis on type A thymoma

Distinguishing type A thymoma from AB thymoma

In the WHO classification the description of type A thymoma was that there was no or only few T cells with expression of CD3 and CD5. Immature T cells with expression of CD1a and CD99 could also present in type A thymoma. In the consensus statement the panels agreed to quantify the proportion of immature T cells of type A thymoma. It should harbor no or only few TdT+ T cells (easy to count) (grade 1) or a moderate amount of TdT+ T cells (I could count if I had to) (grade 2) in 10% or less of a given biopsy (*Table 1*). Moderate numbers of TdT+ T cells above the arbitrary 10% threshold in available biopsies or any area with abundant (impossible to count) TdT+ T cells (grade 3) would favor a diagnosis of AB thymoma over type

Table 1 Major and criteria of "conventional" type A thymomas

Major criteria
Spindle and/or oval-shaped tumor cells lacking nuclear atypia
Paucity[a] or absence of immature, TdT(+) thymocytes throughout the tumor
Minor criteria
Occurrence of rosettes and/or subcapsular (to be distinguished from PVS)
Presence of focal glandular formations
Paucity or absence of PVS contrasting with presence of abundant capillaries
Lack of Hassall's corpuscles
Complete or major encapsulation
Expression of CD20 in epithelial cells; absence of cortex-specific markers[b]

[a], Paucity implies no (immature) lymphocyte-rich with dense, "impossible-to-count" TdT(+) lymphocytes; or at most 10% tumor regions with moderate immature lymphocyte; [b], Beta5t, PRSS16, and cathepsin V by IHC. PVS, perivascular space; IHC, immunohistochemistry.

A thymoma. The role of immunohistochemistry (IHC) was emphasized in the consensus statement: epithelial cells of AB thymomas express both cortical and medullary markers in an intermingled pattern, whereas type A thymomas lack cortical markers (*Table 2*) (10).

Distinguishing type A thymoma from spindle cell B3 thymoma

In the WHO description Th reticulin fibers was applied for differential diagnosis on type A thymoma and spindle cell B3 thymoma (8). In type A thymoma reticulin fiber often presented around single tumor cell with expression of Laminin and collagen IV, whereas B3 thymoma lack of reticulin fibers. The consensus statement proposed reticulin fiber did not reliably distinguish type A from spindle B3 thymomas, while the difference on morphology was more valuable. Prominent and abundant perivascular spaces (PVSs) would strongly favor a diagnosis of type B3 thymoma, whereas uniform nuclei, abundance of capillary vessels, rosette formation, cystic spaces, and epithelial expression of CD20 would favor type A thymoma. Nevertheless, distinction between atypical type A thymoma and spindle cell B3 thymoma can be more difficult because nuclear atypia is present in both, and immunohistochemical studies may be further required.

Differential diagnosis on type B thymomas

Distinguishing B1 thymomas from B2 thymomas

B1 thymomas closely mimic normal thymus (NT) at both low and high magnification, with presence of prominent "medullary islands" that contain epithelial cells with or without Hassall's corpuscles; a majority of mature, TdT (–) T cells; and scattered CD20+ mature B cells. Medullary islands can also occur in B2 thymoma. PVS and abundant TdT+ T cells occur in both B1 and B2 thymomas, but PVSs are often inconspicuous in B1 thymomas. The distinguishing features of B2 thymomas are: (I) increased number of epithelial cells compared with NT often visible at low magnification; and (II) epithelial cell clusters (defined as at least three contiguous epithelial cells). On immunostaining, the network of epithelial cells in B2 thymoma is significantly denser. In the WHO description there was significant difference on tumor cell size, shape and nucleolus between B thymomas, while the consensus achieved is that nuclear size and atypia of epithelial cells are not helpful and reliable distinguishing features.

Distinguishing B2 thymoma from B3 thymoma

According to the statistical results from ChART, the prognosis of B2 thymoma was worse than B3 (10-year overall survival: 80.8% *vs.* 83.0%) (*Figure 1*). As a "rule of thumb" H&E-stained B2 and B3 thymomas give a "blue" *vs.* "pink" impression, respectively, due to the prominent T cells in B2 versus B3 thymomas. In the WHO classification previously described distinguishing criteria such as nuclear size and PVS are not helpful for this distinction.

Differential diagnosis between thymoma and TC

Distinguishing B3 thymoma from thymic squamous cell carcinoma (TSCC)

In general, TCs show the same histological features as analogous extra-TCs (*Table 3*) (11-14). B3 thymomas typically show lobular growth, conspicuous PVS, minor/moderate nuclear atypia, lack of intercellular bridges, presence of TdT+ immature T cells, and lack of expression of CD5, CD117, GLUT1, and MUC1 in neoplastic epithelial cells (15-18). Nevertheless, some following

Table 2 Major and minor histological features encountered in type A and AB thymomas

Features	Type A thymoma	Type AB thymoma
Major criteria		
Biphasic pattern at low magnification due to variable lymphocyte content	No	Common[a]
High epithelial cell content	Yes	Yes
Spindle or oval epithelial cells[b]	Yes	Yes
Paucity[c] or absence of TdT+ T cells	Yes	No
Medullary islands[d]	No	Rarely present[a,e]
Minor criteria		
Small lobular growth pattern	No	Rare
Large lobular growth pattern	Common	Common
Perivascular spaces	Rarely present	Rarely present
CD20 expression in epithelial cells	Common	Common
Cortical marker expression[f]	No	Yes

[a], these feature are minor criteria in type AB thymoma; [b], atypia in type AB thymoma has not been addressed so far; [c], as defined in *Table 1*; [d], detection of medullary islands is usually clear-out on hematoxylin-eosin staining but may require IHC, particularly when Hassall's corpuscles are missing; [e], in lymphocyte-rich areas, usually with lack of Hassall's corpuscles; [f], Beta5t, PRSS16, and cathepsin V (detectable by IHC in epithelial cells within lymphocyte-rich areas). IHC, immunohistochemistry.

Table 3 Criteria for the histological diagnosis of TC

Major (indispensible)
Clear-cut atypia of tumor epithelial cells with the severity typical of carcinoma
Exclusion of "thymoma with atypia and/or anaplasia" and of typical or atypical carcinoids
Exclusion of metastasis to the thymus and germ cell and mesenchymal tumors with epithelial features
Minor (typical)
Infiltrative growth pattern
Small tumor cell nests within desmoplastic stroma
Absence of immature, TdT+ T cells (with rare exceptions)
IHC: epithelial expression of CD5, CD117; extensive expression of GLUT1, MUC1[a]
Features compatible[b] with the diagnosis of TC
Invasion with pushing borders
Occurrence of perivascular spaces
Occurrence of "Hassall-like" epidermoid whorls and/or of myoid cells
Occurrence of (usually rare) immature, TdT+ cells

[a], CD5, CD117, GLUT1, and MUC1 are expressed by many nonthymic cancers; [b], although most of these features are "organotypic," that is, characteristic of thymoma, their presence does not exclude a diagnosis of TC if major diagnostic criteria of TC are fulfilled. IHC, immunohistochemistry; TC, thymic carcinoma.

equivocal situations still needed clarification. If tumors that lack TdT+ T cells in the available histological material but otherwise show features of typical B3 thymomas and CD5/CD117 negativity should be called B3 thymomas. Despite the expression of CD5, CD117, MUC1, or GLUT1 in an otherwise typical B3 thymoma, we should not change the diagnosis to TC (*Table 4*). If tumors with absence of two features of thymic squamous cell carcinoma (TSCC) (clear-

Table 4 Major and minor histological feature of type B1 versus B2 thymomas

Features	Type B1 thymoma	Type B2 thymoma
Major criteria		
Thymus-like pattern throughout	Consistently present	Rarely present
Medullary islands (+/– Hassal's corpuscles)	Consistently present	Occasionally present[a]
Confluence of epithelial cells in cortical areas[b]	No (like in the NT)	Yes
Absence of type A areas (even if <10%)	Yes	Yes
Minor criteria		
Small lobular growth pattern	Rare	Common
Large lobular growth pattern	Common	Rare
Perivascular spaces	Commonly present	Commonly present
Keratin+[c] network like in NT	Yes	Denser than in NT

[a], These features are, therefore, minor criteria of type B2 thymomas; [b], defined as at least three contiguous epithelial cells; [c], on immunostaining. NT, normal thymus.

cut nuclear atypia and intercellular bridges) and lack of an important feature of B3 thymomas (TdT+ T cells), they were tentatively labeled as "B3/TSCC borderline TETs".

Distinguishing atypical type A thymoma from spindle cell TC

As to this borderland, the panel members thought there were no efficient approaches to differential diagnosis. Analysis of TdT is not helpful, as absence of TdT+ thymocytes does not exclude a diagnosis of atypical type A thymoma. Morphologically classical type A thymomas should not be reclassified as TC only on the basis of CD117 and CD5 expression. New "subtype-specific" markers are needed to study this unresolved borderland. The statistical data of ChART revealed that TC patients had lowest prognosis, with 51% 10-year overall survival. As a new subtype, whether the prognosis of atypical A thymoma is worse or not, need more data to verify that (*Figure 1*).

Conclusions

The consensus achieved by the panel of ITMIG on refined definitions and histological criteria is helpful for interobserver reproducibility. The borderland cases often occurred in spectrum of type A and AB thymoma, type B thymoma, and TC. The tables that list major and minor diagnosis criteria and the galleries of figures that illustrate different-to-classify TETs make pathologists easy to grasp and practice on diagnosis. The proposal of new concepts of atypical type A thymoma and B3/TSCC borderline TETs further supplement the WHO classification. IHC play an important role in differential diagnosis, especially on thymomas and TCs, while as an auxiliary approach, the panelists still emphasize the morphology features, including nuclear atypia, mitotic activity, and tumor necrosis, when encountering the borderland cases.

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Footnote

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Clinicopathological analysis of 241 thymic epithelial tumors—experience in the Shanghai Chest Hospital from 1997–2004

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Background: To assess the correlation of WHO histological classification of thymomas and thymic carcinomas (TCs) with prognosis in recently treated patient cohort compared to a historical one from a single institution.

Methods: Retrospective review of clinical charts and histological sections of 241 patients treated during 1997–2004. Univariate and multivariate analysis of associations between risk factors including gender, age, tumor size, myasthenia gravis, WHO histological subtype, Masaoka stage, resection status, (neo-)adjuvant therapies, and survival.

Results: The 5-year overall survival (OS) of A, AB, B1, B2, B3 thymomas and TCs patients was 100%, 100%, 94%, 80%, 94% and 45%. Five-year progression-free survival (PFS) was 100%, 96%, 78%, 80%, 78% and 39%, respectively. The 5-year OS of patients with Masaoka stage I, II, III and IV thymomas and TCs was 96%, 89%, 59% and 50%. (Neo-)adjuvant therapies were administered more often than in the historical cohort. Tumor-related death mainly occurred in patients with stage III, IV and B2, B3 thymomas and TCs. By univariate analysis, gender, tumor size, myasthenia gravis (MG) status, histotype, Masaoka stage, resection status and treatment were associated with OS. By multivariate analysis, histological subtype, Masaoka stage, and (neo-)adjuvant therapy were revealed as independent prognostic indicators.

Conclusions: WHO histological subtype, Masaoka stage and (neo-)adjuvant treatment have remained independent determinants of OS in patients with thymomas and TCs. Compared with the historical cohort during 1969–1996, prognosis of patients with B2, B3 thymomas has improved, which may be partly due to the increased use of adjuvant therapies. Prognosis of patients with TCs remained unsatisfactory, suggesting that neoadjuvant treatment should be tested to improve survival.

Keywords: Thymic epithelial tumors (TET); thymoma; thymic carcinoma (TC); WHO histological subtype; prognosis

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Introduction

Thymic epithelial tumors (TET) comprise of thymomas and thymic carcinomas (TCs). Due to their rarity, heterogeneous morphology, and equivocal diagnostic criteria, histological classification of TET has been controversial (1,2). Since 1999 the WHO classification labels the main thymoma histological subtype as A, AB, B1, B2 and B3 (3,4). Although well-established world-wide, its prognostic value has been under debate (5-8). Most studies (9), including one of 200 cases treated between 1969 and 1996 at Shanghai Chest Hospital (SCH) (8), found A, AB and B1 thymomas to have a better prognosis, while others reported on comparable aggressiveness of B1, B2 and B3 thymomas (7), and aggressive and unresectable cases of A thymomas (6). Hereby, we investigated 244 new patients with thymomas and TCs from the SCH that were treated more than a decade later and compared clinicopathological variables and outcome in the two cohorts.

Materials and methods

Sources of data

A total of 335 consecutive patients underwent surgical resection of TET at SCH from 1997 to 2004. Among them, 244 patients with available treatment and follow-up data were included into the study. All histological sections were reviewed and tumors were classified according to the 2004 WHO classification of thymic tumor (4). All histological sections were first reviewed by 2 senior pathologists (Jie Zhang, Lei Zhu) separately according to the 2004 WHO classification of thymic tumor (4). Tumor sections from all patients who were dead, and some typical and debatable cases (n=110, 45.6% of the cohort) were reviewed by Alexander Marx. Consensus was achieved at a face-to-face microscopy session (J.Z., L.Z., A.M.).

There were 183 thymomas, 58 TCs. Two meta-plastic and 1 micronodular thymoma were excluded for further analysis. The study was approved by the Institutional Review Board of SCH. Clinicopathological data was retrieved from of SCH's files. The deadline of follow-up was June 30th, 2011. The time of follow-up ranged from 6.4 to 14.5 years (median: 7.8 years).

Statistical analysis

Data of 241 patients was statistically analyzed by SPSS 18 statistic software (SPSS Inc., Chicago) and SAS software, release 9.2 (SAS Institute Inc., Cary, NC, USA). Qualitative parameters were presented by their absolute and relative frequencies; for quantitative variables mean values ± standard deviation together with the corresponding ranges were given. In order to compare several groups regarding a qualitative parameter, Chi-square test or Fisher's exact test was used, as appropriate. Mean values were compared by 1-one-ANOVAs; for comparisons of two groups, 2-sample *t*-tests was used.

Overall survival (OS) and progression-free survival (PFS) were analyzed by the Kaplan-Meier method and evaluated for statistical differences by the log-rank test. Multivariate Cox regression analysis was used to investigate simultaneously the effects of possible risk factors [gender, age, myasthenia gravis (MG) status, tumor size, histotype, Masaoka stage, resection status, and (neo-adjuvant) treatment] on survival. Results were considered as statistically significant for $P<0.05$. For multiple Cox regression models significance level was set at 0.10.

Results

Clinicopathologic characteristics of current cases

Details of the tumors and patients are given in *Table 1*. In TCs, the proportion of male patients was higher than that in thymomas. However, among the thymoma subtypes, no statistically significant difference was found.

Patients with B2 and B3 thymomas and TC were significantly younger than patients with A thymomas (P=0.0008, P=0.0101 and P=0.0095, respectively).

No statistically significant differences could be detected between thymoma and TC (P=0.8520) on tumor size.

In our population, more than 95% of patients with A, AB, B1 thymomas showed Masaoka stage I or II. Higher stages increased from B2 through B3 thymomas to TCs.

The difference between resection rate in TCs and all thymomas was highly significant ($P<0.0001$). Between thymoma subtypes, rates of incomplete resections were only slightly significant (P=0.0071).

Among thymoma patients (n=183), 23.7% had MG; it occurred most frequently in B2 thymomas. The difference between thymoma and TC patients (only 2%) was highly significant (P=0.0001). More than that, among B2 thymomas patients MG was significantly more common compared to A-AB, B1 or B3 types (P=0.0401, P=0.0037, P=0.0142 or P=0.0396, respectively). The only one MG-associated TC (squamous cell carcinoma) showed a minor

Table 1 Summary of clinicopathological feature of TET

Histotype**	Type A (n=12)	Type AB (n=74)	Type B1 (n=18)	Type B2 (n=46)	Type B3 (n=33)	TCs (n=58)	Total (n=241)
Gender*							
Male	5 [42]	37 [50]	5 [28]	18 [39]	17 [52]	40 [69]	122 [51]
Female	7 [58]	37 [50]	13 [72]	28 [61]	16 [48]	18 [31]	119 [49]
Age (years)							
Mean ± SD	59.0±10.6	51.8±12.0	51.6±11.2	45.3±13.0	48.2±10.9	48.8±13.6	49.7±12.6
Range	45.0–72.0	17.0–72.0	29.0–70.0	15.0–77.0	29.0–68.0	12.0–72.0	12.0–77.0
Tumor size (cm)*							
Median ± SD	7.6±3.6	7.6±2.3	7.0±2.5	9.0± 3.6	8.0±2.7	8.5±3.5	8.1±3.1
Range	4.0–16.0	3.0–14.0	3.5–12.0	2.5–20.0	2.5–17.0	3.0–20.0	2.5–20.0
MG status*							
Negative	11 [92]	60 [81]	16 [89]	26 [57]	26 [79]	57 [98]	196 [81]
Positive	1 [8]	14 [19]	2 [11]	20 [43]	7 [21]	1 [2]	45 [19]
Masaoka stage**							
I	7 [58]	61 [82]	13 [72]	23 [50]	8 [24]	3 [5]	115 [48]
II	4 [33]	11 [15]	5 [28]	6 [13]	3 [9]	9 [16]	38 [16]
III	1 [8]	2 [3]	0	13 [28]	17 [52]	41 [71]	74 [31]
IV	0	0	0	4 [9]	5 [15]	5 [9]	14 [6]
Resection status*							
Complete	11 [92]	73 [99]	17 [94]	41 [89]	29 [88]	35 [60]	206 [86]
Incomplete	1 [8]	1 [1]	1 [6]	5 [11]	4 [12]	23 [40]	35 [15]
Treatment							
1	8 [67]	45 [61]	9 [50]	25 [54]	17 [52]	18 [31]	122 [51]
2*	0	2 [3]	2 [11]	9 [20]	12 [36]	19 [33]	44 [18]
3**	1 [8]	2 [3]	0	0	1 [3]	7 [12]	11 [5]
4*	0	0	2 [11]	2 [4]	2 [6]	8 [14]	14 [6]
5	3 [25]	25 [34]	5 [28]	10 [22]	1 [3]	6 [10]	50 [21]
Outcome							
Progression	0	1	7	14 [6]#	11 [1]#	39 [17]#	72 [24]#
Alive	12 [100]	71 [96]	16 [89]	34 [74]	28 [85]	20 [34]	181 [75]
Died of tumor	0	0	1 [6]	10 [22]	4 [12]	36 [62]	51 [21]
Died of other causes	0	3 [4]	1 [6]	2 [4]	1 [3]	2 [3]	9 [4]

* or **, significance of association with overall survival in univariate (*) and multivariate (**) analysis; #, number of patients with progression, i.e., relapse or metastasis (number of patients with progression but lack of a clear time to progression). Treatment: 1, postoperative radiotherapy (RT); 2, postoperative RT plus chemotherapy (CT); 3, post-operative CT; 4, therapies including neoadjuvant RT and/or CT; 5, no (neo-)adjuvant therapy.

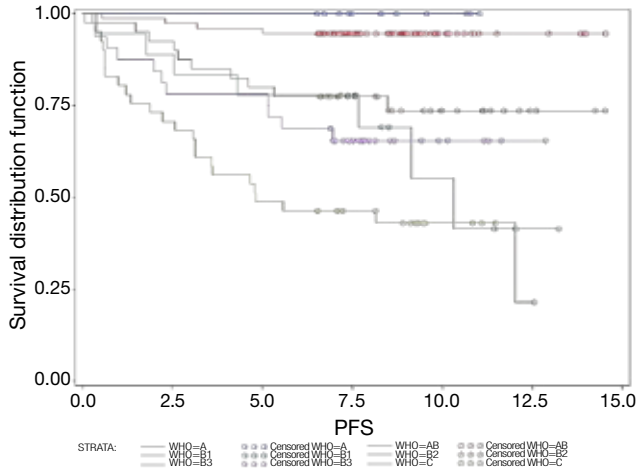

Figure 1 PFS by thymoma subgroup. The total number of cases was 241 (A, n=12; AB, n=74; B1, n=18; B2, n=46; B3, n=33; TCs, n=58). PFS, progression free survival.

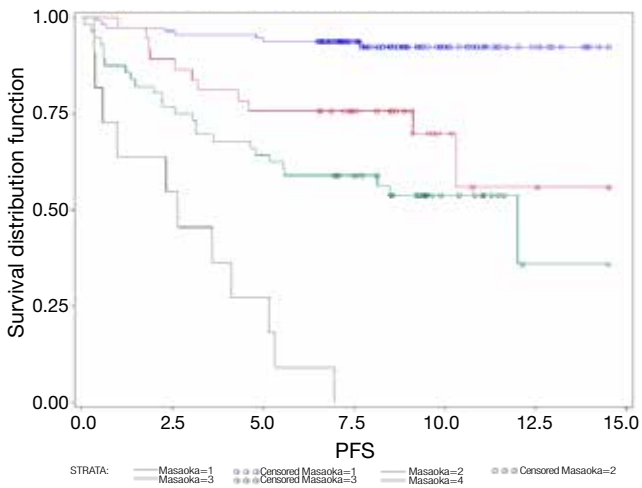

Figure 2 PFS by Masaoka stage. Total number of cases was 241 (stage I, n=115; stage II, n=38; stage III, n=74; stage IV, n=14). PFS, progression free survival.

B3 component. Pure TCs were not associated with MG.

Adjuvant and neoadjuvant treatment of thymic epithelial tumors (TETs)

Due to lack of standardized treatment protocols, therapies for TETs were diverse. Postoperative radiotherapy was used irrespective of stage and resection status in 57% of thymomas, but in only 31% of TCs (P=0.0006). By contrast, neoadjuvant protocols (with or without subsequent adjuvant therapy) were only applied in patients with B1 (2/18), B2 (2/46) and B3 (2/33) thymomas and TCs (8/58).

Follow-up in terms of relapses, metastasis and survival

No patient with A or AB thymoma died of tumor, 1 AB thymoma patient showed relapse. Among 18 B1 thymoma patients, 7 showed relapse or metastasis (39%) and 1 died of tumor. Fourteen of 46 B2 thymomas relapsed or metastasized (30%) and 10 (22%) were the cause of death. Among 33 B3 thymomas, 11 (33%) relapsed or metastasized and 4 (12%) caused death. Relapse/metastasis (67%) and tumor-related death rates (62%) were highest in TC patients. The association between progression and histological subtype as well as between outcome and histotype are highly significant (each P<0.0001). Tumor-related death was most common in advanced stage (Masaoka III or IV) TETs and B2, B3 thymoma and TC.

Detailed survival analysis

Survival and histology

The 5-year OS of patients with A, AB, B1, B2, B3 thymomas and TCs were 100%, 100%, 94%, 80%, 94%, and 45% respectively. In order to assess PFS, data of only 217 patients was available because of 24 missing values regarding PFS. Thus, the 5-year PFS were 100%, 96%, 78%, 80%, 78% and 39% (*Figure 1*). OS and PFS were significantly different between thymoma and TC patients (each P<0.0001). By contrast, neither the differences in OS nor PFS, were significant between B1, B2 and B3 thymoma patients (P=0.3161 and P=0.4872, respectively). Also, PFS of A and AB thymoma patients showed no significant differences (P=0.4825 and P=0.4158).

Survival and Masaoka stage

The 5-year OS of Masaoka stage I, II, III and IV patients were 96%; 89%; 59% and 50%, respectively (P<00001). The 5-year PFS of patients with Masaoka stage I, II, III and IV were 95%; 76%; 64% and 27%, respectively (P<0.0001) (*Figure 2*).

Survival and resection status

The 5-year OS of patients with complete and incomplete resection were 87% and 46%, respectively (P<0.0001). The 5-year PFS of patients with complete and incomplete resection were 85% and 42%, respectively (P<0.0001) (*Figure 3*).

Univariate and multivariate analysis of risk factors in terms of survival

By univariate analysis using Log-rank tests, gender (P=0.0413), tumor size (P=0.0003), MG status (P=0.0518), histotype (P<0.0001), Masaoka stage (P<0.0001), resection status (P<0.0001) and treatment (P<0.0001) were associated with OS, while age was not (P=0.7801). Female gender, small tumor size and presence of MG were favorable prognostic markers. Patients who received postoperative chemotherapy, radiotherapy combined with chemotherapy or neoadjuvant treatment had better OS than patients without postoperative intervention or surgery followed only by radiotherapy.

Multivariate Cox regression analysis showed only histotype, Masaoka stage and treatment (each P<0.0001) were independent prognostic indicators of OS after adjustment for gender, age, tumor size, MG status and resection status. OS of patients with postoperative chemotherapy (either with or without neoadjuvant treatment) was significantly better than OS of patient who received radiotherapy after surgery (P=0.0003).

The comparison of some clinicopathological data of two different periods [previous, 1969–1996 (8) *vs.* current cohort, 1997–2004] in the same institution was listed in *Table 2*. We could conclude epidemiological and pathological findings were almost unchanged, as was the poor prognosis of patients with TC. By contrast, 5-year OS of B2 and B3 thymoma patients improved substantially.

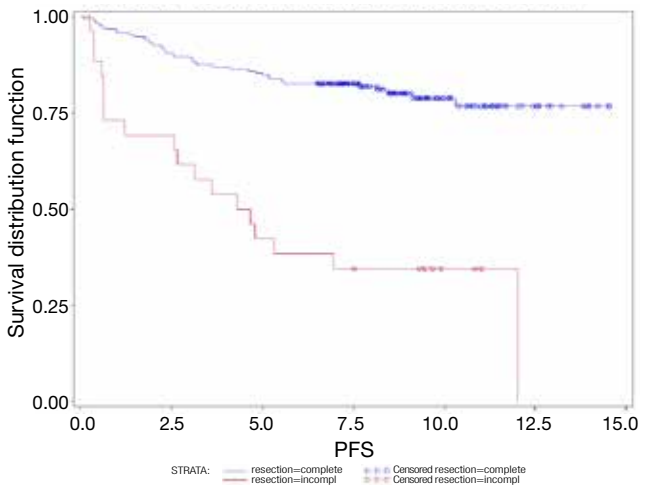

Figure 3 PFS of A, AB, B1, B2 and B3 thymomas and TCs by resection status. Total number of cases was 241 (complete resection: n=206; incomplete resection: n=35). PFS, progression free survival; TCs, thymic carcinomas.

Discussion

In 2002, colleagues of SCH reported 200 patients with TETs treated between 1969 and 1996 (8). To address whether characteristics and survival of TET patients changed since then, we studied a consecutive, non-overlapping cohort of 241 patients with thymoma and TC treated in SCH between 1997 and 2004.

Table 2 Comparison of a previous and more recent ("current") cohort of patients with thymomas (WHO type A–B3) and TC treated in the SCH

Histotype	Type A (%)		Type AB (%)		Type B1 (%)		Type B2 (%)		Type B3 (%)		TC (%)	
	P.	C.	P.	C.	P.	C.	P.	C.	P.	C.	P.	C.
Frequency of subtype	4	5	34	31	9	7	20	19	14	14	19#	24#
Stage III + IV	12	8	4	3	18	0	59#	37#	59	67	83	80
RO resection	NA	92	NA	99	NA	94	NA	NA	NA	88	NA	60#
MG+	25	8	8#	19#	18	11	38	43	30	21	3	2
(Neo-)adjuvant therapy*	43#	75#	43#	66#	43#	72#	25#	78#	25#	97#	25#	90#
5-year OS	100	100	100	100	94	94	75#	84#	70#	90#	48	48

P. C.: previous [1969–1996] (8) compared to current cohort [1997–2004]. *, in the previous study (8) patients received only adjuvant therapies (radiotherapy, chemotherapy or radiochemotherapy) and only average frequencies of adjuvant therapies were reported: 43% for the group of A, AB and B1 thymomas, 25% for B2 and B3 thymomas and TC. #, percentages indicate (I) significant (P<0.05) differences between the previous and current cohorts; and (II) the significant difference between the resection status of current TCs and current thymomas. NA, data not available in ref. (8). TCs, thymic carcinomas; SCH, Shanghai Chest Hospital; MG, myasthenia gravis; OS, overall survival.

Spectrum of thymic epithelial tumors (TETs)

Unlike some reports which found type A and B1 thymomas were highly prevalent (3,10), WHO AB, B2, B3 thymomas and TCs were the predominant tumors in the current and previous study from SCH (8) as well as in most other series (9,11-13). This is at variance with other.

Gender distribution

Male predominance among TC patients (P=0.00) was also found by the previous study from SCH (8) and most other series (14). The thymoma subtypes in the current and previous study from SCH (8) and elsewhere (9) showed no gender difference.

Myasthenia gravis (MG) association

The difference in prevalence of MG in series from different centers likely reflects recruitment bias. Since SCH is a specialized hospital and do not have a neurology department, prevalence of MG among TET patients has been low in the previous (15%) (8) and current series (18.7%). Nevertheless, the higher prevalence of MG in type B2 and B3 compared with other subtypes echoes findings from virtually all other published series (8,9,13-15). Presence of MG was associated with better survival in univariate analysis. This result is opposite to that of the previous SCH cohort (8) but similar to that of Strobel (13). Improved diagnosis and management of MG during recent decades and earlier detection of MG+ thymomas might have contributed to this effect (13).

Histotype and tumor stage

The majority of patients with A and AB thymomas were in Masaoka stage I or II, while Masaoka stages III and IV were seen mainly in B2 and B3 thymomas and TCs. This association was observed by most researchers previously (8,10-18). Stage III and IV TC were as frequent in the current (80%) as in the historical cohort (83%) (8), ruling out the potential selection bias and assuring the consistently poor prognosis of TC. By contrast, there were more stage I (50%) and less stage III (28%) B2 thymomas in the current series than the historical cohort (stage I: 28% and III: 49%) (8) suggesting earlier tumor detection. The latter could be due to the particularly high association of B2 thymoma with MG which might have led to earlier detection of the disease (13).

Survival related parameters

Histotype and survival

Like many previous studies, we observed an association between histological subtype and survival (6,8,14,16,19). The well-known (8,13) excellent prognosis of A and AB thymomas was confirmed. Nevertheless, they should be considered as tumors of low malignant potential, since lethal A and AB thymomas have been reported (6,7,11,17,18,20). OS was significantly better in thymomas than TCs, while differences between B1, B2 and B3 thymomas were not significant. The latter finding is different from that of the previous study from the SCH (8). Furthermore, OS of recent B2 and B3 thymoma patients was better (80% and 94%, respectively) than that of their historic counterparts (75% and 70%, respectively) (8,21). Both observations could be related to the higher number of low stage B2 thymomas in the recent cohort and broader use of (neo-)adjuvant therapies in B2 and B3 thymomas (see below). B2, B3 thymomas and TCs were clearly malignant, while B1 thymomas behaved in an intermediate way between type A/AB and B2/B3 thymomas.

Tumor stage and survival

As in most literature (10,12,14,16-18,22), OS of previous (8,21) and current patients with stage III and IV disease was significantly worse than OS of patients with stage I disease, while there was no significant difference between stage I and II and between stage III and IV tumors. Among stage I and II tumors, OS of TCs was significantly worse than that of thymomas, while there was no difference among thymoma subtypes. Among stage III and IV tumors, OS of B3 thymoma patients was still better than of TC.

Similar to the previous series (8), OS of current B2 thymoma patients was different in lower-stage (I, II; 1 of 29 patients died) and advanced stage tumors (III, IV; 9 of 17 patients died) (P=0.00). By contrast, and against a background of improved OS, this difference was not significant in current B3 thymoma patients (1 of 11 stage I/II versus 4 of 22 stage III/IV patients died). OS of TCs patients were not associated with tumor stage, however, even stage I and II TC patients showed poor outcome. This reflected unique biological features of TCs, as already suggested by genetic (23,24), immunohistochemical (19) and functional studies (25).

Tumor size and survival

Multivariate analysis suggested that tumor size was not an independent prognostic factor for OS. This result appears

different from that of Wright *et al.* (26), who described an association between size and recurrence. Tumor diameters were not recorded in the previous SCH study (8), therefore we do not know whether TETs in the current series were detected at a smaller size. Unspecific symptoms or tumor markers herald only advanced tumors, while specific markers (e.g., autoantibodies) may help identify thymomas but not TCs (13,27).

Resection status and survival

Resection status was not mentioned in the previous paper (8), but reported in subsequent paper (21). Complete resection has been reported as prognostic factor of TETs (9,13,16,21) as confirmed here by univariate but not multivariate analysis. However, when (neo-)adjuvant treatment was omitted from the Cox regression analysis, resection status became a significant variable (P=0.025), suggesting a correlation between positive margins and use of (neo-)adjuvant interventions. Complete resection was associated with improved OS in patients with B2 and B3 thymomas and TCs (P=0.0366; P=0.0863; and P=0.0196, respectively). Only after complete was OS of B2 or B3 thymomas statistically different from OS of TCs (P<0.0001 and P=0.0848, respectively).

Adjuvant and neoadjuvant treatment and survival

Compared to surgery as the only treatment, postoperative combined chemoradiation, adjuvant chemotherapy alone, and neoadjuvant approaches but not postoperative radiation alone (see below) were associated with improved OS in TETs patients. However, the current and historical patients with A, AB and B1 thymomas showed almost 100% OS irrespective of adjuvant therapies. For unknown reasons, adjuvant therapies were used more frequently in current than historical A, AB and B1 thymoma patients. In fact, it has already been widely accepted that adjuvant therapies might be of no benefit in stage I and II thymomas (28). Therefore, almost all current A, AB and B1 thymoma patients who received adjuvant therapies were apparently overtreated.

The insignificant association between postoperative radiotherapy and OS might also be due to the fact that 62 of 122 patients with postoperative radiotherapy had A, AB and B1 thymomas and excellent survival irrespective of adjuvant treatment. In the other 60 B2, B3 thymomas or TC patients who received radiation, OS was not significantly different from OS of the 17 patients treated by surgery alone. But it is difficult to reach definite conclusion due to the small case number. Prospective clinical trials are needed to define the role of adjuvant radiation in stage III thymoma and TC patients.

The significant association between (neo-)adjuvant therapies and improved OS was mainly attributable to better OS in B2 and B3 thymomas. This finding confirms the association between the use of (neo-)adjuvant therapies and improved OS of B2, B3 thymoma patients in our historical cohort (8). These identical observations in two independent cohorts are in line with the finding that broader use of (neo-)adjuvant therapy in recent (97%) compared to historical (~25%) but otherwise similar B3 thymomas from the SCH was associated with better OS. Similar conclusion in B2 thymomas is less safe, since their improved OS was associated not only with intensified (neo-)adjuvant therapy but also with more stage I and II tumors. The hypothetical favorable effect of (neo-)adjuvant therapy would also explain the surprisingly better 5-year OS of current B3 (OS 90%) compared to current B2 thymoma patients (84%): 97% of the former received (neo-)adjuvant treatment, compared to 78.2% of the latter. Obviously, we cannot exclude that better anesthesia, surgery and postoperative care contributed to the better outcome of current B2 and B3 thymoma patients. However, if these factors were of critical relevance, one would expect a similar improvement of OS in the current patients with TCs—which was not the case: in spite of much broader use of (neo-)adjuvant therapies, the 5-year OS of recent TC patients remained at the historical level of 48%. Therefore, we cautiously prefer the interpretation that recent B3 (and maybe B2) thymoma patients profited from the broader use of (neo-)adjuvant approaches, while there was no benefit for TC patients. Consequently, the effect of (neo-)adjuvant therapies in stage III and IV thymomas needs to be confirmed by prospective randomized trials. Considering the poor effects of intensified adjuvant treatments and infrequent use of neo-adjuvant therapies in the current (14%) and historical (0%) cohorts, neo-adjuvant or other innovative approach (e.g., target therapy) may be more preferable in TC patients.

In summary, we found that prognosis of stage III and IV, B2 and B3 thymomas at a single institution improved during the last decade, in parallel with the broader use of adjuvant chemotherapy or combined chemo-radiation. By contrast, the poor outcome in TCs remained unaltered in spite of the same broader use of adjuvant therapies, suggesting that neo-adjuvant and innovative strategies should be tested in these patients.

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None.

Footnote

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

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Thymic epithelial tumors in a worldwide perspective: lessons from observational studies

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Progress in the understanding of thymic epithelial tumors (TET) are expected by improvement in tumor management as well as from discoveries in biological sciences. The data provided by the routine activity in health care of patients are as precious as the most advanced molecular investigation in tumor research. Therefore the recent JTD issue authored by the Chinese Alliance for Research in Thymomas (ChART), focused on thymic epithelial malignancy and covering a vast majority of clinical issues on these rare tumors, provides a summary of a longstanding experience on TET from the perspective of an authoritative scientific society/collaborative research group. Among the papers included in the ChART issue focusing on TET, an interesting paper from Zhu *et al.* is referring on the evaluation of clinicopathological features and outcome indicators in a TET series occurred at the Shanghai Chest Hospital (SCH) (1). The paper also discuss and compares the current findings with the previous results of a clinicopathological study on a 200 case cohort from the same Institution, published in 2002 (2). The "resection status" of the cases included in the study from Fang *et al.* was published in 2005 (3). Therefore we aim to comment here shortly the 2 case cohorts (the present and the historical cohort) together with the surgical report on the "R" status; in addition we considered for comparison other studies derived from other areas of the world, provided by single Institutions or based on large multicenter databases (DBs) dealing with clinicopathological and prognostic features in TET.

TET management at the Shanghai Chest Hospital

The present cohort (1) provides a detailed profile of 241 TET patients treated during 1997–2004, with a mean follow-up time of 6.4 to 14.5 years (median: 7.8 years). The centralized pathological review of the series has been performed on the basis of the 2004 WHO classification (4), involving the SCH Pathology Staff and one Pathologist (Prof. A.M.) who was also co-Author in the previous study (2). In the present cohort the WHO histological subtype, Masaoka stage and neoadjuvant treatment have been found independent determinants of overall survival (OS) in patients with thymomas and thymic carcinomas (TCs). It is worth to note that the two cohorts, the previous and the current, show very similar histotype distribution, with a slight increase in the TC percentage in the present cohort (*Table 1*) (24% *vs.* 18%). We noticed that in the current series no "combined" TET, such as described in the 2004 WHO classification, have been reported. Also the Stage distribution is rather similar in the two cohorts (*Table 2*). As an interesting feature, both series show a high percentage of cases detected in Stage I according to Masaoka (9): 48%. In Stage III and IV a definite increase of B2 and B3 thymoma was actually found in comparison with the other histological types, stage III disease representing the prevailing esordium of TC [*Table 1* in the original article, (1)]. The "resection status" of the present series was compared with the "R" status from the previous cohort (3): the R0 was reached in similar percentage (88 % *vs.* 85%) (1,2). In the historical

Table 1 WHO distribution of TET reported in the papers commented here

WHO type	Chen *et al*. (1969–1996), 2002, No. [%]	Zhu *et al*. (1997–2004), 2016, No. [%]	Harnath *et al*. (1966–2004) modified, 2012, No. [%]	Wang *et al*. (1992–2012) modified, 2016, No. [%]	Huang *et al*. (2000–2010), 2014, No. (%)	Ruffini *et al*. (1990–2010), 2013, No. [%]
Histotype						
A	8 [4]	12 [5]	10 [11]	107 [6]	497 [10]	–
AB	68 [34]	74 [31]	15 [16]	436 [24]	1026 [20]	–
B1	17 [8]	18 [7]	8 [9]	232 [13]	737 [14]	–
B2	39 [19]	46 [19]	17***[18]	297 [16]	1273 [25]	–
B3	27 [14]	33 [14]	19*** [20]	363 [20]	894 [17]	–
C*	36 [18]	58 [24]	15*** [16]	370****[20]	602 [12]	–
NETT	–	–	–	–	–	–
Others**	5 [3]	–	–	–	102 [2]	–
Not classified	–	–	9 [10]	–	–	–
Total	200	241	93	1,805	5,131	2,030
Histotype grouping						
A-AB-B1	93 [48]	104 [43]	33 [39]	775 [43]	2260 [45]	1018 [50]
B2-B3	66 [34]	79 [33]	36 [43]	660 [37]	2167 [43]	780 [38]
C*	36 [18]	58 [24]	15 [18]	370 [20]	602 [12]	191 [9]
NETT	–	–	–	–	–	41 [2]
Total	195	241	84	1,805	5,029	2,030

The data reported in this Table have been collected in order to allow a comparison of similar indicators. However the studies show some differences in the modality of data aggregation, therefore few modifications/clarifications have been made as it follows: in the first part of *Table 1* five papers could be compared (11 lines); in the second part of the *Table 1* (lines 12-17) six papers have been compared basing on the histotype aggregation reported in the ESTS paper (Ruffini *et al*., 2014) (5): for the other papers a similar subtype aggregation has been performed (1,2,5-8). *, all subtypes of thymic carcinomas; NETT: Thymic neuroendocrine tumors as mentioned in ref 5; **, rare thymomas not mentioned in the WHO, Micronodular and Metaplastic thymoma; ***, B1 + B2 (3 cases) were grouped in B2, B2 + B3 (13 cases) were grouped in B3, B3 + thymic carcinoma (1 case) was grouped in C; ****, carcinoid (45 cases) were not included.

Table 2 Stage distribution of TET as reported in the papers commented here

Masaoka staging	Chen *et al*. (1969–1996), 2002 (2), No. [%]	Zhu *et al*. (1997–2004), 2016 (1), No. [%]	Harnath *et al*. (1966–2004) modified, 2012 (7), No. [%]	Wang *et al*. (1992–2012) modified, 2016 (6), No. [%]	Huang *et al*. (2000–2010), 2014 (8), No. [%]	Ruffini *et al*. (1990–2010), 2014 (5), No. [%]
I	96 [48]	115 [48]	28 [32]	743 [40]	1582 [32]	672 [34]
II	26 [13]	38 [16]	29 [32]	360 [19]	1565** [31]	699 [35]
III	65 [33]	74 [31]	29 [32]	574 [31]	1167 [23]	410 [21]
IV	13 [7]	14 [6]	5 [5]	173 [9]	673** [13]	215 [11]
Total	200	241	91*	1,850***	4,987	1,996*

*, missing information for 2 patients in Harnath *et al*., missing information for 34 patients in Ruffini *et al*.; **, II a and II b were grouped in stage II, IV a and IV b were grouped in stage IV; ***, also carcinoid were considered (1,2,5-8).

cohort, including cases occurring from 1969 to 1996 (mean follow-up time of 15 years, range, 1–246 months), most of them only surgically treated, tumor stage was the most important determinant of survival and the WHO histologic subtype was found to be an independent prognostic factor in Stage I and II, among which WHO Type A, AB, and B1 thymomas formed altogether a low-risk group. Patients with high-risk TET were indicated as possible target for novel adjuvant radiochemotherapy regimens. It should be pointed out that these two categories—low and high risk group thymomas diagnosed on the basis of the 1999 WHO classification (10)—were first mentioned in this paper. By comparison with the historical cohort, the prognosis of patients with B2 and B3 thymoma in the present series (1) has improved, probably partly due to the increased application of adjuvant therapies. However, the prognosis of patients with TCs remained unsatisfactory. The findings suggested that neoadjuvant treatment protocols should be improved. In the same issue of *JTD* Wei *et al.* (11) provide their experience in the induction therapy with thymomas and TCs in the framework of the ChART database (DB) (derived from several tertiary centers in China), reporting detailed informations on thymoma downstaging. Further data on the criteria to neoadjuvant therapy adoption and a treatment algorithm have been recently presented (12), and could be discussed among the health care professionals involved in TET care all around the world.

In the present cohort (1), the 5-year OS according to Masaoka stage of Thymoma and TC was 59% and 50%, respectively. The 5-year OS of patients with A, AB, B1, B2, B3 thymomas and TCs reported were 100%, 100%, 94%, 80%, 94%, and 45% respectively. As far as progression free survival (PFS) is concerned, the 5-year PFS were 100%, 96%, 78%, 80%, 78% and 39% (for PFS data were available for 217 cases out of 241). OS and PFS were significantly different between thymoma and TC patients. By contrast, no significant differences in OS nor PFS were found among B1, B2 and B3 thymoma patients. Similarly, PFS of A and AB thymoma patients showed no significant differences. The association between disease progression and histological type, as well as between outcome and histological types, were highly significant. Thus a possible future study focused on the same series might concern the relapsed cases and their treatment. As far as the historical cohort (2) is concerned, it should be pointed out that the paper from Chen *et al.* in 2002 was one of the two papers (13) first evaluating TET with the tool of the 1999 WHO classification addressing the pathological review of all cases, and providing data on its prognostic value. Nowadays the situation is changed, as the WHO classification, although debated, has gained general wide acceptance, through the 2004 and the 2015 editions (4,14). A worldwide collaboration among health care professionals has been established also due to the activity of the International Thymic Malignancy Interest Group (ITMIG), promoting collaboration and workshops on refinements of diagnostic criteria as well as several studies dealing with TET Staging and treatment (15,16).

TET observational studies: comparison with other series

It would be impossible to comment here the whole amount of clinicopathological data on TET series recently provided by several Institutions and clinical researchers from all around the world. Therefore we aimed to comment briefly the findings provided in the present (1) and from the historical cohort series (2) with preliminary data from the ChART database including 18 centers in China, presented in the same issue of *JTD* and addressed on the Myasthenia Gravis (MG) occurrence in a 1,850 case cohort (6), with the findings deriving from an European series described by Harnath *et al.*, in 2012 (7), with data from the European Society of Thoracic Surgeons (ESTS) (5), and finally with those from the ITMIG retrospective DB reported by Huang *et al.* (8), concerning the first aggregated data in a worldwide-based case series. Moreover a very complex analysis of the histotype impact of a large Thymoma series has been furtherly reported on the basis of the ITMIG retrospective DB (17), however, TC cases were not included in this series and therefore a direct comparison of data was not possible here.

Thus, referring to an overview of histological profile distribution, in the preliminary data assembly of the ITMIG retrospective DB, six hundred two (602 cases) TCs were reported out of 5,131 TET cases, corresponding to 12% of tumors (8), therefore in line with other reports but slightly fewer than in the paper from Zhu *et al.* (*Table 1*). By comparison, in the ESTS series (*Table 1*) (15), the reported incidence for TC was 9% with comparison to the SCH series (18% for the historical and 24% for the present cohort); in the Harnath series there were 15/93 (16%) TCs. In the ITMIG aggregated data, neuroendocrine tumors were not included (18). Similarly, we didn't included neuroendocrine neoplasms in our comments to other studies discussed here. Thus, at first glance, a slightly

higher incidence of TC cases is suggested from Chinese data with respect to European cases and in the worldwide ITMIG retrospective DB. A male prevalence of TC cases was found by Zhu *et al*., and the same finding was reported by the ITMIG DB, whereas other series did not showed prevalence of the male gender in TC cases. This observation could foster further studies on the incidence of TC and on the related pathogenetic factors in China. By histological subgroupings, which showed prognostic value (2,13,19,20), no relevant change in the risk group distribution in the cohorts considered was found by comparing the ESTS DB with other cohorts (*Table 1*). Myasthenia gravis (MG) was less frequent in the SCH series, as already discussed by the Authors, because the SCH doesn't have a referral Neurology department. However, the presence of MG was associated with improved survival in the present cohort, similarly to the findings reported by Ströbel *et al.* (19). As already mentioned, not only the SCH series, but also the ChART series shows a high percentage of cases detected in Stage I according to Masaoka (48% in the SCH series, and 40% in the paper from Wang *et al.*) (*Table 2*).

Conclusions

Observational studies provide several relevant informations also in the evaluation of rare tumors. Thanks to the recently growing attention to TET, cohort studies were often reported, providing amount of data useful to detect prognostic factors and in promoting progresses in treatment. The centralized pathological review of the Institutional series is an essential prerequisite, although large DB-derived series usually do not receive a pathological review due to its complexity and to the still limited diffusion of telepathological tools. Nevertheless, it appears that in the last fourteen years a considerable progress has been achieved in diagnostic and therapeutical approaches to TET, and high level care standard has been achieved. Among factors influencing this progress there are the technological surgical improvement and the standardization of care. A substantial improvement is certainly due to the increasing spontaneous collaborative efforts in the multidisciplinary team involved in TET care, as evident from the ChART activity. An important input was also given by the worldwide diffusion and promoting capability of ITMIG and of its collaborative projects. However, from the present, although limited, review of retrospective data it appears that probably genetic and/or environmental factors could play a role in contributing to the history of TET patients. Progress in understanding the biology of the disease in different ethnographic frameworks and genetic contexts should be considered prioritary. Molecular data and—among these—the upcoming results of the Cancer Genome Atlas of Thymoma (TCGA-THYM) (https://tcga-data.nci.nih.gov/tcga/) are expected to provide relevant findings on the oncological pathways involved and on somatic changes in neoplastic *vs.* normal tissues. However, observational studies still constitute the fundament of any cancer research, by providing the "basic datasets" for molecular correlations and therapeutical developments.

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Footnote

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Pretreatment biopsy for histological diagnosis and induction therapy in thymic tumors

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Background: This study was to investigate the value of pretreatment biopsy for histological diagnosis and induction therapies in the management of locally advanced thymic malignancies.

Methods: The clinical pathological data of patients with thymic tumors in the Chinese Alliance for Research in Thymomas (ChART) who underwent biopsy before treatment from 1994 to December 2012 were retrospectively reviewed. The application trend of preoperative histological diagnosis and its influence on treatment outcome were analyzed.

Results: Of 1,902 cases of thymic tumors, 336 (17.1%) had undergone biopsy for histological diagnosis before therapeutic decision was decided. In recent years, percentage of pretreatment histological diagnosis significantly increased in the later ten years than the former during the study period (P=0.008). There was also a significant increase in thoracoscopy/mediastinoscopy/E-BUS biopsy as compared to open biopsy (P=0.029). Survival in Patients with preoperative biopsy for histology had significantly higher stage lesions (P=0.000) and higher grade malignancy (P=0.000), thus a significantly lower complete resection rate (P=0.000) and therefore a significantly worse survival than those without preoperative biopsy (P=0.000). In the biopsied 336 patients, those who received upfront surgery had significantly better survival than those received surgery after induction therapy (P=0.000). In stage III and IVa diseases, the R0 resection rate after induction therapies increased significantly as compared to the surgery upfront cases (65.5% *vs.* 46.2%, P=0.025). Tumors downstaged after induction had similar outcomes as those having upfront surgery (92.3% *vs.* 84.2%, P=0.51). However, tumors not downstaged by induction had significantly worse prognosis than those downstaged (P=0.004), and fared even worse than those having definitive chemoradiation without surgery (37.2% *vs.* 62.4%, P=0.216).

Conclusions: It is crucial to get histological diagnosis for thymoma before surgery or adjuvant treatment and minimally invasive biopsy should be undertaken. Although in our study we could not find the benefit of induction chemotherapy before surgery in survival and recurrence rate, it could increase the R0 resection rate compared with direct surgery in late stage (III and IVa).

Keywords: Thymoma; histology; surgery; prognosis; biopsy

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Introduction

Thymic malignancies are one of the most common tumors in the anterior mediastinum, accounted for about 17%~30% of all mediastinal tumors. Thymomas are hard to study because of their relatively indolent nature. Thymic carcinomas are more malignant in behavior but even rarer in incidence. Surgical resection is considered the mainstay of treatment for early stage thymic tumors, and complete resection renders favorable long-term outcome. However, prognosis of locally advanced tumors, especially those unresectable lesions, remains unsatisfactory (1,2). So far, there has been no large sample prospective randomized controlled study concerning thymic tumors. In addition to the widely accepted Masaoka surgical-pathologic staging, the World Health Organization (WHO) histological classification is another potential prognostic factor for thymic tumors and thus should also be taken into consideration in clinical decision making, especially in advanced stage tumors (3,4). Biopsy for histological diagnosis is sometimes necessary for therapeutic decision making, especially for choosing potential induction therapies, or to rule out other malignancies in the anterior mediastinum.

In this study, we retrospectively analyzed the clinical pathological data of the patients with locally advanced tumors using the Chinese Alliance for Research in Thymomas (ChART) retrospective database. We investigated the use of preoperative biopsy for histological diagnosis, its impact on management mode and outcome, to provide useful information for future clinical research and practice.

Materials and methods

Clinical pathological data of 2104 patients treated between 1994 to 2012 were retrieved from the ChART retrospective database. After excluding 202 cases with unknown biopsy status, 1902 patients were included in the study. The use of pretreatment histological diagnosis and its influence on management mode and prognosis of patients were analyzed.

Histologic classification was assessed according to the 2004 WHO classification system (5). Extent of disease was defined by Masaoka-Koga surgico-pathological staging (6).

There was no standard management policy during the study period at different institutions. After clinical evaluation, diagnosis and treatment was decided by the physician in charge according to their own expertise. For patients having biopsy, treatment mode included surgery upfront, surgery after induction therapy, or definitive chemo/radiotherapy without surgery.

All statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) software. Student's *t*-test was used to evaluate the continuous variables. The correlation between categorical variables was determined using Person χ^2 or Fisher's exact tests when appropriate. Survival analysis was established using the Kaplan-Meier method and compared with log-rank test. A P value <0.05 was considered to be statistically significant.

Results

The use of pretreatment histological diagnosis

Of the 1,902 patients, 336 (17.7%) underwent pretreatment biopsy for histological diagnosis, while the remaining 1,566 (82.3%) went directly to surgery. From 1994 to 2003, 30 (11.8%) patients had pretreatment biopsy for histological diagnosis. This increased to 306 (18.6%) patients in 2004–2012. The difference between these two time periods was statistically significant (P=0.008).

Of the 336 patients who had pretreatment biopsy, there were 192 males (57.1%) and 144 females (42.9%). The mean age was 46.6±14.1 years. Only 37 (11.0%) patients had concomitant myasthenia gravis (MG) upon presentation. Methods used for biopsy are shown in *Table 1*. 157 (46.7%) cases underwent needle biopsy, 129 (38.4%) cases underwent surgical biopsy through a small anterior chest wall incision, and 50 (14.9%) cases underwent thoracoscope/mediastinoscope/E-BUS biopsy. There was a significant increase in the use of minimally invasive approaches (thoracoscope/mediastinoscope/E-BUS) and decrease in open surgery for biopsy in the time trend (P=0.029).

Results of pathologic review of the biopsy specimen are shown in *Table 2*. Histological diagnosis was achieved in 89% of the cases, with only 37 (11%) in which a definite diagnosis could not be defined.

Kaplan-Meier survival analysis showed that 5- and 10-year overall survival rates for patients who underwent direct surgery without preoperative histological diagnosis were 89.5%, 82.2%, respectively. And 5- and 10-year overall survival rates for patients who underwent surgical treatment after preoperative histological diagnosis were 79.4%, 58.7%, respectively. The survival difference between these two groups was statistically significant (P=0.000, *Figure 1*).

Impact of preoperative histological diagnosis on treatment mode

Of the 336 patients, 190 (56.5%) cases went directly to

Table 1 Approaches for biopsy in different time period

Treatment time interval	No.	Needle biopsy (%)	Anterior chest wall incision biopsy (%)	Thoracoscopy/mediastinoscopy/ E-BUS biopsy (%)	P value
Total	336	157 (46.7)	129 (38.4)	50 (14.9)	0.029
2004–2012	306	140 (45.8)	116 (37.9)	50 (16.3)	
1994–2003	30	17 (56.7)	13 (43.3)	0 (0)	

Table 2 Histological diagnosis of biopsy according to WHO classification

WHO type	No.	Percent (%)
A	16	4.8
AB	49	14.6
B1	37	11
B2	39	11.6
B3	52	15.5
C	99	29.5
Carcinoid	7	2.1
Undefined	37	11

WHO, World Health Organization.

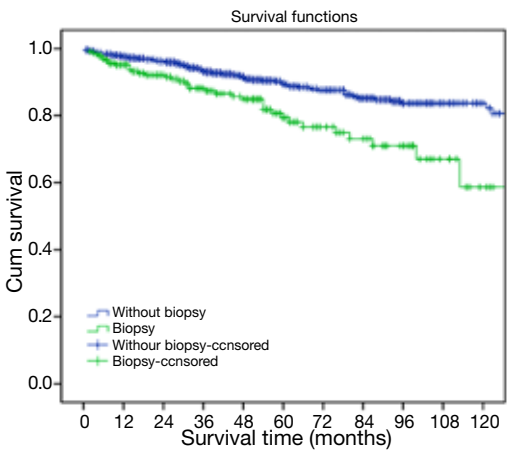

Figure 1 Survivals in patients with or without pretreatment biopsy for histological diagnosis.

surgical resection after biopsy, 58 (17.3%) cases underwent induction therapies followed by surgery, and 88 (26.2%) cases underwent definitive chemo/radiotherapy without surgery. Of the 18 patients with undefined diagnosis, 16 underwent surgical treatment directly and 2 had induction treatment followed by surgery.

From 1994 to 2003, Percentages of patients who had upfront surgery, induction therapy, and definitive chemo/radiotherapy were 40.0%, 36.7%, 23.3%, respectively. And in 2004~2012, the percentages were 58.2%, 15.4%, and 26.5%, respectively, showing a significant increase in upfront surgery and decrease in induction therapies (P=0.012).

Impact of preoperative histological diagnosis on the prognosis of patients

The tumor size was 7.8±3.0 cm in the 190 cases with upfront surgery and 7.9±2.9 cm in the 58 cases underwent induction therapy (P=0.696). Patients having induction therapies had significantly higher stage, higher grade tumors, and lower resection rate, as were shown in *Table 3* (P=0.000, P=0.016, P=0.000, respectively).

Since all patients in the induction group were over clinical stage III, we selected only stage III-IV patients who had upfront surgery after biopsy and compared them with patients treated with preoperative induction therapy. The results showed that there was a borderline significant difference in histological types, with a higher percentage of thymic carcinomas in the induction group. Patients receiving induction therapies had higher resection rate and lower final pathological staging, probably due to downstaging of their tumors (P=0.000, P=0.025, respectively, *Table 4*). Kaplan-Meier survival analysis showed that the 5-, 10-year overall survivals for patients underwent upfront surgery after biopsy were 84.2% and 53%, respectively. The 5-, 10-year overall survivals for patients underwent preoperative induction therapy were 53.5%, 26.2%, respectively. The difference was statistically significant (P=0.03, *Figure 2*).

Subgroup survival analysis

In order to further study the effect of surgical resection directly after histological diagnosis and surgical resection after preoperative inductive therapy on the prognosis, the patients were divided into different subgroups and stratified according to tumor stage, histology, and resection status.

Table 3 The relationship between preoperative histological diagnosis and clinical pathological characteristics of the patients in this group

Classification	No.	Purpose of histological diagnosis		P value
		Upfront surgery	Induction therapy	
Tumor size		7.8±3	7.9±2.9	0.696
Masaoka stage				0.000
I	88	81 (42.6%)	7 (12.1%)	
II	32	25 (13.2%)	7 (12.1%)	
III	93	60 (31.6%)	33 (56.9%)	
IV	35	24 (12.6%)	11 (19.0%)	
R resection				0.025
R_0	178	140 (73.7%)	38 (65.5%)	
R_1	22	19 (10%)	3 (5.2%)	
R_2	48	31 (16.3%)	17 (29.3%)	
WHO type				0.000
A + AB	62	59 (33.9%)	3 (5.4%)	
B1 + B2 + B3	93	70 (40.2%)	23 (41.1%)	
C + NETT	75	45 (25.9%)	30 (53.6%)	

WHO, World Health Organization; NETT, neuroendocrine thymic tumour.

Table 4 The relationship between preoperative histological diagnosis and clinical pathological characteristics of the stage III + IV patients in this group

Classification	No.	Purpose of histological diagnosis (%)		P value
		Upfront surgery	Induction therapy	
Masaoka stage				0.000
I	7	0 (0)	7 (12.1)	
II	7	0 (0)	7 (12.1)	
III	93	60 (71.4)	33 (56.9)	
IV	35	24 (28.6)	11 (19.0)	
R resection				0.025
R_0	77	39 (46.2)	38 (65.5)	
$R_1 + R_2$	65	45 (53.6)	20 (34.5)	
Pathology				0.095
Thymoma	73	47 (61.0)	26 (46.4)	
Thymic carcinoma	60	30 (39.0)	30 (53.6)	

No difference was statistically significant in all subgroups, except for patients with stage III tumors (P=0.003, *Table 5*). Overall survival for tumors not downstaged by induction therapies was only 37.2% at 5-year, significantly lower than those undergone direct surgery (P=0.004). For tumors downstaged by induction, however, overall survival was as high as 92.3%, similar to those receiving direct surgery (P=0.51, *Figure 3*).

Forty-nine patients were deemed inoperable and received definitive chemoradiotherapy. Their overall 5-year survival was 62.4%, significantly lower than those tumors downstaged and then resected after induction therapy (92.3%), but higher than those not downstaged by induction therapy (37.2%), as shown in *Figure 4* (P=0.08).

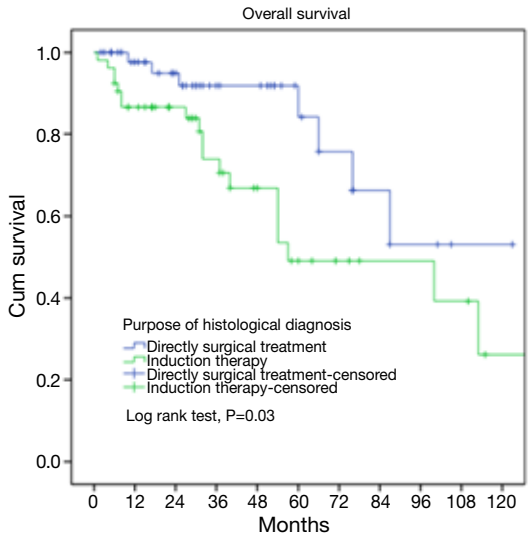

Figure 2 Survivals in patients who had induction therapy or upfront surgery after biopsy.

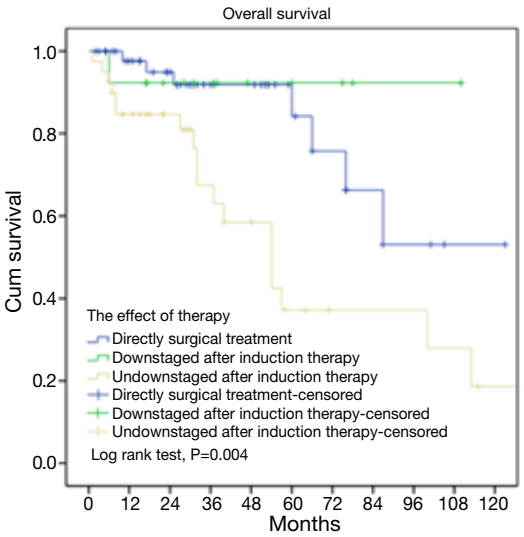

Figure 3 Survivals in tumors downstaged or not downstaged after induction therapy (subgroup) and those having upfront surgery after biopsy.

Table 5 Subgroup survival analysis

Characteristics	Overall survival (5-year OS)	P value
R_0		0.127
Preoperative induction therapy	0.557	
Surgical treatment directly	0.72	
$R_1 + R_2$		0.061
Preoperative induction therapy	0.225	
Surgical treatment directly	0.58	
Thymoma		0.084
Preoperative induction therapy	0.57	
Surgical treatment directly	0.87	
Thymic carcinoma		0.165
Preoperative induction therapy	0.36	
Surgical treatment directly	0.646	
Stage III		0.003
Preoperative induction therapy	0.325	
Surgical treatment directly	0.85	
Stage IV		0.595
Preoperative induction therapy	0.00	
Surgical treatment directly	0.559	

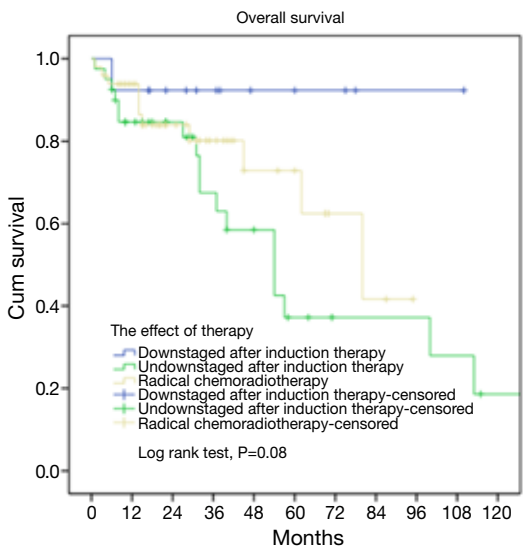

Figure 4 Survivals in tumors downstaged or not downstaged after induction therapy (subgroup) and those having definitive chemoradiotherapy.

Discussion

Thymic tumors are relative rare neoplasms, mostly seen in the anterior mediastinum. Because of the low incidence of this neoplasm, there is still much debate about the histological classification, the predictors and treatment. Histological typing established by the World Health Organization and the clinical staging system proposed by Masaoka are the most widely accepted. Both have been proved to be strongly related to patient survival (6). According to the morphology of the epithelial cells of the thymus and the amount of associated T lymphocytes, thymomas are classified as Type A, B, AB and C. Different Types have different biological behavior and thus should be managed differently. Although complete resection remains the key treatment of thymoma, chemotherapy and radiotherapy also play important roles, especially for advanced-stage diseases. There is evidence that a multimodality approach incorporating chemotherapy or chemoradiotherapy before surgery may improve respectability and outcomes in locally advanced thymoma (7). Also there are many other kinds of diseases in anterior mediastinum such as lymphomas and germ cell tumors. The treatment of these malignancies could be very different (8). It is thus crucial to get histological diagnosis for thymoma before surgery or adjuvant treatment.

Diagnostic material can be obtained by image-guided fine needle aspiration or core needle biopsy, surgical mediastinoscopy, thoracoscopy, or mini-thoracotomy. We retrospectively analyzed 336 patients undergone biopsy before treatment between 1994 and 2012. The biopsy rate in the latter nine years increased significantly from 11.8% to 18.6% compared with that in earlier ten years in the study period. While there was no significant difference either in tumor stage or histology between these two time periods, an increasing awareness of the importance of histologic information in therapeutic decision making could clearly be observed. And from the changing in biopsy methods, it is shown that minimally invasive concept was increasingly accepted.

However, it is intriguing that there was actually a decrease in the use of induction therapy but increase in upfront surgery. This was in correspondence with significantly higher percentage of thymomas, as opposed to thymic carcinomas, and stage I–II tumors in the upfront surgery group. Potential explanations may include an increased use of biopsy even in early stage tumors to rule out other malignancies such as lymphoma or germ cell tumors for which surgery should not be used as first-line therapy. In the meantime, there was also a marked increase along with time in the use of definitive chemoradiation, without surgery, for advanced stage disease.

There is no doubt that surgery remains the mainstay of thymoma treatment and complete resection should be pursued whenever possible. But in locally advanced tumors (Masaoka stages III and IVa) complete resection is not always feasible (9). It has been suggested that a multimodality approach incorporating chemotherapy or chemoradiotherapy before surgery may improve resectability and outcomes in locally advanced thymomas (7). Modh *et al.* (10) recently retrospectively reviewed 110 patients with Masaoka stages III to IVa invasive thymoma and found that aggressive treatment with chemotherapy, surgical resection, and postoperative radiation therapy might produce long-term survival for these patients with advanced disease. Cardillo *et al.* (9) presented a comparison between multimodality treatments in Masaoka stage III and IVa thymomas comparing 31 patients undergoing surgery after induction chemotherapy and 30 undergoing direct surgery. They showed induction chemotherapy to be an independent predictor of survival in locally advanced lesions (10-year survival: 57.9% *vs.* 38.1%). Similarly, in 56 patients in stage III, Lucchi *et al.* (11) found that neo-adjuvant treatment could be effective both in down-staging and increasing resectability and improving survival. Different from the above studies, Rea *et al.* (12) were unable to find any difference when they compared induction chemotherapy group and no induction group in 75 patients with stage III (n=51), IVa (n=18) and IVB (n=6) thymic tumors (10-year survival: 52% *vs.* 56%; P=0.54). But the two groups in that study were not comparable, with significant difference in tumor stage, completeness of resection and adjuvant therapies.

In our study, we did not found a benefit in survival with induction therapy prior to surgery in all patients after biopsy for histology diagnosis. The induction group showed significantly worse survival rate than upfront surgery group when all patients were included (5-year survival: 53.5% *vs.* 93.1% and 10-year survival: 26.2% *vs.* 85.1%, P=0.000). Selection bias clearly existed as there were significantly more (55.8%) early stage (I–II) diseases in the surgery upfront group, as opposed to a mere 24.2%, even after neoadjuvant therapies, in the induction group. Indeed in the current study, R0 resection rate after induction was still lower than the surgery upfront group (73.7% *vs.* 65.5%, P=0.025).

No doubt neoadjuvant therapy would most often be considered when preoperative workup indicates that complete resection may not be feasible (above stage III) (13).

For this reason, we chose to compare only patients with stage III–IV diseases in the upfront surgery group with the induction group. There were 24.2% patients downstaged to stage I/II after induction, and R0 resection rate was significantly higher than the upfront surgery group (65.5% *vs.* 46.2%, P=0.025). Our results were in consistency with several other reports indicating increased complete resection rate after preoperative induction therapy (14-16). Kim *et al.* conducted a prospective clinical trial in which patients with locally advanced thymoma received induction cisplatin, doxorubicin, cyclophosphamide, and prednisone, followed by surgery, radiation, and consolidation chemotherapy (17). Seventeen out of 22 patients had a radiographic response after chemotherapy. Kunitoh *et al.* evaluated weekly dose-dense chemotherapy (cisplatin, vincristine, doxorubicin and etoposide) followed by surgery and post-operative radiotherapy for patients in stage III diseases (18). Of the 21 eligible patients, 13 achieved a partial response and 9 underwent complete resection. Most chemotherapy regimens were cisplatin based. Dose-dense chemotherapy was not different from standard-dose chemotherapy (19). It is recommended that surgery be performed within 8 weeks of preoperative chemotherapy (20,21).

Unfortunately we failed to observe an overall survival benefit with induction therapy, in spite of the significant increase in resection rate. The 5- and 10-year overall survivals for stage III–IV patients receiving preoperative induction therapy were 53.5% and 26.2%, respectively, still significantly lower than those with upfront surgery (84.2% and 53%, P=0.000). In addition to the potential inherent bias (patients with resectable diseases tend to be selected for upfront surgery), a higher percentage of thymic carcinoma, which is known to be a higher grade malignancy than thymomas, may also help explain the lower survival in the induction group, even after early-stage tumors were excluded. Histological subtype is known to be related to outcome in thymic epithelial tumors. We previously reported that WHO histology was predictive of prognosis in thymic tumor patients after surgery (22). Okumura *et al.* (23) also reported that the average intervals from the initial resection to re-resection were 10.3, 7.8, 6.0, 2.4 and 2.6 years for patients with type AB, B1, B2, B3 recurrent tumors. And 20-year survival rate following initial resection of type B2 and B3 tumors was lower than that of type A, AB and B1 tumors which was more than 90%.

Based on this concern, we further compared those patients downstaged or not downstaged after induction with those having upfront surgery and those having definitive chemoradiation without surgery. We found that patients downstaged after induction had much higher 5-year overall survival than those not downstaged (92.3% *vs.* 37.2%, P=0.037). In fact the 5-year overall survival of those downstaged were similar to those received upfront surgery (92.3% *vs.* 84.2, P=0.51). For those not downstaged after induction, their 5-year overall survival was even worse than those who receive no surgery but only definitive chemoradiation (37.2% *vs.* 62.4%, P=0.216). These indicate that advanced stage thymic tumors would benefit from effective induction therapies by increased chance of complete resection and improved long-term survival. However, surgery has little value in advanced tumors that do not respond to induction therapies. Definitive chemoradiation may be a better choice in this subset of patients.

This study has the usual limitations of retrospective studies on a long time period, heterogeneous treatment modality, chemotherapy regimen and follow-up policy. However, we tried our best to rule out potential biases by stratified analysis in subgroups of patients. In view of the results, prospective randomized trials are warranted to further investigate the effectiveness of induction therapies based on histological diagnosis achieved by pretreatment biopsy.

In conclusion, it is crucial to get histological diagnosis for advanced stage thymic tumors before treatment decision is decided. Minimally invasive biopsy is playing an increasingly important role in this concern. Effective induction therapies based on biopsy proven histology may help increase complete resection rate and transfer into better long-term outcome. Future prospective studies on the optimal induction therapy would be necessary so as to improve the prognosis of advanced stage thymic tumors.

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Footnote

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Pretreatment biopsy for thymic epithelial tumors—does histology subtype matter for treatment strategy?

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Thymic epithelial tumors (TETs) originate from thymic epithelial cells and represent a heterogeneous group of malignancies including thymomas and thymic carcinomas. Thymomas are relatively rare tumors, with an estimated incidence of 0.13 per 100,000 person-years in the United States (US) (1). Thymomas are the most frequently encountered masses in the anterior mediastinum. However, differentiating thymomas from more malignant considerations such as thymic carcinomas, lymphomas, neuroendocrine tumors, malignant germ cell tumors and metastasis is important as the treatment approach can differ drastically (2). However, it is unclear if further defining the World Health Organization (WHO) histologic subtype of TET adds to the importance of clinical staging in deciding the treatment approach.

Brief summary of Chinese Alliance for Research in Thymomas (ChART) results

In this issue of the *Journal of Thoracic Disease*, Yue *et al*. report the value of pretreatment biopsy for TETs for histologic diagnosis and induction therapy (3). The ChART database was retrospectively reviewed, and included 1,902 patients treated from 1994 to 2012. Three hundred thirty-six patients (17.1%) had a pretreatment biopsy in this cohort. An increase in pretreatment biopsies was observed in the most recent time period reported [2004–2012]. Patients who underwent a pretreatment biopsy had significantly higher stage lesions and higher grade histology (P=0.000). When all patients who underwent preoperative biopsy were included, those who received induction therapy had a worse overall survival (OS) compared to those who had upfront surgical resection (5-year OS 53.5% *vs*. 93.1%, respectively; P=0.000). However, patients who were downstaged after induction therapy did not have a statistically significant different OS than those who received upfront surgical resection (5-year OS 92.3% *vs*. 84.2%, respectively; P=0.51). Patients who were not downstaged after induction therapy had a significantly worse 5-year OS than those who received upfront surgical resection (37.2% *vs*. 84.2%; P=0.004), and also had a trend for worse 5-year OS than those who received definitive chemoradiation (37.2% *vs*. 62.4%; P=0.216). These data suggest the potential importance of downstaging of an initially "unresectable" tumor prior to attempted surgery. The authors conclude "it is crucial to get histological diagnosis for advanced stage TETs before treatment decision is decided."

Review of current guidelines on preoperative biopsy for thymic malignancies

The National Comprehensive Cancer Network (NCCN) guidelines recommend that TETs are managed by an experienced multidisciplinary team. Tissue diagnosis is

recommended for clinically and radiographically suspected locally advanced unresectable TETs, with either a core needle biopsy or an open biopsy (with avoidance of a transpleural approach to prevent tumor seeding) (4). The NCCN also states that a surgical biopsy should be avoided if the diagnosis of thymoma is strongly suspected and it is resectable. These recommendations are in agreement with the European Society of Medical Oncology (ESMO) guidelines, which recommend either percutaneous core needle biopsy or surgical biopsy via mediastinotomy or mini-thoracotomy approach for suspected unresectable TETs (5). The International Thymic Malignancy Interest Group (ITMIG) has previously reviewed that biopsy can be obtained by multiple approaches including fine-needle aspirations (FNA), needle core biopsies, minimally invasive surgical techniques such as video-assisted thoracoscopic surgery (VATS) and mediastinoscopy, or more invasive surgical techniques such as a thoracotomy. The sensitivity for needle biopsies ranges between 43%–93% and the sensitivity is higher for surgical biopsies (6). Yue *et al.* did not address the factors that were associated with the performance of pretreatment biopsy for patients with TETs but focused on the factors that were associated with receipt of induction therapy *vs.* upfront surgical resection in patients who underwent preoperative biopsy. We would hypothesize there would be differences in patients who receive pretreatment biopsies compared to those who do not, including a higher proportion of advanced stage disease (III-IV) and thymic carcinoma. Since pretreatment biopsy is generally performed in more advanced disease, observing a difference in stage distribution could have relieved concerns of potential misclassification of this variable and any bias related to missing information. We do know that the patients who underwent preoperative biopsy had worse prognostic features indirectly since it was reported that patients who underwent upfront surgical resection with preoperative biopsy had a statistically significant worse OS than those who underwent upfront surgical resection without preoperative biopsy (5-year OS 79.4% *vs.* 89.5%; P=0.000). Interestingly, of the patients who underwent upfront surgical resection and had a preoperative biopsy, 56% were early stage. These early stage biopsies were potentially performed to rule out other competing diagnoses.

Increased use of biopsies in most recent time period in ChART database

Yue *et al.* reported that the percentage of pretreatment biopsies increased significantly in the most recent time period (2004–2012, 18.6% *vs.* 1994–2003, 11.8%; P=0.008). It should be noted that fewer patients were included in the database between 1994–2003 compared with the time period 2004–2012 (254 *vs.* 1,645 patients). The authors also observed that minimally invasive biopsies [thoracoscopy/mediastinoscopy/endobronchial ultrasound (EBUS) biopsy] were increasingly performed in the time period 2004–2012 (16.3% *vs.* 0%, respectively P=0.029) and there was a slight decrease in the performance of needle biopsies (45.8% *vs.* 56.7%, respectively.) When performing a pretreatment biopsy, disrupting the capsule of an early stage thymoma and inducing tumor seeding of the biopsy tract remains a concern (7). In the available literature, tumor seeding is reported at exceedingly low rates (7-9). However, biopsies violating the pleural space, such as VATS biopsy of an anterior mediastinal mass, should be avoided due to potential pleural seeding which has been reported (10,11). Thoracoscopic approaches were reported in ChART but it is unclear how many were performed since they were analyzed in conjunction with mediastinoscopy and EBUS.

The reason for increasing pretreatment biopsies is likely two-fold: (I) improved radiologic techniques for detection of invasion of tumor and evaluation of resectability with computed tomography (CT) (12,13), magnetic resonance imaging (14), and even positron emission tomography (PET) modalities (15) and (II) increasing use of minimally invasive surgical techniques (6). The use of these imaging techniques in the most recent time period may have identified more invasive disease and increased the use of biopsy. CT imaging with intravenous (iv) contrast is recommended by both the NCCN and ESMO guidelines for the diagnostic workup of a mediastinal mass suspicious for thymoma (4,5). CT use has spiked in the last decade due to its improvement in resolution and its ease of use for both physicians and patients. As a reflection of CT's widespread use, many publications warning of its radiation exposure were published in the mid-late 2000s (16,17). There have been several reports examining specific preoperative CT characteristics that predict for higher stage and/or resection status for TETs (18). This is critical since the mainstay of thymoma treatment is achievement of a complete (R0) resection as this has been the strongest independent prognostic factor for survival (19). MRI can also help with assessment of invasion and resectability when CT is equivocal (20). PET is not recommended by ESMO guidelines but is optional per NCCN guidelines (4,5).

Although some reports have shown CT characteristics to be associated with histology (18), PET is being increasingly used to assist with determination of histology, with thymic carcinomas having higher standard uptake value (SUV) than thymomas (21,22). There is no discussion of what imaging modalities were used prior to diagnosis in this study, but we expect it would be variable in such a large multicenter retrospective database. Imaging plays an integral role in whether or not to proceed with biopsy and other treatment decisions for TETs because of its ability to evaluate clinical Masaoka-Koga staging and potential resectability. However, the authors report there was no stage or histologic migration in these time periods, and therefore, the increased use of pretreatment biopsy may have been performed increasingly to rule out competing diagnoses.

Histologic findings in ChART cohort

A histologic diagnosis based on WHO classification could be achieved in 89% of patients' biopsy samples. Forty-seven percent only had a needle biopsy. TETs can be quite heterogeneous with 30%–50% having several histologies found in a single tumor after extensive sampling (23,24). ITMIG generally recommends caution in classifying WHO subtype on a FNA or biopsy specimen since it is usually not possible due to the heterogeneity. Also, the highest proportion of tumors in this cohort were thymic carcinomas (~30%), the rarest subtype of TETs, but this is expected as the majority of thymic carcinomas are advanced stage and unresectable at diagnosis (25).

Biopsy for patients with an anterior mediastinal mass and myasthenia gravis (MG)

A different approach could be taken for MG patients who have an anterior mediastinal mass. MG is an antibody-mediated disease of the neuromuscular junction in which a thymoma is found in 15% of patients (26,27), most commonly type B1, B2 and B3 thymoma. Approximately 30% of thymoma patients have concomitant MG. Because of this high correlation, performing a biopsy may not always be necessary for MG patients, even when a locally advanced suspected TET is seen on imaging (28). Yue *et al.* reported that only 11% of patients with pretreatment biopsy had concomitant MG upon presentation, which is much less than the expected 30% of patients.

Worse survival in patients with induction therapy—an issue of selection bias in a retrospective database study

Yue *et al.* reported that of the patients who had a pretreatment biopsy, 56.5% underwent upfront surgical resection, 17.3% induction therapy, and 26.2% definitive chemoradiation. In patients who had a surgical resection, the induction therapy group had worse OS compared to the upfront surgical resection group (5-year OS 53.5% *vs.* 93.1%, P=0.000). This is most likely because of selection bias as the authors acknowledge, with higher risk tumors more likely to receive induction therapy. In their discussion, the authors acknowledge examples in the literature with opposite findings of the induction therapy group either doing better or equivalent to the upfront surgical group (29-32). In the ChART cohort, patients who received induction therapy had a statistically significant higher stage and grade of tumors along with a lower complete resection rate, which are all poor prognostic features and could explain the worse OS. To address these biases, the authors examined 5-year OS stratified by resection status (R0 or R1/R2), histology (thymoma or thymic carcinoma), and stage (III or IV), with all strata favoring upfront surgical treatment numerically. The upfront surgical treatment group had a statistically significant improved 5-year OS in the stage III disease strata (85% *vs.* 32.5%; P=0.003). The improved outcomes of upfront surgical treatment in stage III disease could also be attributed to selection bias since stage III disease is heterogeneous, encompassing a spectrum of involved organs or vessels, some of which are more amenable to upfront surgical resection (i.e., pericardium or lung). When examining only pathologic stage III-IV disease in the upfront surgical resection group, there was higher stage and more incomplete resections but a lower proportion of thymic carcinomas compared to the induction therapy group. Despite this, the outcomes were still worse for those who received induction therapy *vs.* upfront surgical resection (5-year OS 53.5% *vs.* 84.2%; P=0.03). It is plausible that the higher proportion of thymic carcinomas could be driving the worse outcomes for the patients who received induction treatment. However, this is not definitive as the patients with thymoma also had a trend for worse outcome with induction therapy (5-year OS 57% *vs.* 87%; P=0.084). These subgroup analyses involving stratification of specific factors don't account for all potential confounding factors, since there is a strong correlation between Masaoka-Koga stage

and histologic subtype of TETs (33). A multivariate model adjusted for these factors may have assisted in estimating the true effect of induction therapy.

Induction therapy for stage III-IV TETs

In addition, the authors did not specify which kind of induction therapy patients received. However, another analysis of the ChART database in this issue of the *Journal of Thoracic Disease* describes the varied induction therapies in 68 patients, including 30 with preoperative chemotherapy, 9 with radiotherapy alone, and 29 with chemoradiation. Induction chemotherapy is currently recommended by ITMIG, NCCN, and ESMO (4,5,34) for the treatment of locally advanced TETs (35). The role of induction chemoradiotherapy has been demonstrated in pilot studies as it may enhance the response rate, however, it is currently not routinely recommended (36). Despite the recommendation from guidelines for induction therapy for locally advanced TETs, in ChART, 44.2% with stage III/IV disease underwent upfront surgical resection without induction therapy (4,5). Upfront surgery could be considered for the treatment of stage III TETs where there is macroscopic invasion of neighboring structures (i.e., lung, pericardium) if a complete resection is feasible (37). These patients can be treated with adjuvant radiotherapy to reduce the risk of local recurrences (29). This highlights that outcome data needs to be reported in relation to the use of adjuvant treatment, especially since 9% had R1 resection and 19% had R2 resection in the ChART cohort.

The importance of 'downstaging'

Of all the patients in the induction therapy group (all clinical stage III and higher), only 25% of patients were downstaged and the R0 resection rate was 65.5%. The complete resection rate is in line with other reports. Kim *et al*. reported that after cisplatin-based induction therapy in patients with stage III-IV TETs, 17 out of 22 patients had a major response and a R0 resection rate of 76% (38). Kunitoh *et al*. reported that after induction therapy in patients with stage III TETs, 13 of 21 patients achieved a partial response, and of those, 9 had a R0 resection (39).

Patients in the ChART cohort who were downstaged after induction therapy had a similar 5-year OS as upfront surgery patients. However, those who were not downstaged had worse outcomes than those who received upfront surgical resection and also a trend for worse outcomes than those who received definitive chemoradiation. The authors did not specify how downstaging related to resection status. Based on this data, however, if a clinical stage III or higher tumor is not downstaged, the benefit of surgery is questionable.

Does TET WHO subtype help us tailor therapy in preoperative setting?

Although we agree with the authors that TETs, particularly thymomas *vs*. thymic carcinomas, have different biologic behavior, other WHO subtypes are less important in the initial management of TETs. The first line therapies for induction treatment (and also in the palliative-intent setting) are platinum-based ± the addition of an anthracycline, irrespective of the TET WHO subtype. In our opinion, the authors could more strongly conclude the importance of stage and "downstaging" since it was the only factor that had a clear impact on outcome. WHO histology may be a surrogate for stage and analyses adjusting for stage may eliminate the importance of WHO histology as a prognostic factor (33).

Currently there are no biomarkers that allow for selection of therapy in the neoadjuvant or palliative setting, except for positive octreotide scan for use of octreotide (40), and the rare c-KIT mutation in thymic carcinomas for use of imatinib (41). Even targeted therapies like sunitinib and everolimus are in use in the palliative setting without a corresponding biomarker (42). The search for biologic agents in thymoma and thymic carcinoma has been challenging (43). However, when data becomes available from ongoing systematic genomic analyses of TETs (i.e., The Cancer Genome Atlas), targeted therapies could be a more effective induction therapy in the right subset of TETs, although the 70%–80% response rate achieved with chemotherapy will be difficult to surpass. In addition, with the recent detection of programmed-death receptor-ligand-1 in TETs (44), there may be a role for immune-based therapies, though development of this approach must be made with extreme caution given the high rates of autoimmune disease in patients with thymoma. We see the most important role for histological biopsies in advanced TETs for the exclusion of other malignancies rather than the identification of TET WHO subtype.

The authors should be commended on this work, which adds significantly to our understanding of the preoperative treatment of TETs. As the authors addressed, this study suffers from its retrospective design and thus well-known limitations. There was no uniform standard for the

chemotherapy regimen and incorporation of radiation therapy in the induction setting was not elucidated. Adjuvant radiotherapy after incomplete R1/R2 resection is important in eradicating residual disease and this was not addressed (5). It is unclear if patients underwent a thymectomy or a thymomectomy, which in some reports may affect clinical outcomes (45). The ChART database is of great value for better understanding TETs. It is only with the collaboration of multiple institutions internationally that we will be able to solve questions around the management of TETs. Prospective studies of an individualized neoadjuvant approach for TETs will be necessary when more molecular information becomes available.

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None.

Footnote

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

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Preoperative induction therapy for locally advanced thymic tumors: a retrospective analysis using the ChART database

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Background: To evaluate the role of preoperative induction therapy on prognosis of locally advanced thymic malignancies.

Methods: Between 1994 and 2012, patients received preoperative induction therapies (IT group) in the Chinese Alliance for Research in Thymomas (ChART) database, were compared with those having surgery directly after preoperative evaluation (DS group). All tumors receiving induction therapies were locally advanced (clinically stage III–IV) before treatment and those turned out to be in pathological stage I and II were considered downstaged by induction. Clinical pathological characteristics were retrospectively analyzed. To more accurately study the effect of induction therapies, stage IV patients were then excluded. Only stage I-III tumors in the IT group and stage III cases in the DS group were selected for further comparison in a subgroup analysis.

Results: Only 68 (4%) out of 1,713 patients had induction therapies, with a R0 resection of 67.6%, 5-year recurrence of 44.9%, and 5- and 10-year overall survivals (OS) of 49.7% and 19.9%. Seventeen patients (25%) were downstaged after induction. Significantly more thymomas were downstaged than thymic carcinomas (38.7% *vs.* 13.9%, P=0.02). Tumors downstaged after induction had significantly higher 5-year OS than those not downstaged (93.8% *vs.* 35.6%, P=0.013). For the subgroup analysis when stage IV patients

were excluded, 5-year OS was 85.2% in the DS group and 68.1% in the IT group (P=0.000), although R0 resection were similar (76.4% *vs.* 73.3%, P=0.63). However, 5-year OS in tumors downstaged after induction (93.8%) was similar to those in the DS group (85.2%, P=0.438), both significantly higher than those not downstaged after induction (35.6%, P=0.000).

Conclusions: Preoperative neoadjuvant therapy have been used only occasionally in locally advanced thymic malignances. Effective induction therapy leading to tumor downstaging may be beneficial for potentially unresectable diseases, especially in patients with thymomas. These findings would be helpful to related studies in the future.

Keywords: Thymic malignancy; induction therapy; surgery; survival

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Introduction

Until now, surgical resection remains the mainstay for the management of thymic tumors. Complete resection, along with Masaoka-Koga staging and WHO histologic classification, have been revealed as the most important prognostic factors. But for local advanced lesion (Masaoka-Koga stage III~IVa), complete resection is challenging and often not easily attainable. Although extensive procedures such as extrapleural pneumonectomy or reconstruction of superior vena cava are applied in some cases, complete resection is still difficult to achieve, and early recurrence often occurs. So the optimal treatment for local advanced thymic tumors is still controversial. Preoperative induction therapies have been tried before, with increased R0 resection rate and survival benefit in some cases. Because of the rarity of the disease and its relatively indolent nature, it is difficult, if not completely impossible, to reach any definite conclusion with single center experiences. We hereby retrospectively studied the effectiveness of induction therapies for locally advanced thymic tumors using the Chinese Alliance for Research in Thymomas (ChART) database.

Materials and methods

The ChART retrospective database included 2,104 patients treated at 18 tertiary referral centers in China from January 1, 1994 to December 31, 2012. Because only de-identified data were used for the study, informed consent was waived by IRB. After excluding cases with no detailed information in management, histology, or tumor staging, 1,713 cases were included for the study. Among them, 68 patients received preoperative induction therapies (IT group).

Pretreatment in the IT group were quite heterogeneous, decided by physicians in charge according to their own preference. These included different cycles of chemotherapy using CAP (cyclophosphamide + doxorubicin + cisplatin) or PE (etoposide + cisplatin) or Carboplatin + Paclitaxel regimens, radiation alone, or sequential/concurrent chemoradiation. Patients then proceeded to surgical resection based on the judgment of their physicians. The other 1,645 patients received surgical resection directly after preoperative evaluation (DS group). Clinical pathological features, resection status, and follow-up results of these two groups of patients were analyzed accordingly.

All tumors receiving induction therapies were locally advanced (clinically stage III–IV) before treatment and considered potentially unresectable. Thus, those staged as Masaoka-Koga stage I–II after surgery were considered downstaged by induction therapy. To more accurately study the effect of induction therapies, stage IV patients were then excluded and only stages I–III tumors in the IT group and stage III cases in the DS group were selected for further comparison in a subgroup analysis.

Statistical analysis was undertaken using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). A 2-sided P<0.05 was considered to be statistically significant. Variables were compared using the Mann-Whitney u test, Student *t* test, Chi-square test and Fisher exact test when appropriate. Survival curves were estimated using the Kaplan-Meier method, and the significance of the between-group differences was assessed with the Log-rank test.

Table 1 Percentages of preoperative induction therapy in two time periods, 1994–2003 and 2004–2012

Treatment period	Induction therapy, n (%)		Total, n (%)
	No	Yes	
2014–2012	1,430 (96.2)	57 (3.8)	1,487 (100.0)
1994–2003	215 (95.1)	11 (4.9)	226 (100.0)
Total	1,645 (96.0)	68 (4.0)	1,713 (100.0)

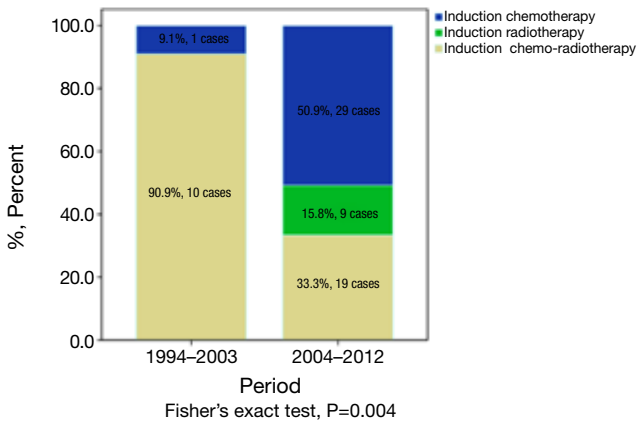

Figure 1 Mode of induction therapies in two time periods (1994–2003 and 2004–2012).

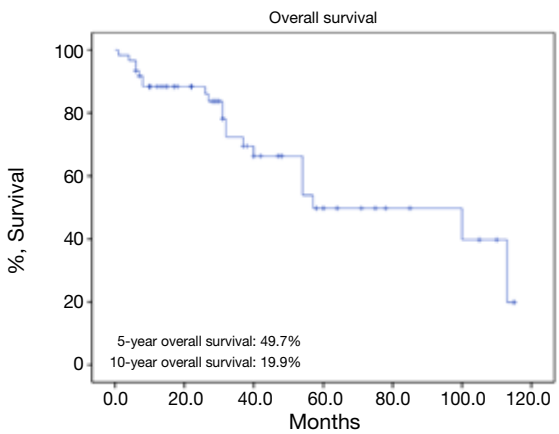

Figure 2 Five-year overall survival rate of patients in the induction therapy group.

Results

Among all 1,713 patients in the ChART retrospective database, only 4% [68] received preoperative induction therapy (*Table 1*). Altogether, 30 patients in the IT group received preoperative

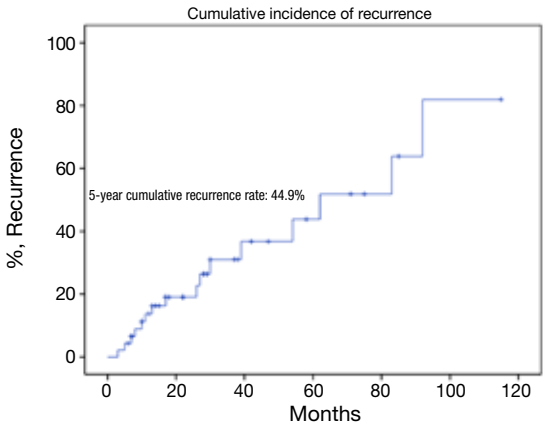

Figure 3 Five-year cumulative incidence of recurrence in the induction therapy group.

chemotherapy, 9 received radiotherapy alone, and 29 had chemoradiotherapy. There was no significant difference in the rate of induction therapies between the early or the later half time periods during the study (3.8% *vs.* 4.9%, P=0.458, *Table 1*). But some changes in the mode of induction therapies were observed, with increased use of chemotherapy or radiation alone but decreased use of chemoradiation in the latter period (*Figure 1*).

There were 43 male and 25 female patients in the IT group, with a mean age of 44.8±14.9 years. Five (7.4%) patients had concomitant myasthenia gravis upon presentation. Average tumor size was 8.1±2.9 cm. The complete resection rate was 67.6% in this group. Upon pathological examination, 9 (13.2%) and 8 (11.8%) tumors were downstaged to stages I and II, while 38 (55.9%) and 13 (19.1%) remained to be in stages III and IV. There were 2 (2.9%) WHO type A, 5 (7.4%) AB, 5 (7.4%) B1, 8 (11.8%) B2, 12 (17.6%) B3 thymomas, 34 (50%) thymic carcinomas, and 2 (2.9%) carcinoids in this group. Five- and 10-year overall survivals (OS) were 49.7% and 19.9%, with a 5-year cumulative incidence of recurrence (CIR) at 44.9% (*Figures 2,3*). Significantly more thymomas (38.7%) were downstaged after induction than thymic carcinomas and carcinoids (13.9%, P=0.02). Five-year OS in patients who had their tumors resected completely (R0, 58.2%) was higher than those with incomplete resections (R1 and R2, 19.6%). But the difference did not reach statistical significance (P=0.134, *Figure 4*). On the other hand, 5-year OS was significantly higher in those tumors downstaged by induction (93.8%) than those not downstaged (35.6%, P=0.013, *Figure 5*).

For the subgroup analysis Masaoka-Koga stage III patients in the DS group were compared with none stage IV patients in the IT group. There were 17 patients (30.9%)

downstaged to stage I or II in the IT group. Baseline features of the two groups were similar except for a lower rate of myasthenia gravis and higher percentage of thymic carcinoma and carcinoids in the IT group (*Table 2*). The two subgroups had similar tumor size and R0 resection rates (76.4% *vs.* 73.3%, P=0.63). Five-year OS was 85.2% in the DS group and 68.1% in the IT group (P=0.000, *Figure 6*).

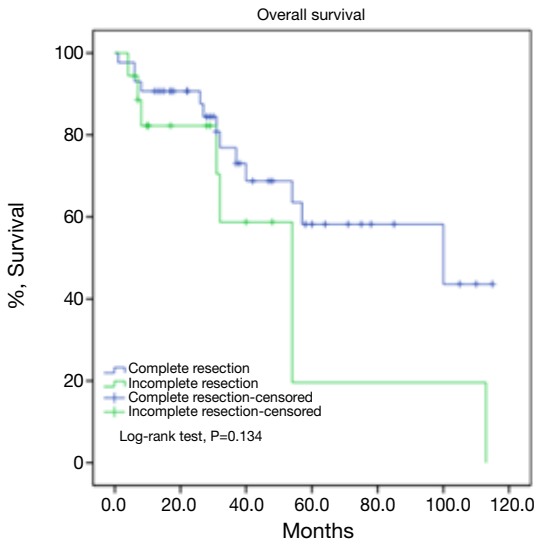

Figure 4 Five-year overall survivals after complete resection (R0, 58.2%) and incomplete resection (R1 and R2, 19.6%, P=0.134) in the induction therapy group.

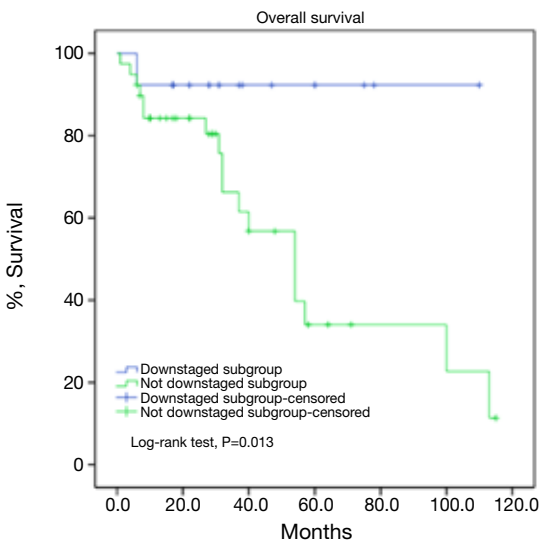

Figure 5 Five-year overall survivals in tumors downstaged or not downstaged after induction therapy (93.8% *vs.* 35.6%, P=0.013).

Table 2 Comparison of clinico-pathological features of the induction therapy group and the direct surgery group (not including stage IV diseases)

Variables	IT (n=55)	DS (n=499)	P value
Gender			0.941
Male	34 (61.8%)	311 (62.3%)	
Female	21 (38.2%)	188 (37.7%)	
Age (yr, mean ± SD)	45.3±14.7	51.6±13	0.135
Tumor size (cm, mean ± SD)	7.96±2.7	7.92±3.2	0.224
Preoperative MG			0.000
No	50 (90.9%)	379 (76%)	
Yes	5 (9.1%)	120 (24%)	
WHO histology			0.022
Thymoma	26 (47.3%)	300 (60.1%)	
C + NETT	29 (52.7%)	199 (39.9%)	
Resection state			0.63
R0	42 (76.4%)	366 (73.3%)	
R1 + R2	13 (23.6%)	133 (26.7%)	

IT, induction therapies; DS, directly surgery; SD, standard deviation; MG, myasthenia gravis; C, carcinoma; NETT, neuroendocrine thymic tumor.

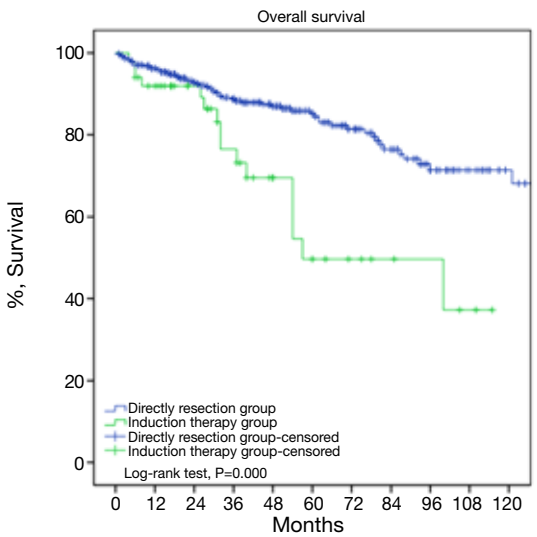

Figure 6 Five-year overall survival of Masaoka-Koga pStaging III patients in the direct surgery group was significantly higher than Masaoka-Koga pStage I–III patients in the induction therapy group (85.2% *vs.* 68.1%, P=0.000).

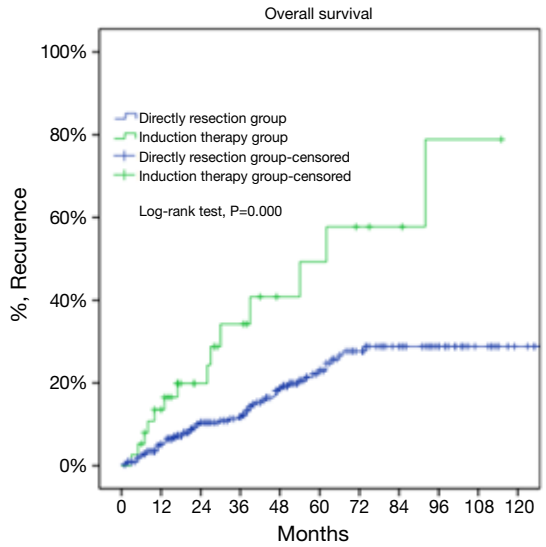

Figure 7 Cumulative incidence of recurrence in Masaoka-Koga pStage III patients in the direct surgery group was significantly lower than in Masaoka-Koga pStage I–III in the induction therapy group (23% *vs.* 58%, P=0.000).

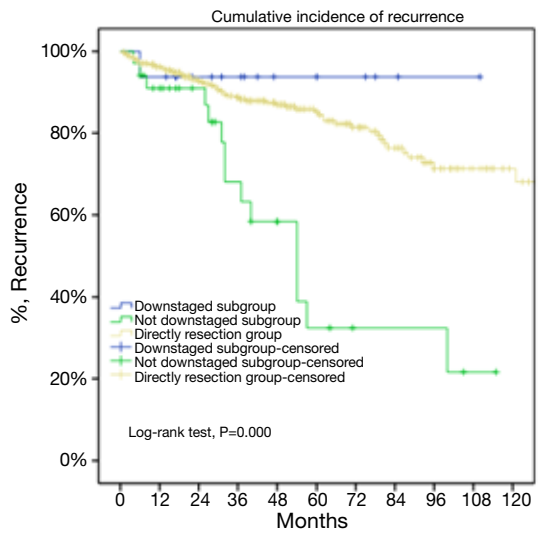

Figure 8 For locally advanced thymic malignancies, 5-year overall survival of tumors downstaged after induction was similar to those in the direct surgery group (93.8% *vs.* 85.2%, P=0.438), both significantly higher than those not downstaged by induction (P=0.000).

And their 5-year CIR were 23% and 58% (P=0.000, *Figure 7*). However, 5-year OS in tumors downstaged after induction (93.8%) was similar to those in the DS group (85.2%, P=0.438), both significantly higher than those not downstaged after induction (35.6%, P=0.000, *Figure 8*). Upon stratification according to tumor histology by thymomas and thymic carcinomas, the survival benefit from downstage after induction therapies could still be observed. And the difference was statistically significant in thymomas (100% *vs.* 91.1% *vs.* 39.6%, P=0.000), although the difference did not reach statistical significance in thymic carcinomas (80% *vs.* 70.6% *vs.* 24.4%, P=0.182; downstaged *vs.* not downstaged P=0.517).

Discussion

The prognosis of thymic malignancy has been consistently related to tumor stage, histology, and completeness of resection (1-3). When the previous two factors were preset and could not be changed upon presentation, complete removal of the disease stands out as an uttermost important issue in the management of thymic tumors. Unfortunately, complete surgical resection is not always feasible in locally advanced (stage III and IVA) diseases, even with the improvement in surgical techniques. In the current study, complete resection rate was 67.6% in the IT group, even after induction therapies. Preoperative induction therapy has been shown to be effective for other local advanced thymomas due to (I) downstaging of the primary tumor and making complete surgical resection possible; (II) obtaining early and increased systemic control; (III) preventing dissemination of tumor cells during the operation (4). Up till now, there has been no controlled randomized trial studying the effect of induction therapies in patients with locally advanced thymic tumors. Although there were sporadic reports, induction therapy was used only occasionally in clinical practice (5). In the ChART retrospective database of 1,713 patients, only 68 of them received neoadjuvant therapies before surgery.

The so far largest retrospective study enrolled 63 cases of locally advanced thymic tumors. Thirty-three patients receiving induction therapies (radiotherapy in 8 and chemotherapy in 25) were compared with 30 cases receiving upfront surgery (6). With the use of neoadjuvant therapies, complete resection rate was increased from 46% to 65% in stage III tumors, and from 0 to 20% in stage IVa diseases, respectively. These results are in accordance with the 67.6% resection rate in the current study. Although progression free survival was slightly lower in patients receiving preoperative induction therapy than in those having upfront surgery, OS turned out to be similar between the two groups. Another single center retrospective study included 61 cases of local advanced thymic tumors.

Complete resection, Masaoka staging, WHO histological classification, and induction chemotherapy were revealed as independent predictors of survival in their patients (7).

In the ChART retrospective database, only 4% of patients received neoadjuvant therapies before surgery in the past 20 years. And there was no increase in the use of induction therapies in recent years. This may be due to the lack of randomized trials and thus high level evidences to build up consensus on the management of locally advanced thymic tumors. What is more, there has been an increased use of chemotherapy and radiation alone, but decrease use of chemoradiation in the induction setting, probably for fear of the difficulty in surgical resection and postoperative care. In the current study, only 25% of the patients in the IT group were considered downstaged, with a higher percentage in thymomas than in thymic carcinomas and carcinoids (38.7% *vs.* 13.9%, P=0.02). Overall 5-year survival in completely resected patients was much higher than those had either R1 or R2 resections (58.2% *vs.* 19.6%). The difference did not reach statistical difference, probably because of the small number of cases in the IT group. However, significantly higher survival difference was noticed in tumors downstaged after induction than those not downstaged (93.8% *vs.* 35.6%, P=0.013). Clearly prospective randomized study is in need to prove the benefit of induction approaches, while more effective neoadjuvant therapies should also be explored.

Since complete removal of the tumor is most often than not impossible in stage IV diseases, we selected only stage III tumors to further evaluate the impact of induction therapies on thymic tumors. With 30.9% of the tumors downstaged, the IT group turned out to have a similar resection rate as stage III patients in the DS group (76.4% *vs.* 73.3%, P=0.63). Unfortunately OS was still much worse and CIR higher in the IT subgroup than the DS subgroup. Apart from the potential inherent bias of predilection for more advanced tumors to be selected for induction, the higher percentage of thymic carcinomas in the IT subgroup may also explain for its worse outcome. Thymic carcinomas are known to be higher grade malignancies than thymomas. What is more, one interesting finding from the current study is that thymomas respond better to induction therapies than thymic carcinomas. This would suggest that different approaches should be tried for thymomas and thymic carcinomas in related future studies.

Again in the subgroup analysis of stage III tumors, a significant survival benefit was detected in tumors downstaged by induction to those not downstaged. Five-year OS were similar in tumors downstaged (93.8%) and those had upfront surgery (85.2%), both significantly higher than those not downstaged (35.6%, P=0.000). Upon stratification by histology, the survival benefit induced by downstaging after induction could still be observed in thymomas. Also OS was much higher in downstaged than in those not downstaged carcinomas as well (80% *vs.* 24.4%, P=0.517). The lack of statistical significance in the results most probably owes to the small number of cases involved in the study. With merely 29 cases of thymic carcinomas in the IT subgroup it is difficult to reach a definite conclusion. None the less, potential survival benefit from downstaging as well as the tendency toward worse outcome in tumors not responding to induction was seen in both histologic subtypes. This would indicate that surgery might add little value to those unresectable tumors not responding to induction therapy. In such circumstances other approaches, such as definitive chemoradiation, might be a better alternative.

Owing to the retrospective nature and limited use of neoadjuvant therapies in the database, it is hard for us to study, which might be the most effective induction modality. A wide variety of chemotherapy regimens, including the ones used in our patients, have been tried before with objective response rates ranging from 25% to 90% (8-11). A dose-dense chemotherapy, with weekly administration for nine weeks, was reported to have a response rate of 62% (10). Also the use of glucocorticoid along with chemotherapy was associated with increased response rate and therefore complete resection rate, especially in type B and AB thymic tumors, although no impact on long-term prognosis was detected (12,13). Radiation in conjunction with chemotherapy may be more effective in tumor response and downstaging, as chemotherapy agents such as cisplatin and paclitaxel may enhance tumor sensitivity to radiation (14). On the other hand, efforts have also been made to explore the molecular targets for the management of thymic malignancies (15-17). Signaling pathways involved in carcinogenesis and therefore may act as potential targets for thymic tumors include the EGF receptor (EGFR), the KIT/mast/stem-cell growth factor receptor, and the IGF-1 receptor (IGF-1R) (18). In fact, there is already an ongoing phase II trial on preoperative induction using cetuximab combined with cisplatin, doxorubicin, and cyclophosphamide chemotherapy in patients with locally advanced thymic tumors (NCT01025089) (5). Hopefully the result of this trial may shed new light on novel approaches for late staged thymic malignancy.

Conclusions

Given the rarity of thymic tumors, prospective randomized trials concerning induction therapies for locally advanced diseases are still lacking. Our study using a large cumulative data from the ChART retrospective database suggests that non-resectable cases at presentation and those in which the feasibility of complete resection is uncertain, may benefit from effective preoperative neoadjuvant therapy. Those who have good response to induction therapies may have improved long-term outcome, although the best mode of induction therapy still wait exploring. On the other hand, tumors not responding to induction would benefit little from subsequent surgery and therefore, should be considered with an alternative approach. Additionally, our results indicate that thymomas and thymic carcinomas have distinct clinical features and respond differently to induction therapies. These findings would be helpful to future studies in the related fields.

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Footnote

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Multimodality therapy for locally-advanced thymic epithelial tumors: where are we now?

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The interest on surgical management of thymic neoplasms has never been so evident as in the last few years, following the publication of several multi-institutional large series, especially thanks to a formidable scientific effort by the European Society for Thoracic Surgeons (ESTS) and the International Thymic Malignancy Interest Group (ITMIG) (1-6).

Thymic epithelial tumors (TETs) are the most frequent tumors in the anterior mediastinum in adults (7) with a reported annual incidence ranging from 1.3 to 3.2 cases per million (8). The majority of patients present with an early stage disease, confined to the mediastinum and capsulated, usually treated with a surgical excision, with or without postoperative radiotherapy (RT). Tumor clinical stage and a radical resection have been shown to be the most important prognostic factors (1,9,10).

Locally advanced TETs (stages III, IVa) occur in 20% to 29% of all surgically treated tumors (1,11), being subject to different range of radical resections (R0) (50%–78% in the most recent clinical series), with incomplete ones being significantly more common than in early stage tumors.

Furthermore, more than 50% of these patients may develop tumor recurrences after surgery and postoperative RT (12-14) being pleura, pericardium, diaphragm and lung the most common sites of tumor relapses. Also, the overall survival (OS) and the cancer free survival (CFS) decrease in advanced stage TETs, especially after incomplete resections, while the recurrence rate increases in stage III–IV TETs and in more aggressive histological tumor subtypes (1,11-14).

The optimal treatment for stage III–IVa TETs still remains challenging, and results are based on retrospective clinical series with a small cohort of patients. Due the rarity of the disease and the subsequent difficulty to enrol patients, to date, no randomized clinical trials have yet been designed.

From the clinical point of view, advanced tumor resectability is judged on the basis of radiological appearance on thoracic chemotherapy (CT) scan/MRI (tumor size, invasiveness into adjacent anatomical structures) and usually it is strictly surgeon's dependent. TETs' strong chemosensitivity, as demonstrated in unresectable/metastatic setting (cisplatin regimens were, in fact effective in 50% to 90% of CT-naive patients) (15-17), led possible, in the last two decades, some retrospective/prospective clinical studies of induction CT and RT in locally advanced TETs. Those studies were, unfortunately limited by: (I) the retrospective design (in the majority); (II) the limited number of patients; and (III) the absence of an upfront surgery control group. The article by Wei *et al*. (18) published in this *Journal of Thoracic Disease* (*JTD*) issue, reports the results of a multi-institutional retrospective Chinese database [the Chinese Alliance for Research in Thymomas (ChART)] on management of locally advanced thymic tumors, between 1994 and 2012. Among 1,713 patients included in this study, 68 (4%), judged potentially unresectable, received an induction treatment (IT). In this series, the authors included thymomas, thymic carcinomas and thymic neuroendocrine carcinomas. A quite heterogeneous variety of therapies (CT/RT alone or a combination of both) were administered on the basis of the physician's preference; in accordance

to the most common guidelines, CT regimens were platin based (CAP-cisplatin, doxorubicin, cyclophosphamide-, PE-cisplatin, etoposide- or carboplatin-paclitaxel). Stage III TETs receiving upfront surgery became the control group; stage IV TETs were excluded from the analyses, to be more accurate on IT effects evaluation. Interestingly, in the latest study period, advanced tumors were more frequently treated with induction CT or RT, alone.

The authors were able to demonstrate an R0 rate of 67.5% after IT; in particular, 17 patients were downstaged to stage I–II, while the majority remained stages III/IV. Overall 5- and 10-year OS were 49.7% and 19.9%, respectively, and the 5-year cumulative incidence of recurrence (CIR) was 44.9%. As expected, the OS was significantly higher in downstaged TETs, and in those who received R0 resection. Quite surprisingly, there was a significant difference for both cumulative OS and CIR in advanced TETs treated with upfront surgery compared to those who received IT, but downstaged tumors' OS was similar to ipsistage control tumors. Also, after IT, thymomas were significantly more frequently downstaged, and this improved their survival compared to thymic carcinomas.

One of the most important reasons to induce a locally advanced TET is to potentially lead back to a surgical resection a potentially unresectable tumor. Resectability rates have historically ranged from 25% and 76% in the published clinical series (19-23). A recent meta-analysis (24) reviewed papers published between 2003 and 2014, including more than 10 patients with locally advanced TETs who were preoperatively treated with CT, RT or both: the reported pooled R0 rate was 73% (95% CI, 67%–79%). The 5- and 10-year OS pooled rates were 87% and 76%, respectively (24). Not surprisingly, whenever a distinction between histological tumor subgroup was performed, a decreased survival was seen in thymic carcinoma group.

CT was usually well-tolerated in all published series: in fact, as observed by Huang *et al*. (25), patients with advanced TETs are commonly younger and fitter than those with lung or esophageal tumors, and thus can better tolerate intensive multimodality treatments as well as more extended resections.

The goal of any induction therapy remains the achievement of a complete resection of the tumor: RT may offer potential synergism to concurrent CT but, at the same time, may also increase toxicity and possible surgical morbidity. Actually, there is no consensus whether or not RT should be added to CT in the preoperative setting. In fact, only two studies included patients who received both CT and RT (21,23). Toxicity was acceptable in both, and complications were mostly surgical; on the other hand, R0 rate were 80% and 77%, respectively.

In conclusion, Wei *et al*. (18) are to be commended because they collected one of the largest clinical series on patients with advanced TETs treated with an induction protocol. The same authors have outlined possible study limitations: (I) the retrospective and multi-institutional study design; (II) the large period of the study; (III) differences in the preoperative treatment across the centres. However, results are very interesting since they compared IT TETs with those treated with upfront surgery, consenting to conclude that: (I) tumor downstaging may represent an important prognostic factor; (II) tumor downstaging strongly depends on histology; (III) OS in downstaged patients was similar to those who received upfront surgery; (IV) surgery has added little in term of OS to non-downstaged tumors.

Recent identification of molecular alterations which may occur in KIT, vascular endothelial growth factors receptors (VEGFRs) and mammalian target of rapamycin (mTOR) signalling pathways, has led the use, in an off-label setting, of targeted agents also in advanced TETs, possibly reducing the classical CT adverse effects.

Further efforts are required by the most important international scientific societies to design randomized clinical trials to definitively outline guidelines for a better approach in advanced TETs patients. This will be the future.

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Footnote

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The role of postoperative radiotherapy for stage I/II/III thymic tumor—results of the ChART retrospective database

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Background: Postoperative radiotherapy (PORT) for thymic tumor is still controversial. The object of the study is to evaluate the role of PORT for stage I to III thymic tumors.

Methods: The Chinese Alliance for Research in Thymomas (ChART) was searched for patients with stage I to III thymic tumors who underwent surgical resection without neoajuvant therapy between 1994 and 2012. Univariate and multivariate survival analyses were performed. Cox proportional hazard model was used to determine the hazard ratio for death.

Result: From the ChART database, 1,546 stage I to III patients were identified. Among these patients, 649 (41.98%) received PORT. PORT was associated with gender, histological type (World Health Organization, WHO), thymectomy extent, resection status, Masaoka-Koga stage and adjuvant chemotherapy. The 5-year and 10-year overall survival (OS) rates and disease-free survival (DFS) rates for patients underwent surgery followed by PORT were 90% and 80%, 81% and 63%, comparing with 96% and 95%, 92% and 90% for patients underwent surgery alone (P=0.001, P<0.001) respectively. In univariate analysis, age, histological type (WHO), Masaoka-Koga stage, completeness of resection, and PORT were associated with OS. Multivariable analysis showed that histological type (WHO) (P=0.001),

Masaoka-Koga stage (P=0.029) and completeness of resection (P=0.003) were independently prognostic factors of OS. In univariate analysis, gender, myasthenia gravis, histological subtype, Masaoka-Koga stage, surgical approach, PORT and completeness of resection were associated with DFS. Multivariate analysis showed that histological subtype (P<0.001), Masaoka-Koga stage (P=0.005) and completeness of resection (P=0.006) were independent prognostic factors for DFS. Subgroup analysis showed that patients with incomplete resection underwent PORT achieved better OS and DFS (P=0.010, 0.017, respectively). However, patients with complete resection underwent PORT had the worse OS and DFS (P<0.001, P<0.001, respectively).

Conclusions: The current retrospective study indicates that PORT after incomplete resection could improve OS and DFS for patients with stage I to III thymic tumors. However for those after complete resection, PORT does not seem to have any survival benefit on the whole.

Keywords: Thymic tumor; postoperative radiotherapy (PORT); overall survival (OS)

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Introduction

Thymic tumors, including thymoma and thymic carcinoma, are the most common primary malignancies located in anterior mediastinum. They are relatively rare and usually grow indolently. The incidence of thymic tumors in the USA is 0.13 per 100,000 person-years according to the Surveillance, Epidemiology, and End Results (SEER) database (1). More than 30% of thymic tumors may be accompanied with myasthenia gravis (2). Surgical resection is the most important treatment for thymic tumors. Complete resection of the entire tumor has consistently been found to be an independent prognostic factor (3-6). The International Thymic Malignancy Interest Group (ITMIG) recommended that en bloc resection of the entire thymus gland and surrounding areolar tissue for complete resection (7). Local recurrence is the major failure pattern after surgery (3,5,8,9). The recurrence rate was lower for patients received complete resection than those received incomplete resection, resulted in a better survival in the former group (10). Chemotherapy has been used commonly, especially at the induction setting. Preoperative chemotherapy has been reported to increased R0 resection rate (7). Postoperative chemotherapy is not recommended for thymoma after complete resection. Chemotherapy is adopted in inoperable or gross residual disease after local treatment (11,12). Postoperative radiotherapy (PORT) is usually administrated in Masaoka-Koga stage IV thymoma for the purpose of local control (5,8,13). Indications of PORT for complete resected Masaoka-Koga stage I to III thymic tumors are controversial, although it has been used frequently in clinical practice. Most authors suggested that complete resection alone be adequate for Masaoka-Koga stage I to III thymic tumors, although some studies indicated potential survival benefits from PORT (4,5,9,14-21). Most of the knowledge on thymic tumors comes from retrospective, single-institutional studies. No randomized prospective trial has ever been conducted to date to evaluate the effect of PORT on thymic malignancies. The Chinese Alliance for Research in Thymomas (ChART) was founded in 2012, with the purpose of improving treatment for thymic tumors through collaborative studies. A retrospective database was established, gathering data from 18 tertiary referral centers in China. Our objective was to investigate the role of PORT in patients who underwent surgery for stage I to III thymic epithelial tumors using the ChART registry.

Materials and methods

Records of surgical patients between 1994 and 2012 in ChART database were retrospectively reviewed. Patients were included in the analysis if there was complete information on tumor stage, surgery and radiation therapy. Patients who received neoadjuvant treatment, who had history of other malignance, and who underwent a biopsy alone were excluded. All cases were restaged according to Masaoka-Koga staging system (22). Histological subtypes were classified according to World Health Organization (WHO) criteria published in 2004 (23).

Statistical analysis was performed with SPSS statistical software package version 19.0 (SPSS Inc, Chicago, IL).

Continuous data variables were analyzed using Student's *t*-test. Nominal data were analyzed using crosstabs and Pearson's chi-square test. Kaplan-Meier survival curves were constructed and compared using the log-rank test. Multivariate analysis was performed according to the Cox proportional hazard model. Significance was set at a probability value less than 0.05. Because only de-identified data were used for the study, informed consent was waived by IRB.

Results

We From the ChART database 2,159 patients with Masaoka-Koga stage I to III thymic epithelial tumors were identified. Among them, 1,546 patients with complete data on staging, radiation therapy, and surgery made the final study cohort. There were 717 patients classified as Masaoka-Koga stage I, 318 patients as stage II, and 511 patients as stage III. Patients' baseline characteristics were presented in *Table 1*. These included 649 patients (41.98%) who received PORT and 897 patients (58.02%) who received surgery alone. Significant differences were found in gender, WHO histological subtype, tumor size, thymectomy extent, complete resection, Masaoka-Koga stage and adjuvant chemotherapy between the two groups of patients.

The 5-year and 10-year overall survival (OS) rates and disease-free survival (DFS) rates for patients having surgery followed by PORT were 90% and 80%, 81% and 63%, comparing with 96% and 95%, 92% and 90% for patients having surgery alone (P=0.001, P<0.001) respectively *(Figures 1,2)*. In univariate analysis, age, WHO histological subtype, Masaoka-Koga stage, completeness of resection, and PORT were associated with OS (*Table 2*). Multivariate analysis showed that WHO histological type (P=0.001), Masaoka-Koga stage (P=0.029) and completeness of resection (P=0.003) were independently prognostic factors for OS, while PORT was not (*Table 3*). In univariate analysis, gender, myasthenia gravis, WHO histological type, Masaoka-Koga stage, surgical approach, PORT and completeness of resection were associated with DFS (*Table 4*). Multivariate analysis again showed that only WHO histological type (P<0.001), Masaoka-Koga stage (P=0.005) and completeness of resection (P=0.006) were independently prognostic factors for DFS (*Table 5*). Subgroup analysis showed that patients with incomplete resection underwent PORT achieved better OS and DFS (P=0.010, 0.017, respectively) than those having surgery alone. However for patients with complete resection, PORT was associated with worse OS and DFS (P<0.001, P<0.001, respectively). And no survival difference was detected between patients with or without PORT in the majority of stage or histology categories, except in stage II disease where PORT was associated with a worse DFS (*Tables 6,7*).

Discussion

The role of PORT in thymic tumors remains controversial. Local recurrence is the most common pattern of failure in thymic tumors after surgery. It has been suggested that PORT may reduce the recurrence rate from about 30% to below 5% (24,25). Given the rarity of the thymic tumors, their indolent natural history, and the large number of patients died from unrelated causes, no prospective randomized study has ever investigated the true benefit of PORT.

In this large multicenter study, a total of 1,546 patients with Masaoka-Koga stage I to III thymic tumors were elected from the ChART database. Unfortunately, PORT was not found to be associated with improved OS. The 5- and 10-year OS rates for patients who underwent surgery followed by PORT were 90% and 80%, comparing with 96% and 95% for patients who underwent surgery alone (P=0.001), respectively. This may be attributed to the higher proportion of patients with thymic carcinoma, stage III disease, and palliative surgery in the PORT group. However, PORT was significantly associated with improved OS in patients having palliative surgery.

The available data suggested that Masaoka-Koga stage, completeness of resection and histological classification were the independent prognostic factors (3,4,8). No significant differences in survival were noted among subgroup of thymoma, which was consistent with the result of the meta-analysis conducted by Detterbeck *et al*. (3). We also demonstrated that complete resection alone was sufficient to achieve a satisfactory outcome in the thymoma, saving the patients from the potential side effects caused by mediastinal radiation. These would include radiation pneumonitis, chronic pulmonary fibrosis, hematopoietic malignancies, esophageal malignancies, restrictive cardiomyopathy and pericardial effusion (26-30). A retrospective study by Mangi *et al*. found that most patients with stage III disease could undergo complete resection, and the addition of radiation therapy for patients receiving complete resection did not reduce the recurrence rate (21). The use of adjuvant radiation after complete resection of stage III thymoma

Table 1 Patients' baseline characteristics

Characteristics	Surgery alone, N (%)	Port, N (%)	P value[a]
Gender			0.000
Male	425 (52.3)	387 (47.7)	
Female	472 (64.3)	262 (35.7)	
Age	51.69	50.53	0.075
Myasthenia gravis			0.161
Yes	231 (61.1)	147 (38.9)	
No	666 (57.0)	502 (43.0)	
WHO classification			0.000
A	83 (83.0)	17 (17.0)	
AB	318 (78.9)	85 (21.1)	
B1	159 (72.9)	59 (27.1)	
B2	135 (55.8)	107 (44.2)	
B3	114 (40.1)	170 (59.9)	
C	74 (28.0)	190 (72.0)	
NETT	14 (40.0)	21 (60.0)	
WHO classification (combined)			0.000
A+AB	401 (79.7)	102 (20.3)	
B1+B2+B3	408 (54.8)	336 (45.2)	
C+NETT	88 (29.4)	211 (70.6)	
Thymectomy extent			0.000
Partial	182 (47.6)	200 (52.4)	
Total	714 (61.5)	447 (38.5)	
Completeness of resection			0.000
R0	854 (61.1)	543 (38.9)	
R1	27 (43.5)	35 (56.5)	
R2	16 (18.4)	71 (81.6)	
Tumor size (cm)	6.58	7.04	0.008
Masaoka-Koga stage			0.000
I	535 (72.6)	182 (27.4)	
II	190 (59.7)	128 (40.3)	
III	172 (33.7)	339 (66.3)	
Adjuvant chemotherapy			0.000
No	854 (63.9)	482 (36.1)	
Yes	32 (18.2)	144 (81.8)	

[a], χ test. WHO, World Health Organization; NETT, neuroendocrine thymic tumor; PORT, postoperative radiotherapy.

needs to be re-addressed. For thymoma in WHO types A, AB, B1, as well as those classified as having Masaoka-Koga stage I and II disease, Utsumi *et al.* insisted that complete resection alone was sufficient treatment strategy (19). Furthermore, there was no significant difference in survival noted with regard to the status of PORT among the patients classified as stage III/IV, and WHO types B2/B3 (19). Kondo *et al.* reviewed 1,320 patients with stage II and III thymomas, and their finding revealed that local recurrence rates were not significantly decreased by PORT,

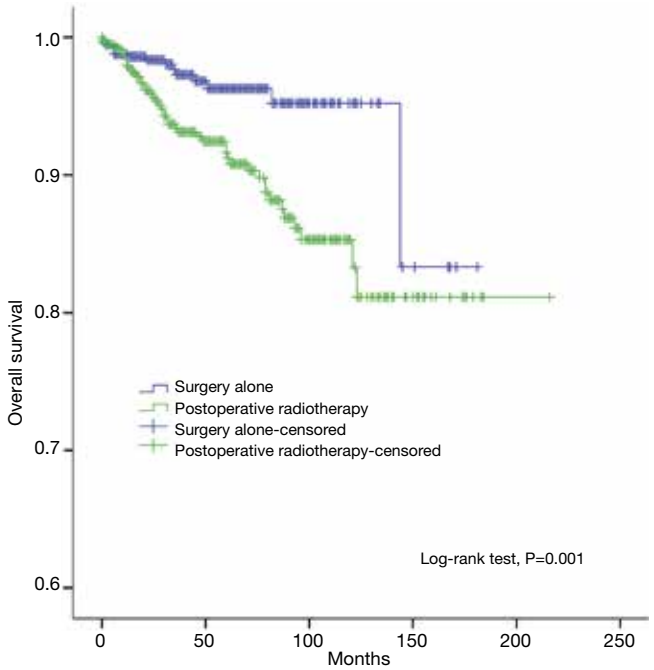

Figure 1 Kaplan-Meir overall survival curve of patients treated with surgery alone, and those treated with PORT. PORT decreased OS of stage I/II/III thymic epithelial tumor (P=0.001).

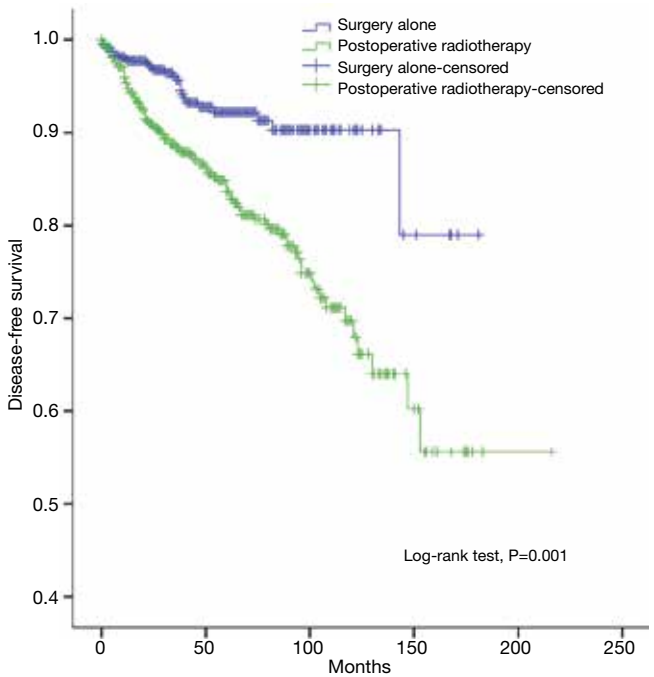

Figure 2 Kaplan-Meir disease-free survival curve of patients treated with surgery alone, and those treated with PORT. PORT decreased DFS of stage I/II/III thymic epithelial tumor (P<0.001).

Table 2 Univariate analysis of factors affecting overall survival

Characteristics	P value
Gender (MaleMale/FemaleFemale)	0.072
Age (≥50/<50)	0.050
Myasthenia gravis (Yes/No)	0.081
Tumor size (≤5 cm/>5 cm)	0.524
Histological type (WHO) (A or AB/B1 or B2 or B3/C)	0.000
Masaoka-Koga stage (I/II/III)	0.000
Surgical approach (VATS/Open)	0.107
Thymectomy extent (Partial/Total)	0.159
PORT (No/Yes)	0.001
Completeness of resection (R0/R1+R2)	0.000

WHO, World Health Organization; VATS, video-assisted thoracic surgery; PORT, postoperative radiotherapy.

Table 3 Multivariate analysis of factors affecting overall survival

Characteristics	P value	OR
Gender (Male/Female)	0.994	1.002
Age (<50/ ≥50)	0.165	1.518
Myasthenia gravis (No/Yes)	0.811	1.117
Histological type (WHO) (A or AB / B1 or B2 or B3/ C)	0.001	
B1+B2+B3	0.073	3.226
C	0.001	8.631
Masaoka-Koga stage (I/II/III)	0.029	
II	0.124	2.425
III	0.008	3.901
PORT	0.338	0.726
Completeness of resection (R0/R1+R2)	0.003	0.381

WHO, World Health Organization; PORT, postoperative radiotherapy.

and the prognosis of invasive thymoma were not improved by PORT (5). Complete resection was the most important factor in the treatment of thymic epithelial tumors. A meta-analysis by Korst *et al.* reviewed no statistically significant reduction in recurrence after adjuvant radiotherapy for patients with completely resected stage II or III thymic epithelial tumors (20). Weksler *et al.* reported a retrospective study using SEER database. This large population-based study demonstrated that adding PORT to surgery was associated with improved disease-specific survival. However, in multivariate analysis, postoperative

Table 4 Univariate analysis of factors affecting disease-free survival

Characteristics	P value
Gender (Male/Female)	0.008
Age (≥50/<50)	0.254
Myasthenia gravis (Yes/No)	0.002
Tumor size (≤5 cm/>5 cm)	0.094
Histological type (WHO) (A or AB/B1 or B2 or B3/C)	0.000
Masaoka-Koga stage (I/II/III)	0.000
Surgical approach (VATS/Open)	0.027
Thymectomy extent (Partial / Total)	0.629
PORT (No/Yes)	0.000
Completeness of resection (R0/R1+R2)	0.000

WHO, World Health Organization; VATS, video-assisted thoracic surgery; PORT, postoperative radiotherapy.

Table 5 Multivariate analysis of factors affecting disease-free survival

Characteristics	P value	OR
Gender (Male/Female)	0.675	0.914
Myasthenia gravis (No/Yes)	0.099	0.517
Histological type (WHO) (A or AB / B1or B2 or B3/ C)	0.000	
B1+B2+B3	0.001	4.909
C	0.000	10.194
Masaoka-Koga stage (I/II/III)	0.005	
II	0.014	2.549
III	0.001	3.056
Surgical approach (VATS/Open)	0.447	1.601
PORT (No/Yes)	0.971	0.991
Completeness of resection (R0/R1+R2)	0.006	0.513

WHO, World Health Organization; VATS, video-assisted thoracic surgery; PORT, postoperative radiotherapy.

Table 6 Stratified disease-free survival analysis of the role of PORT

Characteristics	Patients, N (%)	DFS		P value
		5-year	10-year	
R0	1,027			0.000
PORT	457 (44.50)	0.86	0.70	
Surgery alone	570 (55.50)	0.96	0.95	
R1+R2	99			0.017
PORT	78 (78.79)	0.60	0.39	
Surgery alone	21 (21.21)	0.35	0.35	
A+AB	365			0.646
PORT	89 (24.38)	0.99	0.90	
Surgery alone	276 (75.62)	0.98	0.98	
B1+B2+B3	549			0.053
PORT	285 (51.91)	0.89	0.66	
Surgery alone	264 (48.09)	0.93	0.90	
C+NETT	212			0.702
PORT	161 (75.94)	0.61	0.39	
Surgery alone	51 (24.06)	0.67	0.67	
Stage I	513			0.096
PORT	155 (30.21)	0.97	0.81	
Surgery alone	358 (69.79)	0.98	0.97	
Stage II	243			0.003
PORT	108 (44.44)	0.85	0.66	
Surgery alone	135 (55.56)	0.99	0.99	
Stage III	370			0.728
PORT	272 (73.51)	0.71	0.51	
Surgery alone	98 (26.49)	0.70	0.70	

PORT, postoperative radiotherapy; NETT, neuroendocrine thymic tumor; DFS, disease-free survival.

adjuvant radiation therapy was not significantly associated with improved overall survival (18). Based on the current results and existing literature, it seems that future studies on PORT for thymomas after resection should be focused on patients at high risk of developing local recurrence.

Thymic carcinoma consists the most aggressive subtype of thymic neoplasms,. Surgery provides the best chance of cure for resectable thymic carcinoma. Patients who received complete excision had a significantly better prognosis than those who did not received surgical therapy. Due to the rarity of this disease, lack of high level of evidences, the role of chemotherapy and radiation after surgery are not well established. Using SEER database, Weksler *et al*. studied 290 patients with thymic carcinoma. They found that PORT could not improve the overall survival for patients after complete resection, and complete resection was the preferred primary treatment for thymic carcinoma (31). We also found that PORT did not improve the prognosis for patients with thymic carcinoma in this study. However, Hsu *et al*. suggested that PORT seemed to improve the prognosis for patients with thymic carcinoma, although the difference was not statistically significant (32). Omasa *et al*. also reported that PORT did not increase RFS or OS for stage II or III thymoma but increased RFS for stage II

Table 7 Stratified overall survival analysis of the role of PORT

Characteristics	Patients, N (%)	OS		P value
		5-year	10-year	
R0	1023			0.000
PORT	454(44.38)	0.93	0.87	
Surgery alone	569(55.62)	0.98	0.98	
R1+R2	96			0.010
PORT	77(80.21)	0.75	0.51	
Surgery alone	19(19.79)	0.59	0.30	
A+AB	365			0.285
PORT	89(24.38)	0.99	0.90	
Surgery alone	276(75.62)	1.00	1.00	
B1+B2+B3	547			0.280
PORT	285(52.10)	0.92	0.91	
Surgery alone	262(47.90)	0.95	0.95	
C+NETT	207			0.930
PORT	157(75.85)	0.80	0.53	
Surgery alone	50(24.15)	0.85	0.76	
Stage I	511			0.067
PORT	153(29.94)	0.97	0.91	
Surgery alone	358(70.06)	0.99	0.99	
Stage II	243			0.537
PORT	108(44.44)	0.94	0.89	
Surgery alone	135(55.56)	0.98	0.98	
Stage III	365			0.717
PORT	270(73.97)	0.84	0.69	
Surgery alone	95(26.03)	0.85	0.79	

PORT, postoperative radiotherapy; NETT, neuroendocrine thymic tumor; OS, overall survival.

and III thymic carcinoma (33). Ahmad *et al*. reported that radiation therapy was associated with improved OS and longer RFS for patients with thymic carcinoma (34).

Radical resection, WHO histology classification, and Masaoka-Koga stage were revealed as t independent prognostic factors for thymic malignancy in the current study. Our results also showed that PORT could not bring any survival benefit to patients with completely resected stage I, II and III diseases. PORT should be administrated to the patients with palliative surgery, as it did improve the outcomes in these patients. However, because of the retrospective nature of this study and that the radiation field and dosage were highly varied, prospective randomized trials aiming at patients at high risk of developing recurrent disease should be conducted to evaluate the true effect of PORT in thymic epithelial tumors.

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Footnote

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The application of postoperative chemotherapy in thymic tumors and its prognostic effect

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Background: To study the role of postoperative chemotherapy and its prognostic effect in Masaoka-Koga stage III and IV thymic tumors.

Methods: Between 1994 and 2012, 1,700 patients with thymic tumors who underwent surgery without neoadjuvant therapy were enrolled for the study. Among them, 665 patients in Masaoka-Koga stage III and IV were further analyzed to evaluate the clinical value of postoperative chemotherapy. The Kaplan-Meier method was used to obtain the survival curve of the patients divided into different subgroups, and the Cox regression analysis was used to make multivariate analysis on the factors affecting prognosis. A Propensity-Matched Study was used to evaluate the clinical value of chemotherapy.

Results: Two-hundred and twenty-one patients were treated with postoperative chemotherapy, while the rest 444 cases were not. The two groups showed significant differences ($P<0.05$) regarding the incidence of myasthenia gravis, World Health Organization (WHO) histological subtypes, pathological staging, resection status and the use of postoperative radiotherapy. WHO type C tumors, incomplete resection, and postoperative radiotherapy were significantly related to increased recurrence and worse survival ($P<0.05$). Five-year and 10-year disease free survivals (DFS) and recurrence rates in patients who underwent surgery followed by postoperative chemotherapy were 51% and 30%, 46% and 68%, comparing with 73% and 58%, 26% and 40% in patients who had no adjuvant chemotherapy after surgery ($P=0.001$, $P=0.001$, respectively).

In propensity-matched study, 158 pairs of patients with or without postoperative chemotherapy (316 patients in total) were selected and compared accordingly. Similar 5-year survival rates were detected between the two groups (P=0.332).

Conclusions: Pathologically higher grade histology, incomplete resection, and postoperative radiotherapy were found to be associated with worse outcomes in advanced stage thymic tumors. At present, there is no evidence to show that postoperative chemotherapy may help improve prognosis in patients with Masaoka-Koga stage III and IV thymic tumors.

Keywords: Thymic tumors; chemotherapy; surgery; prognosis

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Introduction

Thymic malignancies are relatively rare tumors most commonly seen in the anterior mediastinum. While most thymic tumors have favorable outcomes after surgical resection (1), around 1/3 of the patients may already have advanced disease upon presentation, making radical surgery inapplicable. As reported by Masaoka *et al.* (2), the 5-year survival rate was about 67% for locally advanced cases, and only 50% for patients with distant metastasis. There are still controversies concerning chemotherapy for thymic tumors. The purposes of chemotherapy are to reduce the tumor burden to enable the possibility of later surgery or radiotherapy on the one hand, and to extend the time for controlling the diseases on the other. Chemotherapy can be applied at different stages of the treatment, with the normal treatment modes including preoperative chemotherapy and surgery, surgery and postoperative chemotherapy, or chemoradiotherapy. Besides, for thymic tumors patients with distant metastasis, palliative chemotherapy is usually the major therapeutic approach. At present, there are no standard chemotherapy regimens for thymic tumors, and even these limited data comes mostly from the single-institution retrospective reports, with largely varied results. The Chinese Alliance for Research in Thymomas (ChART) retrospectively collected patient data from 18 centers nationwide, and used this collective data to study the management outcomes in thymic tumors patients. The current study aimed at elucidating the value of postoperative chemotherapy in Masaoka-Koga stage III and IV tumors (3), using the ChART database.

Materials and methods

Clinical data and research method

From March 1994 to December 2012, ChART database registered 2,306 thymic tumor cases. After excluding patients with unclear information on staging (224 cases), World Health Organization (WHO) histology types (121 cases), whether radiotherapy was applied (96 cases), and those non-surgical patients (97 cases), or those treated with induction therapy (68 cases), 1,700 patients were finally included in the current study. Among them, 294 (17.3%) patients received chemotherapy after surgery, while the rest 1,406 (82.7%) patients did not. For studying the effect of postoperative chemotherapy on prognosis, only tumors in Masaoka-Koga III and IV were included. Because only de-identified data were used for the study, informed consent was waived by Institutional Review Board (IRB).

Statistical processing

Clinical pathological data and follow-up information entered into the database were retrospectively reviewed. The SPSS 19.0 software was used for statistical analysis. Ratios were compared with χ^2 test. Regarding survival analysis, Kaplan-Meier method was used to chart the survival curves, and log-rank test was used for inter-group comparison. Cox regression was used in multivariate analysis to reveal the factors affecting the prognosis, with a 95% confidence interval (CI). To reduce the impact of unbalanced distribution of factors due to the retrospective nature of the study, 1:1 caliper

propensity-matched study was used to further compare the survival in patients having or not having chemotherapy after surgery. Differences were considered statistically significant if P<0.05.

Results

Overall incidence of postoperative chemotherapy

Percentages of patients having postoperative chemotherapy in different tumor stages were listed in *Table 1*. As can be seen from *Figure 1*, the use of adjuvant chemotherapy increased significantly with Masaoka-Koga tumor stage (P=0.000). In stage I and II tumors, chemotherapy was used in less than 10% cases.

Postoperative chemotherapy in Masaoka-Koga III and IV patients

For the purpose of the study, patients with stage I (716 cases) and stage II (319 cases) tumors were further excluded. In the remaining 665 Masaoka-Koga III and IV patients, 221 received postoperative chemotherapy (chemo group) and the other 444 did not receive adjuvant chemotherapy (non-chemo group).

Table 1 Percentages of postoperative chemotherapy in different tumor stages

Masaoka-Koga stage [case]	Non-chemo group (%)	Chemo group (%)	P value
I [716]	677 (94.6)	39 (5.4)	0.000
II [319]	285 (89.3)	34 (10.7)	
III [515]	378 (73.4)	137 (26.6)	
IV [150]	66 (44.0)	84 (56.0)	

Clinical analysis on general data

Clinical features and myasthenia of the patients

The results showed that there was no significant difference in patients' gender or age between the chemo and non-chemo groups. Significantly fewer patients in the chemo group had concomitant myasthenia gravis than the non-chemo group (P=0.000) (*Table 2*).

Type of thymic tumors

Significant difference was detected in the percentages of postoperative chemotherapy among different WHO histology types (P=0.000). Postoperative chemotherapy was used significantly more often in type C or neuroendocrine tumors than in type B1 + B2 + B3 or A + AB tumors (P=0.000) (*Table 3*).

Comparison between tumor size, pathological staging and resection status

Tumors size was similar between the two groups (P=0.218). The chemo group had significantly more patients with stage IV diseases (P=0.000). Overall radical resection rate in this cohort was 73.1%. It was significantly higher in the non-chemo group than in the chemo group (P=0.000) (*Table 4*).

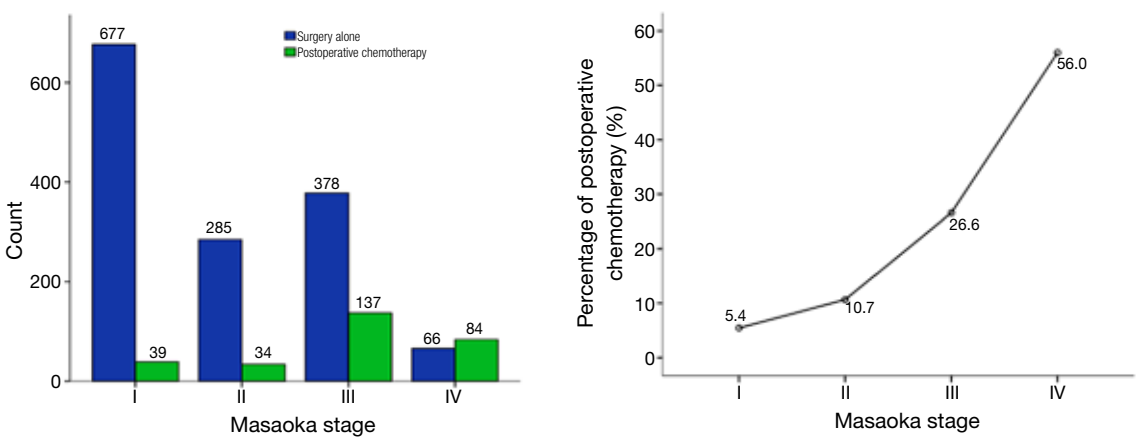

Figure 1 Percentage of postoperative chemotherapy in patients with different stage tumors.

Table 2 Clinical features and the distribution of myasthenia in the two groups

Characteristics	Non-chemo group, n=444 (%)	Chemo group, n=221 (%)	P value
Sex			0.493
Male	265 (65.8)	138 (34.2)	
Female	179 (68.3)	83 (31.7)	
Age, years	51.15	50.53	0.524
With or without myasthenia			0.000
Yes	121 (87.7)	17 (12.3)	
No	323 (61.3)	204 (38.7)	

Table 3 Comparison of WHO histology subtypes between the two groups

Characteristics	Non-chemo group, n=444 (%)	Chemo group, n=221 (%)	P value
WHO types			0.000
A	14 (87.5)	2 (12.5)	
AB	42 (87.5)	6 (12.5)	
B1	37 (86.0)	6 (14.0)	
B2	80 (87.0)	12 (13.0)	
B3	136 (71.6)	54 (28.4)	
C	123 (48.8)	129 (51.2)	
NETT	12 (50.0)	12 (50.0)	
WHO type (three classification)			0.000
A + AB	56 (87.5)	8 (12.5)	
B1 + B2 + B3	253 (77.8)	72 (22.2)	
C + NETT	135 (48.9)	141 (51.1)	

WHO, World Health Organization; NETT, neuroendocrine thymic tumor.

Table 4 Contrast between the two groups of tumor size, pathological staging, and resection status

Characteristics	Non-chemo group, n=444 (%)	Chemo group, n=221 (%)	P value
Tumor size (cm)	7.46	7.83	0.218
Pathological staging			0.000
III	378 (73.4)	137 (26.6)	
IV	66 (44.0)	84 (56.0)	
Resection status			0.000
R0	326 (73.1)	120 (26.9)	
R1	47 (69.1)	21 (30.9)	
R2	71 (47.0)	80 (53.0)	

Table 5 Comparison of other adjuvant therapies between the two groups

Characteristics	Non-chemo group, n=444 (%)	Chemo group, n=216 (%)	P value
Other adjuvant therapies			0.000
No	191 (86.4)	30 (13.6)	
Yes	253 (57.6)	186 (42.4)	

Modes of adjuvant therapy

Detailed information on postoperative adjuvant therapy was lacking for further analysis in five patients. Among the remaining 660 patients, 191 patients were treated by surgery alone (191/660, 28.9%), and the rest 469 patients received postoperative adjuvant therapies (71.1%). These included 30 patients having chemotherapy alone (30/660, 4.5%), 253 patients having radiotherapy alone (253/660, 38.3%), and 186 patients having postoperative chemoradiotherapy (186/660, 28.2%). In the chemo group, significantly more patients received chemoradiotherapy than chemotherapy alone (P=0.000) (*Table 5*).

Analysis of factors relating to the survival of Masaoka-Koga III and IV patients

Multivariate analysis showed that histological subtypes, resection status and postoperative radiotherapy were the independent predictive factors for overall survival in patients with stage III and IV tumors. WHO type C tumors, incomplete resection, and use of adjuvant radiation were associated with significantly worse outcome (P=0.011, P=0.004, P=0.018). Five-year and 10-year disease free survivals (DFS) were 73% and 58% for the non-chemo group, and 51% and 30% for the chemo group, with significant differences between the two groups (P=0.000) (*Tables 6,7*) (*Figure 2*).

Further stratification analysis showed that the survival rate in Masaoka-Koga III and IV patients having adjuvant chemotherapy alone after surgery was noticeably lower than those having surgery alone, postoperative radiotherapy alone, or postoperative chemoradiotherapy (P=0.000, P=0.000, P=0.003, respectively) (*Figure 3*).

Multivariate analysis of factors related to recurrence in Masaoka-Koga stage III and IV patients

Multivariate analysis showed that histology subtypes, resection status, and postoperative radiotherapy were the independent

Table 6 Multivariate analysis of survival-related risk factors

Risk factors	P value	OR (95% CI)
Myasthenia gravis (no/yes)	0.276	0.502 (0.145, 1.736)
Age (<50/≥50)	0.179	1.485 (0.835, 2.641)
Sex (male/female)	0.737	0.902 (0.495, 1.645)
WHO histology type (A, AB/B1, B2 or B3/C)	0.011	
B1 + B2 + B3	0.577	1.541 (0.337, 7.041)
C	0.067	3.952 (0.908, 17.195)
Masaoka-Koga stage (III and IV)	0.554	1.227 (0.623, 2.420)
Adjuvant chemotherapy (no/yes)	0.502	1.250 (0.652, 2.399)
Tumor size (≤5 cm/>5 cm)	0.876	1.056 (0.531, 2.100)
Complete resection (R0/R1 + R2)	0.004	0.414 (0.226, 0.760)
Extent of thymectomy (partial/total)	0.599	1.184 (0.630, 2.225)
Postoperative radiotherapy (no/yes)	0.018	0.451 (0.233, 0.873)

OR, odd ratio; CI, confidence interval; WHO, World Health Organization.

Table 7 Comparison of survival rates among the different adjuvant therapy subgroups

Log-rank	Surgery alone		Postoperative chemotherapy alone		Postoperative radiotherapy alone		Postoperative chemoradiotherapy	
	Chi-square	Sig.	Chi-square	Sig.	Chi-square	Sig.	Chi-square	Sig.
Surgery alone			13.544	0.000	0.003	0.955	1.805	0.179
Postoperative chemotherapy alone	13.544	0.000			19.483	0.000	8.604	0.003
Postoperative radiotherapy alone	0.003	0.955	19.483	0.000			3.508	0.061
Postoperative chemoradiotherapy	1.805	0.179	8.604	0.003	3.508	0.061		

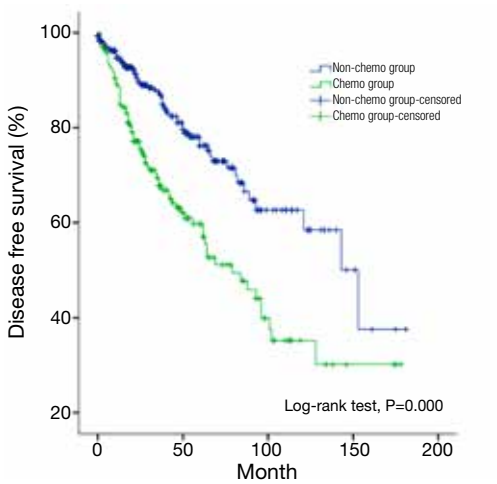

Figure 2 Five- and ten-year disease free survivals (non-chemo group *vs.* chemo group, P=0.000).

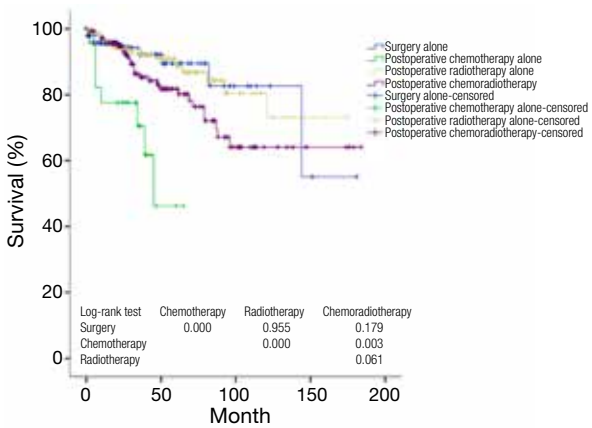

Figure 3 Survival curves for subgroups of patients with surgery alone, postoperative chemotherapy alone, postoperative radiotherapy alone, and postoperative chemoradiotherapy.

Table 8 Multivariate analysis of factors relating to recurrence in Masaoka-Koga stage III and IV patients

Factor	P value	OR (95% CI)
Myasthenia complication (no/yes)	0.090	0.466 (0.193, 1.127)
Age (<50/≥50)	0.344	1.218 (0.809, 1.833)
Sex (male/female)	0.220	0.763 (0.496, 1.175)
WHO pathological type (A, AB/B1, B2 or B3/C)	0.024	
B1 + B2 + B3	0.277	1.809 (0.621, 5.268)
C	0.037	3.083 (1.069, 8.887)
Masaoka-Koga stage (III and IV)	0.062	1.560 (0.978, 2.489)
Adjuvant chemotherapy (no/yes)	0.054	1.623 (0.992, 2.656)
Surgical approach (thoracoscope/open)	0.641	1.411 (0.332, 5.993)
Tumor size (≤5 cm/>5 cm)	0.502	0.843 (0.511, 1.389)
Complete resection (R0/R1 + R2)	0.021	0.617 (0.410, 0.929)
Postoperative radiotherapy (no/yes)	0.014	0.537 (0.326, 0.884)

OR, odd ratio; CI, confidence interval; WHO, World Health Organization.

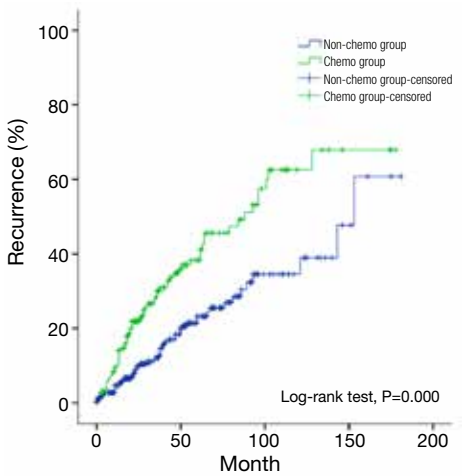

Figure 4 Five- and ten-year recurrence rates (chemo group *vs.* non-chemo group, P=0.000).

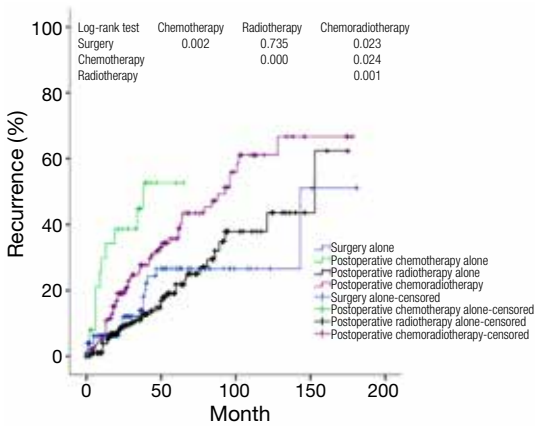

Figure 5 Cumulative incidence of recurrence for subgroups of patients with surgery alone, chemotherapy alone, radiotherapy alone, and chemoradiotherapy.

risk factors predicting recurrence in Masaoka-Koga stage III and IV tumors. Recurrence was significantly more frequent in those patients with WHO type C tumors, incomplete resection, or postoperative radiation (P=0.024, P=0.021, P=0.014, respectively). Five-year and 10-year recurrence rates were 26% and 40% in the non-chemo group, and were 46% and 68% in the chemo group, with statistical significance between the groups (P=0.000) (*Table 8*) (*Figure 4*).

Further stratification analysis showed that recurrence rate in Masaoka-Koga stage III and IV patients having adjuvant chemotherapy alone after surgery was noticeably higher than those of having surgery alone, postoperative radiotherapy alone, or postoperative chemoradiotherapy (P=0.002, P=0.000, P=0.024, respectively) (*Figure 5*) (*Table 9*).

Propensity-matched study comparing survival in patients having or not having adjuvant chemotherapy

The study was carried out by matching factors including the presence of myasthenia gravis, WHO histology type, pathological staging, resection status, and postoperative adjuvant radiotherapy. Three-hundred and sixteen patients were obtained after matching, with 158 cases each in the chemo and non-chemo groups. Patient characteristics

Table 9 Comparison of recurrence rates among different adjuvant therapy subgroups

Log-rank	Surgery alone		Postoperative chemotherapy alone		Postoperative radiotherapy alone		Postoperative chemoradiotherapy	
	Chi-square	Sig.	Chi-square	Sig.	Chi-square	Sig.	Chi-square	Sig.
Surgery alone			9.875	0.002	0.115	0.735	5.145	0.023
Postoperative chemotherapy alone	9.875	0.002			23.845	0.000	5.062	0.024
Postoperative radiotherapy alone	0.115	0.735	23.845	0.000			10.477	0.001
Postoperative chemoradiotherapy	5.145	0.023	5.062	0.024	10.477	0.001		

Table 10 1:1 caliper propensity-matched study results

Factor	Non-chemo group, n=158	Chemo group, n=158	P value
Sex			0.816
Male	100	98	
Female	58	60	
Myasthenia gravis			0.489
Yes	21	17	
No	137	141	
WHO type three classifications			0.709
A + AB	8	8	
B1 + B2 + B3	62	55	
C + NETT	88	95	
Pathological staging			0.496
III	121	126	
IV	37	32	
Resection status			0.224
R0	91	82	
R1	22	17	
R2	45	59	
Adjuvant radiotherapy			0.458
No	25	30	
Yes	133	128	

WHO, World Health Organization; NETT, neuroendocrine thymic tumor.

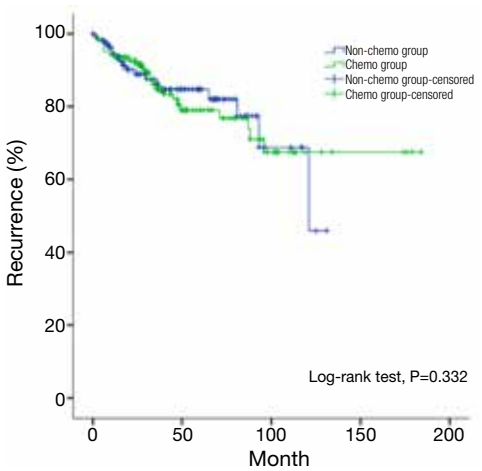

Figure 6 Survival curves of the two groups in the propensity-matched study.

were listed in *Table 10*. Again no survival benefit from postoperative chemotherapy was detected, although this time the survivals in patients having or not having chemotherapy after surgery became similar (P=0.332, *Figure 6*).

Discussion

Long-term survival of thymic tumors patients varies according to their histological subtypes, tumor staging, and resection status, which have repeatedly been identified as independent predictive factors for prognosis. As reported by Kondo *et al.* (4), 5-year survival rates for patients at stages I, II, III and IV were 100%, 98%, 89% and 71% respectively. Most published results showed that for tumors at stages I and II, no postoperative adjuvant therapy is necessary after complete resection (5,6). But in stage III and IV diseases, radical resection rate is much lower due to extensive local invasion or tumor spread. Postoperative adjuvant therapies, including chemotherapy, are often accepted as a common practice. Our results also found that WHO type C tumors, incomplete resection, and postoperative radiotherapy were adversely related to survival and recurrence in thymic tumor patients. The worse outcome in patients receiving adjuvant radiotherapy may be contributed to its use in higher grade tumors in more advanced stages. Unfortunately, we failed to find any survival benefit of adjuvant chemotherapy for stage III and IV tumors in our study.

Currently, postoperative chemotherapy is mainly used

with the purpose to reduce tumor burden after incomplete surgery, or to enhance disease control after complete resection. Its prognostic value is highly controversial, as there have been only limited data from retrospective studies of small sample researches (7-11). Ströbel *et al.* (12) reported a retrospective analysis on their experiences in 228 cases thymomas and thymic squamous cell carcinomas. The results showed that postoperative chemotherapy did not improve long-term survival in type A, AB and B1 thymomas, or in stage II type B2 and B3 tumors, while postoperative radiotherapy seemed to extend survival in stage III patients. Kim *et al.* (13) analyzed the clinical data from 100 cases of thymic tumors and found that comparing to postoperative radiotherapy alone, adding chemotherapy to radiation failed to show any significant difference in 5-year survival rates of stage II and IV tumor patients. Kondo *et al.* (4) reported the largest retrospective cohort yet published, including 1,320 cases of thymic tumors treated at 115 medical centers in Japan. Again, they found that neither postoperative radiotherapy nor postoperative chemotherapy could improve the outcomes in stage III and IV thymic tumors after radical surgery. Attaran *et al.* (14) concluded that although primary chemotherapy and palliative chemotherapy might have favorable therapeutic effect in certain patients, no evidence till now showed that postoperative chemotherapy could help prolong survival in patients with thymic tumors in general. Using the ChART retrospective database, the results from the current study were in consistency with the previous reports. Our results indicate that for Masaoka-Koga stage III and IV thymomas and thymic carcinomas, postoperative chemotherapy has no clear advantage with regard to recurrence and survival time.

The retrospective nature of our study and the lack of consistence in the sources of data from different centers may help explain the causes of relatively unfavorable survival and higher recurrence in patients receiving adjuvant chemotherapy after surgery. The chemo group was found to have higher grade of tumor, more stage IV diseases, and less radical resection comparing to the non-chemo group, all of which have been shown to be associated with worse prognosis in thymic malignancy. The Japanese Association for Research in Thymus (JART) results (4) showed that 10-year survival rates in completely resected stage III and IV thymomas were 70.9%, 70.4%, 77.9% and 95% respectively for the subgroups of postoperative chemotherapy, postoperative chemoradiotherapy, postoperative radiotherapy and surgery alone, with a significant difference between the subgroups of surgery alone and of postoperative chemoradiotherapy (P=0.0353). The 5-year survival rates in completely resected stage III and IV thymic carcinomas were 81.5%, 46.6%, 73.6%, and 72.2% respectively, for the subgroups of postoperative chemotherapy alone, postoperative chemoradiotherapy, postoperative radiotherapy, and surgery alone, with significant differences among the subgroups of postoperative chemoradiotherapy, postoperative chemotherapy and surgery alone (P=0.0213, P=0.0397). In the current study from the ChART database, survival rates in the subgroups of postoperative chemoradiotherapy and of postoperative chemotherapy were even worse compared to the subgroups of surgery alone or surgery followed by radiotherapy. In view of the unbalanced distribution of potential risk factors in each group, we are in no position to conclude that chemotherapy lead to worse outcome. But neither did we found any survival benefit brought by the application of postoperative chemotherapy to our patients with Masaoka-Koga stage III and IV thymic tumors.

To rule out the potential selection bias and other intrinsic bias associated with all retrospective studies, we further carried out a propensity matched study so as to balance the distribution of all risk factors. The 158 pairs of patients having or not having postoperative chemotherapy after surgery were comparable in tumor stage and histology, myasthenia gravis, resection status, and postoperative radiotherapy. Still there was no significant difference in overall survival rates between the subgroups having or not having postoperative chemotherapy (P=0.332). Thus at current stage it is reasonable to conclude that, postoperative chemotherapy may not have any survival benefits for advanced stage thymic tumors.

Because of the multiple centers involved and long time span, the chemotherapy regimens, cycles and dosage used in the current study were highly heterogeneous. It was thus impossible for us to evaluate the difference of any specific regimen. Only prospectively designed study could help answer such questions. However, our study again shows that histological subtypes and completeness of resection play major roles in determining the prognosis of thymic tumors, even for advanced stage diseases. Currently available chemotherapy regimens do not seem likely to provide significant survival benefit for this group of patients. The hope of improving management outcomes would lie in the use of chemotherapy in neoadjuvant setting, or in the search of more effective new agents for thymic tumors.

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None.

Footnote

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How large databases may impact clinical practices for rare tumors—postoperative chemotherapy in thymic malignancies

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In this issue of the *Journal of Thoracic Disease*, Ma *et al*. report on the analysis of a cohort of 665 patients with advanced thymic epithelial tumors, looking at the long-term effects of postoperative chemotherapy on recurrence and survival rates (1). This cohort of the Chinese Alliance for Research in Thymomas (ChART) is the largest to date to investigate this question. Postoperative chemotherapy is actually not routine practice (2), as the vast majority of patients operated on for a thymic epithelial tumor do have early-stage disease (1,015 patients out of 2,306 cases in the ChART database), and/or receive primary/induction chemotherapy in the setting of advanced, non-resectable disease to subsequently achieve complete resection (3)—surprisingly a rare situation in the ChART database, only 68 out of 2,306 cases. Ultimately, the rationale for postoperative chemotherapy is limited in thymomas, as the risk of systemic metastases is low, ranging from 8% in stage I/II tumors, to 29% in stage III/IV tumors in the International Thymic Malignancy Interest Group (ITMIG) retrospective database (4); moreover, the majority of recurrences occur loco-regionally, in the pleura, with possible eligibility to re-resection. Meanwhile, recurrences, including systemic recurrences, are more frequent in thymic carcinomas, occurring in 29% of stage I/II cases, and in 51% of stage III/IV cases (4).

The results of the ChART database analysis confirm, with an even higher statistical power, that of previously reported series; postoperative chemotherapy was most frequently delivered in the setting of higher stage (27% of stage III, 56% of stage IV tumors)—and thus higher histological grade, type B3 thymomas (28% of cases) and thymic carcinomas (51% of cases), given the well established correlation between stage and histology in thymic epithelial tumors (5)—and incomplete, R2 resection (51% of cases, *vs*. 27%–30% of R0–R1 cases).

This is in line with existing recommendations in the field. Especially, the Clinical Practice Guidelines of the European Society for Medical Oncology (ESMO) recommends postoperative chemotherapy to be administered after R2 resection of a thymoma, and to be systematically considered in stage II/III/IV thymic carcinomas, especially if not delivered as induction treatment (2). Actual evidence is sparse: only one prospective phase II study was conducted in advanced thymoma, showing, in 22 patients, the feasibility of multimodal strategy with induction chemotherapy, surgical resection, and radiation therapy, followed by consolidation chemotherapy with cyclophosphamide, doxorubicin, cisplatin and prednisone (6); in thymic carcinoma, recent reports from the ITMIG and European Society of Thoracic Surgery databases indicate that postoperative chemotherapy was delivered to 30% to 42% of patients, with unclear benefit (7,8); combination with radiotherapy was then reported in the majority of patients (7).

Those data also illustrate the difficulties in identifying the clinical relevance of retrospective data, even if large cohorts of patients are analyzed. In the ChART study, stratification analyses further indicate that patients who received postoperative chemotherapy or chemoradiotherapy

had a significantly worse outcome, with recurrence rates of 46% *vs*. 26% in the non-chemotherapy group. As stated by the authors, postoperative chemotherapy may have preferably been administered for high-risk patients (thymic carcinoma histology, high stage, R2 resection), then hampering the statistical identification of its potential benefit. Indeed, in the propensity-matched analysis, no differences in the chemotherapy and non-chemotherapy groups were observed.

Ultimately, the analysis of large databases would be facilitated if pre-defined treatment strategies are prospectively implemented on homogeneous subsets of patients, across multiple institutions, based on consensual guidelines. In France, RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a nationwide network for thymic malignancies, which was appointed in 2012 by the French National Cancer Institute, as part of its rare cancer program. Since then, the management of all patients diagnosed with thymic tumors has been discussed on a real-time basis at a national multidisciplinary tumor board (MTB), which is organized twice a month basis using a web-based conferencing system. Decision-making is based on consensual recommendations that were originally established based on available evidence, and are updated and approved each year by all members of the network. A prospective database of all patients is hosted by the French Thoracic Cancer Intergroup. Overall, more than 1,000 patients have been enrolled, demonstrating the feasibility of a national MTB for thymic malignancies, that, besides ensuring patients an equal access to highly specialized management, provides with a comprehensive tool to monitor dedicated actions to improve the management of patients (9).

While prospectively ensuring the stringency of the decision-making at each step of the management of patients with thymic tumors, what represents a major commitment of multi-disciplinary teams, one limitation of such organization are the low levels of evidence and grades of recommendation of available guidelines. The ESMO Clinical Practice Guidelines, even if representing the most comprehensive recommendations for the management of thymic malignancies, are still based on level of evidence of III (prospective cohorts), IV (retrospective studies), and even V (expert opinions).

To conclude, the global and comprehensive effort of ChART has to be congratulated, emphasized, and should lay the foundations of prospective, controlled studies, possibly integrating innovative approaches such as adaptive, Bayesian designs. As a landmark of rare diseases, collaboration may make a success, and thymic malignancies represent a model of incremental effort in this setting.

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Footnote

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Outcome of nonsurgical treatment for locally advanced thymic tumors

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Background: Surgical resection remains the mainstay of treatment for patients with early-staged thymic tumors, while chemotherapy is most commonly used in stage IV cases. As for locally advanced thymic tumors, especially those unsuitable for surgery, the optimal therapy is still controversial. Thus, we conducted this retrospective study by comparing three nonsurgical treatment modalities to find some clues.

Methods: Three treatment modalities were used in 42 patients from October 2000 to December 2010, including radiotherapy (RT) alone, sequential chemoradiation (SCRT) and concurrent chemoradiation (CCRT). Objective response rate (ORR), overall survival (OS) and toxicity of the three regimens were compared accordingly.

Results: The ORR in all 42 patients was 61.9%, and 5-year OS was 46%. The ORR of RT, SCRT and CCRT were 43.8%, 50% and 87.5%, respectively (RT *vs.* SCRT, P=0.692; RT *vs.* CCRT, P=0.009; SCRT *vs.* CCRT, P=0.051). The 5-year OS of RT, SCRT and CCRT were 30%, 50% and 61.9%, respectively. (RT *vs.* SCRT, P=0.230; RT *vs.* CCRT, P=0.011; SCRT *vs.* CCRT, P=0.282). Eleven patients developed neutropenia of grade 3–4, with 7 in CCRT group and 4 in SCRT, respectively. Nine patients experienced esophagitis of grade 3 with 2 in RT, 3 in SCRT and 4 in CCRT. There were also two cases of grade 3 radiation induced pneumonitis in CCRT group. No life-threatening side effects were noted.

Conclusions: When used to treat locally advanced thymic tumors unsuitable for surgery, CCRT performed more favorably than RT alone or SCRT in both tumor response and long time survival, but probably with the increasing risk of pulmonary damage. CCRT may offer the best chance of disease control in the management of locally advanced disease.

Keywords: Thymic tumor; radiotherapy (RT); chemotherapy

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Introduction

Thymic epithelial tumor is an uncommon neoplasm originated from epithelial cells of the thymus. Its incidence is reported to be as low as 0.13/100,000 (1). Surgical resection remains the mainstay of treatment for patients with early-staged disease, with a 10-year-survival of 71% to 100% (2). By contrast, chemotherapy-based regimens are most commonly used in stage IV cases. As for locally advanced thymic tumors, surgical resections are usually pursued after neoadjuvant chemo- or radiotherapy (RT), because complete resection has been proved to be the most significant prognostic factor for survival (3). In clinical practice, however, there are situations in which surgery is inapplicable, either due to extensive tumor invasion into

Table 1 Clinical characteristics of patients at baseline

Variables	N (%)
Age [range, y]	54 [17–77]*
Gender	
Male	28 (66.7)
Female	14 (33.3)
Tumor size [range, cm]	6 [4–15]*
WHO classification	
B2	4 (9.5)
B3	7 (16.7)
C	31 (73.8)
Masaoka stage	
III	35 (83.3)
IVa	4 (9.5)
IVb	3 (7.2)

*, median [range].

critical organs, or poor cardiopulmonary functions of the patients. By far, the optimal therapy for these inoperable patients has yet to be established. Reports aiming at comparing different nonsurgical treatment modalities in a short time period have been scanty, mainly because of the rarity of the disease. We thereby retrospectively studied 42 patients treated during a 10-year span at a single institution, trying to shed some light on this challenging clinical scenario.

Materials and methods

From October 2000 to December 2010, a total of 61 patients with thymic tumors were treated at the Department of Radiation Oncology, Shanghai Chest Hospital with definitive RT, sequential chemoradiation (SCRT) or concurrent chemoradiation (CCRT) plus consolidation chemotherapy. Among them, 42 were enrolled in the current study. The criteria for enrollment are as follows: (I) histology proven diagnosis as thymic tumor by pre-treatment biopsy; (II) invasive stage III upon radiological images; (III) stage IV with only adjacent pleural implant or lymph-node enlargement which could be covered by one radiation field along with the primary tumor; (IV) no metastasis to distant organs. This retrospective study was approved by the Institutional Review Board. All patients' demographic information and tumor-related data were obtained by reviewing medical record.

Between 2000 and 2006, all RT was delivered by three-dimension conformal radiation (3-D CRT). After that, it was replaced by intensity modulated radiation (IMRT). Chemotherapy was used as initial treatment in SCRT group, followed by RT at a time point when tumors shrunk to a stable size or tumors showed no response to chemotherapy. In the CCRT group, chemotherapy and RT were started simultaneously on the first day, and the cycles of consolidation chemotherapy varied based on patients' status and oncologist's judgment. According to medical record, 16 patients did not receive chemotherapy mainly due to medical reasons (compromised renal function, old age, Parkinson disease, etc.).

Evaluation of response and toxicity

The radiographic response was evaluated according to a new Response Evaluation Criteria in Solid Tumors (RECIST) guideline proposed by International Thymic Malignancy Interest Group (ITMIG) (4). Toxicity associated with treatment was assessed by Common Terminology Criteria for Adverse Events (CTCAE 4.0).

Statistical analysis

The χ^2 or Fisher's exact tests were used to compare categorical data when appropriate. Survival was estimated by Kaplan-Meier curves, and differences among groups were compared by log-rank test. A Cox regression model was used to calculate hazard ratio (HR) and its 95% confidence interval (CI). Statistical analysis was performed using SPSS version 16.0 software. All tests were two-sided, with $P<0.05$ deemed as statistically significant.

Results

There were 42 patients included in this study. The characteristics of these patients are summarized in *Table 1*. Of these patients, 16 were treated by RT alone, 10 by SCRT and 16 by CCRT. The median dose of RT was 60 Gy (range, 34–70 Gy). Chemotherapy regimens varied during a 10-year period, but docetaxol and cisplatin (DP) was most frequently used. The details of regimens are shown in *Table 2*.

Response data and survival analysis

The overall objective response rate (ORR) in all 42 patients was 61.9% (26/42). The ORR in different subgroups was

Table 2 Chemotherapy regimen and cycles used in 26 patients

Treatment	Regimen	Cycles (n)
Concurrent	DP	20
	CAP	2
Sequential	DP	19
	IVP	11
	CAP	6
	MVP	3
	NP	1

DP, docetaxel + cisplatin; CAP, cyclophosphamide + doxorubicin + cisplatin; IVP, ifosfamide + etopiside + cisplatin; MVP, mitomycin + vindesine + cisplatin; NP, vindesine + cisplatine.

Table 3 The overall response rate in different subgroups

Subgroup	Number	ORR (%)	P value
Treatment modality			
RT	16	43.8	1 *vs.* 2=0.69
SCRT	10	50.0	2 *vs.* 3=0.05
CCRT	16	87.5	1 *vs.* 3=0.01
Histology type			
Thymoma	11	81.8	0.10
Thymic carcinoma	31	54.8	0.10
Masaoka stage			
Stage III	35	68.6	–
Stage IV	7	28.6	0.05

ORR, overall response rate; RT, radiotherapy; SCRT, sequential chemoradiation; CCRT, concurrent chemoradiation.

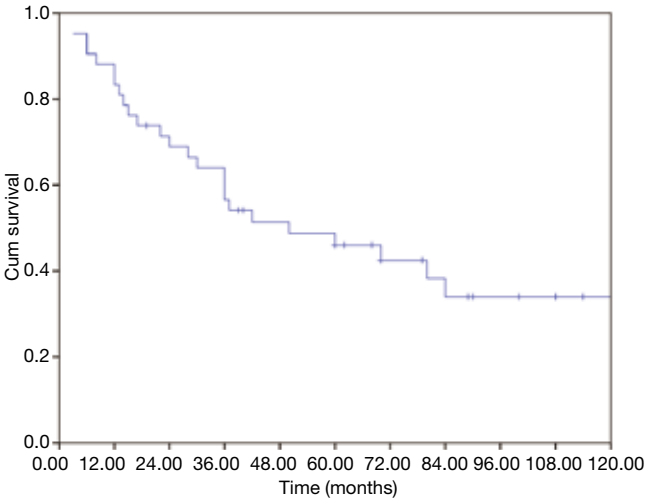

Figure 1 Overall survival (OS) of all 42 patients.

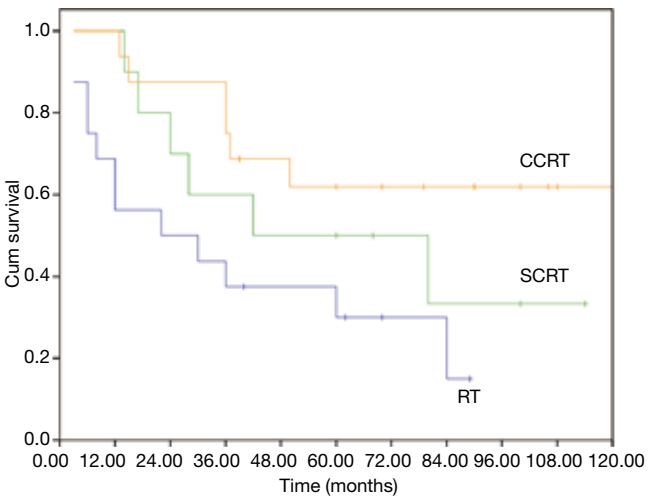

Figure 2 Survival curves of three treatment regimens (CCRT *vs.* SCRT, P=0.282; CCRT *vs.* RT, P=0.011; SCRT *vs.* RT, P=0.230). CCRT, concurrent chemoradiation; SCRT, sequential chemoradiation; RT, radiotherapy.

listed in *Table 3*, and CCRT rendered higher ORR than RT (87.5% *vs.* 43.8%, P=0.009) and SCRT (50%, P=0.051). In SCRT group, a sub-group comparison was made between DP regimen and non-DP regimen, and the result showed no significant difference (75% *vs.* 50%, P=0.571).

The median overall survival (OS) of the whole cohort was 41 months (95% CI, 40.5%–64.5%), with a 5-year OS of 46% (*Figure 1*). The survival curves of different groups are shown in *Figures 2-4*.

In univariate analysis (*Table 4*), age (P=0.031), Masaoka stage (P=0.009) and treatment modality (P=0.031) were significant variables affecting OS, with CCRT providing the best OS. In Cox regression, Masaoka stage, treatment modality and histology type were independent predictors for OS (*Table 5*).

Toxicity

There was no treatment related death in this cohort. The major toxicity was grade 3–4 neutropenia, which was observed in 11 patients. Other adverse events are listed in *Table 6*. The overall complication rate was similar in SCRT and CCRT group (70% *vs.* 80.3%), both higher than that in RT group (12.5%).

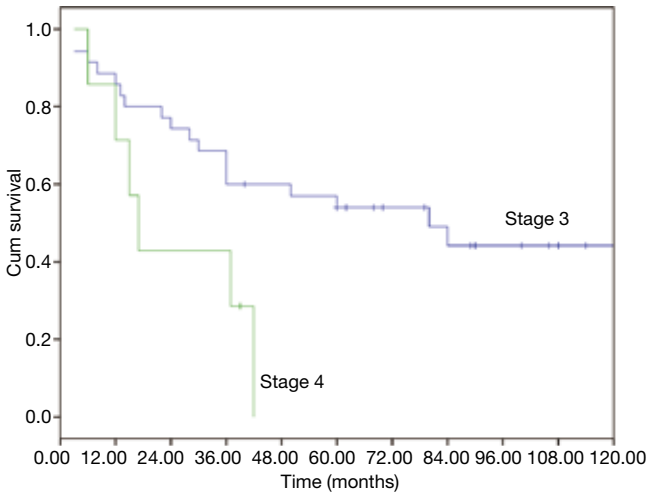

Figure 3 Overall survival (OS) of patients with Masaoka III and IV tumors (P=0.009).

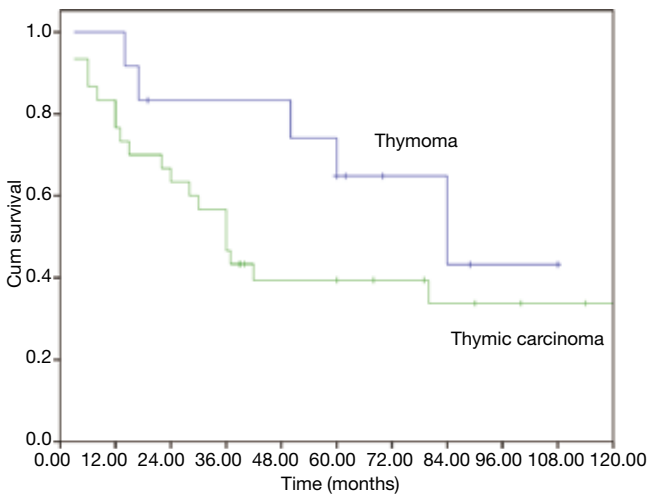

Figure 4 Overall survival (OS) of patients with thymoma and thymic carcinoma (P=0.163).

Discussion

For well-encapsulated, noninvasive thymic epithelial tumors, complete resection is usually curative, with a risk of local recurrence of less than 2% (2). However, there is no standard approach to advanced thymic tumors apart from surgery. Non-surgical modalities, such as RT, chemotherapy, or their combinations, are randomly adopted based on individual oncologist's experience or preference. To the best of our knowledge, this is the first report comparing three different non-surgical treatments for inoperable thymic tumors. Our results showed that CCRT achieved more favorable outcomes than SCRT and RT alone in both tumor response and long time survival.

Apart from complete resection, WHO classification and Masaoka stage are generally accepted as the most important prognostic factors for thymic malignancies (2,5). In the current study for unresectable tumors, we found that in addition to the above factors, treatment modality also had important influence on OS in multivariate analysis as shown in *Table 5*. And CCRT also showed significant superiority over the other two treatment methods in ORR (CCRT *vs.* SCRT: 87.5% *vs.* 50%, P=0.051). When chemotherapy and radiation are applied simultaneously, interaction between the two modalities often shows a

Table 4 Univariate analysis of factors influencing survival

Variables	P value
Gender	0.673
Age (<60 *vs.* >60)	0.031
Tumor diameter (<6 *vs.* ≥6 cm)	0.243
Histology (thymoma *vs.* carcinoma)	0.163
Masaoka stage (III *vs.* IV)	0.009
Treatment (CCRT *vs.* others)	0.031
Radiation dose (<60 *vs.* ≥60 Gy)	0.125

CCRT, concurrent chemoradiation.

Table 5 Multivariate analysis for factors predicting survival

Variables	Hazard ratio (CI)	P value
Age (<60 *vs.* >60)	0.818 (0.333–2.012)	0.662
Histology	3.465 (1.042–11.526)	0.043
Masaoka stage (III *vs.* IV)	3.772 (1.277–11.139)	0.016
Treatment (CCRT *vs.* others)	0.185 (0.054–0.643)	0.008

CCRT, concurrent chemoradiation.

Table 6 Toxicities of grade 3–4 in different groups

Toxicity	RT (%)	SCRT (%)	CCRT (%)	P value (SCRT *vs.* CCRT)
Neutropenia	0	4 (40)	7 (43.8)	0.847
Esophagitis	2 (12.5)	3 (30)	4 (25.0)	0.783
Pneumonitis	0	0	2 (12.5)	0.249

RT, radiotherapy; SCRT, sequential chemoradiation; CCRT, concurrent chemoradiation.

synergistic effect, and eliminates the tumor to the maximum extent. The advantages of CCRT have been explained through the following mechanisms: (I) chemotherapy agents and radiation can cover different tumor components in a heterogeneous tumor; (II) they also have spatial coordination effect; (III) tumor cells in different cell cycle phase show different sensitivity to chemotherapy and radiation, the concomitant use of the two allows a maximum decrease in tumor; (IV) some chemotherapy agents can act as radiation sensitizers and enhance the anti-tumor effect of RT (6-9). By far, there are no large-scale reports regarding CCRT on locally advanced thymic tumors. Chen and his colleagues (10) conducted CCRT on 16 patients with unresectable thymic carcinomas. The 5-year OS was 67.7%, which is similar to our result (61.9%). These results are even better when compared with some treatments involving surgery (11-13), of which the 5-year OS were around 35%. Wright (14) and Korst (15) have both tried CCRT on locally invasive thymic tumors as preoperative induction therapy. After surgical resection, they reported an R0 resection rate of 80% and complete pathologic response rate of 20%, which was better than other inductive modalities (16-18). Therefore, the role of CCRT as an induction therapy for potentially resectable invasive thymic tumors should definitely be studied on a large scale.

Due to its retrospective nature, chemotherapy regimens varied a lot in our study. But it should be notified that in the CCRT group, the most often used chemotherapy regimens (91%) was DP. In Chen's study (10), the ORR was only 50%, much lower than the 87.5% ORR in our CCRT group. Looking into details, the median radiation dose was almost the same in the two groups (60 Gy). But the chemotherapy regimen in Chen's study (5-FU + cisplatin) was different from ours (DP). The ORRs in Korst's (15) and Wright's (14) trials were both around 45%, also lower than the ORR in the current study. Of course the radiation dose in these two trials in an inductive setting (45 Gy) was lower than that in the current study as a definitive therapy (60 Gy). But there was also difference in chemotherapy agents (EP *vs.* DP). Watanabe *et al.* also reported (19) that docetaxol was an active agent against thymic carcinoma, with an ORR of 31%. In our SCRT group, we compared the ORRs between DP regimen and non-DP regimen and found no significant difference. However, there is still the possibility that their roles might be different in CCRT. At least from the current study, concomitant use of DP and radiation showed the highest activity in reducing tumor volume. Therefore, the efficacy of DP in CCRT should be further tested in prospective trials.

In case of toxicities, no fatal events occurred in our patients. Neutropenia and esophagitis were the two major side effects, but most of them were moderate and manageable. It should be specified that almost all of the esophagitis happened before 2006, when 3-D conformal RT was dominant and opposed anteroposterior fields were frequently used at the time. After upgrading the radiation technique to IMRT, severe esophagitis was no longer observed. The overall toxicity rate was similar in the SCRT group and CCRT group. However, the two cases of grade-3 pneumonitis were both found in the CCRT group, suggesting that potential risk of pulmonary damage should not be neglected when definitive CCRT is applied.

There are several limitations to our study due to its retrospective nature with limited number of patients. Treatment was not carried out by unified protocol but based on physician's own experience. And there was lack of consistency in chemotherapy regimen. Nevertheless, we found significantly improved results in response rate and survival with DP based CCRT in our patients. Thus we believe this management modality should be further tested by prospective trials.

In conclusions, when used to treat locally advanced thymic tumors unsuitable for surgical resection, CCRT performed more favorably than RT alone or SCRT in both tumor response and long time survival, but probably with increased risk of radiation pneumonitis. Based on these results, CCRT may offer the best chance of disease control for this group of patients. And the role of CCRT in induction setting for locally advanced thymic tumors should also be tested so as to increase the complete resection rate and to improve long-term outcome.

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Footnote

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Non-surgical treatment of locally advanced thymic epithelial tumors—a need for multicenter trials

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Thymic epithelial tumors (TET) are rare neoplasms that usually occur in the prevascular mediastinum. Complete resection has been shown to be a favorable prognostic parameter for TET (1-4). Resectability of these tumors usually depends on their size and stage with reported rates of complete resection ranging between 100% for Masaoka stage I and 0%–78% for stage IV tumors (1,3). In unresectable or not completely resectable TET, the effects of neoadjuvant chemotherapy and/or radiation might increase the chance of complete resection. Reportedly, complete resection has been achieved in 57% to 80% of TET following chemotherapy (5-7), 90.5% following radiation therapy (8) and 77% to 80% following chemoradiation (9,10). However, these studies were small including only 10 to 21 patients. Furthermore, while some studies included only patients with thymoma, others included both thymomas and thymic carcinomas. In addition, these studies did not compare the efficacy of different treatment modalities.

While in most patients with unresectable TET neoadjuvant therapy is given to increase the likelihood of complete resection of the tumor, in some patients with locally advanced TET that involve vital structures and/or in patients with suboptimal performance status, surgical intervention might not be an option at any time and an alternative treatment is sought. The National Cancer Care Network (NCCN) guidelines recommend a multidisciplinary approach to the treatment of locally advanced, advanced or recurrent TET by a "team with experience in the management of thymoma and thymic carcinoma" (11). For these tumors, chemotherapy followed by re-evaluation of the patient for resectability is recommended by the NCCN. If the TET continues to be unresectable, radiation with or without chemotherapy is advised. However, there are no guidelines or standards for the treatment of patients with inoperable TET and their optimal treatment is unknown. This lack of recommendations and standards is at least in part due to the paucity of the disease and the fact that the vast majority of patients with TET will undergo surgery. Based on the data from the retrospective database of the International Thymic Malignancy Interest Group (ITMIG) only about 1% of patients are not treated surgically in any way. These patients received palliative chemotherapy (0.7%, n=27), chemoradiation (0.3%, n=10) or radiation (0.2%, n=7). All other patients were treated surgically with or without neoadjuvant and/or adjuvant therapy. Although a slightly higher number of non-surgically treated patients (5.5%) was reported in the restrospective database of the Chinese Alliance for Research in Thymomas (ChART) (12), this group of patients still represents a very small subset of all TET, a disease that by itself is very rare.

The paucity of TET and the in general good prognosis and favorable long-term outcome of most patients with the disease hampers the study of the efficacy of treatments other than surgery and large prospective randomized clinical trials become extremely challenging. Only a few retrospective studies have been performed, which were in general small.

One of the largest studies was recently published by Wang *et al*. (13) that was comprised of 42 inoperable patients with TET. This single center, retrospective study from the Shanghai Chest Hospital included 11 patients with thymoma and 31 patients with thymic carcinoma collected over a 10-year period. The study encompassed patients with histologically proven TET, Masaoka stage III disease upon radiologic imaging, stage IV disease with only adjacent pleural implant or lymph node enlargement which could be covered by one radiation field along with the primary tumor and no metastasis to distant organs. The best objective response rate (ORR) was achieved with concurrent chemoradiation with consolidation chemotherapy (ORR, 87%); patients who were treated with radiation therapy had a significantly lower ORR (44%). Sequential chemoradiation showed a trend towards an ORR (50%) that was lower than that of concurrent chemoradiation. Similarly, patients who were treated with concurrent chemoradiation had a significant better overall survival (5-year survival, 62%) than patients treated with radiation alone (30%) and showed a trend toward better survival than patients treated with sequential chemoradiation (50%). Moreover, concurrent chemoradiation was found to be a prognostic factor that was independent of age, Masaoka stage (stage III *vs*. IV) and histology (thymoma *vs*. thymic carcinoma). A similar 5-year survival of 68% was found by Chen *et al*. using concurrent chemoradiation in 16 patients with unresectable thymic carcinoma although the ORR was only 50% in that study (14). In studies by Wright *et al*. (10), including 10 patients with stage III and IV thymic malignancies and Korst *et al*. (9), including 21 patients with thymoma or thymic carcinoma, concomitant chemoradiation led to 40% and 48% ORR, respectively.

Although there are commonalities between these studies in that at least a cohort of patients was treated with concurrent chemoradiation, the studies are difficult to compare given that patients were collected over many years, and chemotherapy regimens and amount of radiation and probably radiation fields were different between studies. In addition, because many of these studies included patients accumulated over many years, there were likely treatment changes even within studies. Furthermore, in some studies concomitant chemoradiation was given with the intent of potential subsequent surgery (9,10). Also, studies included thymic carcinomas only or both, thymomas and thymic carcinomas. The study by Wang *et al*. is unique because of the relative high number of patients with this very rare condition collected at a single institution and the ability of the study to compare different treatment modalities (13). Furthermore, that study included patients that were treated with the intent for chemotherapy and/or radiation to be the ultimate treatment since these patients were thought to be inoperable.

Wang's study suggests that concomitant chemoradiation therapy might offer the best treatment options in inoperable TET patients and might be superior to radiation alone and possibly to sequential chemoradiation (15). Interestingly, a possible beneficial effect of concomitant chemoradiation was also shown in a recent study of patients with TET identified from the ChART database who underwent biopsy before treatment (16). Patients with TET that could be downstaged after neoadjuvant therapy and who subsequently underwent resection had a significant better outcome than patients with TET that could not be downstaged following neoadjuvant therapy but were also subsequently surgically treated (5-year survival, 92% *vs*. 37%, P=0.004). The survival of the latter patients trended to be worse than that of patients who received definite chemoradiation without surgery (5-year overall survival, 62%) (16).

To validate the observations by Wang *et al*. (13), prospective randomized clinical trials are greatly needed. Given the rarity of these tumors, such clinical trials might only be possible as multicenter regional or global endeavors to accrue a higher number of patients to provide sufficient power for a meaningful statistical analysis of outcome. Furthermore, although PD-L1 expression has been shown in at least a subset of thymoma and thymic carcinoma (12,17,18), randomized prospective clinical trials using anti-PD-1 or anti-PD-L1 antibodies have not been reported. National organizations such as ChART or the Japanese Association for Research of the Thymus (JART) and international associations such as the International Thymic Malignancy Interest Group (ITMIG) that are committed to research of TET would be ideal leaders for this effort. For instance, with contribution from 18 tertiary referral centers in 14 provinces and cities, ChART has successfully built a large national database for thymic malignancies, which contains more than 2,500 cases of treated thymic malignancies during 1994–2012 (12). ITMIG established a retrospective database comprised of over 6,000 cases from 47 institutions from 15 countries from North and South America, Europe and Asia (19). This database was already of fundamental value for the 2015 WHO classification of thymic malignancies (20). Conclusions drawn from the analysis of this database also formed the basis for a staging system that was recently proposed by the International

Association of the Study of Lung Cancer (IASLC) and ITMIG that might be useful for thymoma, thymic carcinoma and thymic neuroendocrine tumors as currently no such staging system exist that can be easily applied to all these tumors (21).

In summary, evidence from the study by Wang *et al*. (13) suggests that concomitant chemoradiation might lead to a better outcome in patients with inoperable TET than subsequent chemoradiation or radiation only. These findings need to be validated in large, multicenter trials that would be most successful if headed by the existing national and international interest groups in TET that are dedicated to the research of these rare tumors and have established robust infrastructures that could facilitate such studies.

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Footnote

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Postoperative survival for patients with thymoma complicating myasthenia gravis—preliminary retrospective results of the ChART database

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Background: It is so far not clear that how myasthenia gravis (MG) affected the prognosis of thymoma patients. The aim of this assay is to compare the postoperative survival between patients with thymoma only and those with both thymoma and MG.

Methods: The Chinese Alliance for Research in Thymomas (ChART) registry recruited patients with thymoma from 18 centers over the country on an intention to treat basis from 1992 to 2012. Two groups were formed according to whether the patient complicated MG. Demographic and clinical data were reviewed, patients were followed and their survival status were analyzed.

Results: There were 1,850 patients included in this study, including 421 with and 1,429 without MG. Complete thymectomy were done in 91.2% patients in MG group and 71.0% in non-MG group (P<0.05). There were more percentage of patients with the histology of thymoma AB, B1, or B2 (P<0.05) in MG group, and more percentage of patients with MG were in Masaoka stage I and II. The 5- and 10-year overall survival (OS) rates were both higher in MG group (93% *vs.* 88%; 83% *vs.* 81%, P=0.034) respectively. The survival rate was significantly higher in patients with MG when the Masaoka staging was 3/4 (P=0.003). Among patients with advanced stage thymoma (stage 3, 4a, 4b), the constituent ratios of 3, 4a, 4b were similar between MG and non-MG group. Histologically, however, there were significantly more proportion of AB/B1/B2/B3 in the MG group while there were more C in the non-MG group (P=0.000).

Univariate analyses for all patients showed that MG, WHO classification, Masaoka stage, surgical approach, chemotherapy and radiotherapy and resectability were significant factors, and multivariate analysis showed WHO classification, Masaoka stage, and resectability were strong independent prognostic indicators.

Conclusions: Although MG is not an independent prognostic factor, the survival of patients with thymoma was superior when MG was present, especially in late Masaoka stage patients. Possible reasons included early diagnosis of the tumor, better histologic types, an overall higher R0 resection and less recurrence.

Keywords: Thymoma; myasthenia gravis (MG); survival

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Introduction

Due to the immunologic feature of the thymus, quite a few thymoma patients are accompanied with autoimmune disorders among which myasthenia gravis (MG) is the most important one with the incidence rate ranging 10%–45%. In early times, MG once was reported to be the negative factor (1) because of a lack of experiences to deal with MG related complications after thymothymectomy (2-4). On the other hand, there has been an increasing body of evidences indicating that MG is related to better survival. However, the role of MG in the postoperative outcome for patients with thymoma is so far still not clear. The Chinese Alliance for Research in Thymomas (ChART) registry recruited patients with thymoma from 18 centers over the country in 20 years with the intention to compare the postoperative survival between patients with thymoma only and those with both thymoma and MG so as to have a preliminary understanding of how MG affects the prognosis of patients with thymoma.

Materials and methods

Patients

The ChART registry included patients with thymoma from 18 centers over the country from 1992 to 2012. Demographic and clinical data were reviewed. In this research, two groups were formed according to whether the patient complicated MG—MG group and non-MG group. All the demographic and clinical data were compared between the two groups. Patients were followed before their survival status were compared. Because only de-identified data were used for the study, informed consent was waived by Institutional Review Board (IRB).

The final pathologic staging was based on Masaoka-Coga staging system while the histology types were based on WHO classification. The resectability of thymoma was divided into R0 (no residue tumor), R1 (residue tumor microscopically), R2 (residue tumor macroscopically), and biopsy only according to the pathology of the sample margins and the operation note. The normal thymus was either completely removed (total resection of the thymus) or partly (resection of the tumor and a portion of the thymus) removed according to the surgeon's preference. Data regarding chemotherapy and radiotherapy were also collected.

Statistical analysis

Statistical analysis was performed by the χ^2 test and the unpaired *t* test with the SPSS 14.0 for Windows. Prognostic factors were analyzed by the Kaplan-Meier method and Cox regression with respect to survival. Comparisons between survival curves were made by the log-rank test.

Results

Patients' characteristics: data of 2,306 patients were collected, and 1,850 patients entered this study, including 421 with and 1,429 without MG as showed in *Table 1*, after excluding the following ones: 49 patients only biopsied, 152 lack of surgical information, 124 without WHO classification, and 118 lack of Masaoka staging. There were more proportion of female in MG group than non-MG group (P=0.034) and the average age of MG group was significantly younger (49 *vs.* 52, P=0.000). The overall survival (OS) for MG group was significantly higher (95.95% *vs.* 92.29%, P=0.026). The tumor size of MG group was significantly smaller (5.6 *vs.* 7.2 cm, P=0.000). There were more percentage of patients with the histology

Table 1 Patients' characteristics

Characteristics	MG, n=421 (%)	Non-MG, n=1,429 (%)	P
Sex			0.034
Male	206 (20.9)	782 (79.1)	
Female	215 (24.9)	647 (75.1)	
Age (average), years	49	52	0.000
Overall survival (%)	95.95	92.29	0.026
WHO classification			0.000
A	18 (4.3)	89 (6.2)	
AB	80 (19.0)	356 (24.9)	
B1	68 (16.2)	164 (11.5)	
B2	128 (30.4)	169 (11.8)	
B3	107 (25.4)	256 (17.9)	
C	19 (4.5)	351 (24.6)	
Carcinoid	1 (0.2)	44 (3.1)	
Histology			0.000
Type A thymoma	18 (4.3)	89 (6.2)	
Type B (including AB) thymoma	383 (91.0)	945 (66.1)	
Thymic cancer	20 (4.8)	395 (27.6)	
Thymectomy			0.000
Incomplete	37 (8.8)	412 (29.0)	
Complete	382 (91.2)	1,008 (71.0)	
Tumor size (cm)	5.6	7.2	0.000
Masaoka staging			0.004
1	196 (46.6)	547 (38.3)	
2	83 (19.7)	277 (19.4)	
3	116 (27.6)	458 (32.1)	
4	26 (6.2)	147 (10.3)	
Chemotherapy (given)	36 (8.8)	317 (23.4)	0.000
Radiotherapy (given)	167 (41.0)	636 (47.1)	0.031
Resectability (rate of R0 resection)	379 (90.0)	1,212 (85.1)	0.009

MG, myasthenia gravis.

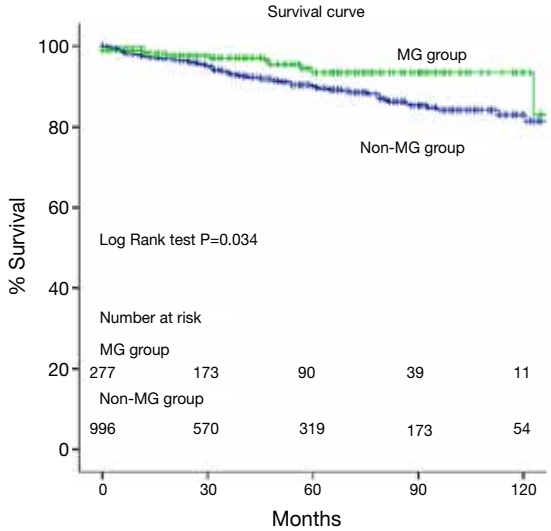

Figure 1 Comparison of overall survival between MG group and non-MG group. MG, myasthenia gravis.

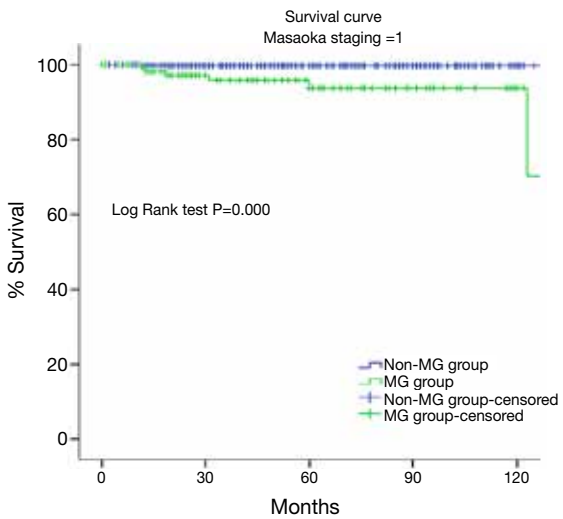

Figure 2 Comparison of overall survival between MG group and non-MG group in Masaoka stage I. MG, myasthenia gravis.

of thymoma A and B (P=0.000) in MG group, and more percentage of patients with MG were in Masaoka stage I and II (P=0.004). R0 resection and complete thymectomy were both done significantly more in MG group (90.0% *vs.* 85.1%, P=0.009; 91.2% *vs.* 71.0%, P=0.000). Postoperative adjuvant chemotherapy or radiotherapy were given more in patients without MG (8.8% *vs.* 23.4%, P=0.000; 41.0% *vs.* 47.1%, P=0.03).

The 5-year and 10-year OS rates were both higher in MG group (93% *vs.* 88%, 83% *vs.* 81%, P=0.034, respectively) (*Figures 1-4*). However, the survival rate was significantly higher in non-MG group when the Masaoka staging was 1 (P=0.000), and the result was opposite when the Masaoka staging was 3/4 (P=0.003).

Among patients with advanced stage thymoma (stage 3, 4a, 4b) (*Table 2*), the constituent ratios of 3 and 4 were

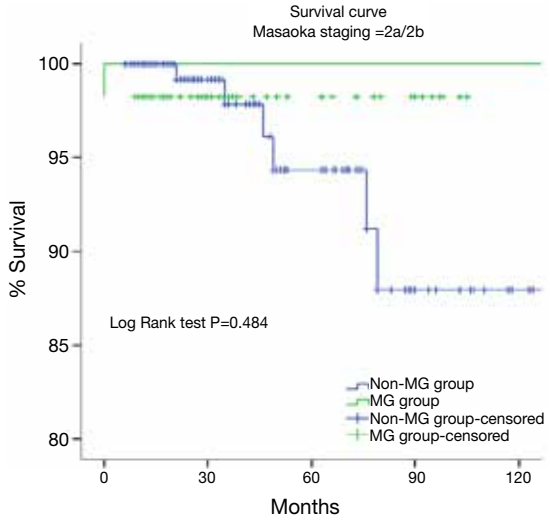

Figure 3 Comparison of overall survival between MG group and non-MG group in Masaoka stage II. MG, myasthenia gravis.

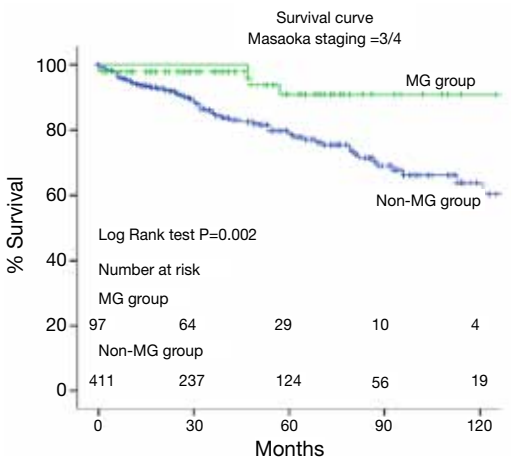

Figure 4 Comparison of overall survival between MG group and non-MG group in Masaoka stage III and IV. MG, myasthenia gravis.

similar between MG and non-MG group. Histologically, however, there were significantly more proportion of AB/B1/B2/B3 in the MG group while there were more C in the non-MG group (P=0.000). The tumor size of MG group was also significantly smaller (6.4 *vs.* 7.9 cm, P=0.000). Total thymectomy had been done in more proportion of patients in MG group (86.5% *vs.* 72.7%, P=0.001), but the two groups were comparable in resectability.

Univariate analyses showed that MG, WHO classification, Masaoka stage, approach of operation, chemotherapy and radiotherapy and resectability were significant factors for survival (*Table 3*). Whereas in multivariate analyses of Cox regression model (*Table 4*), WHO classification, Masaoka stage, and resectability were strong independent prognostic indicators.

In patients with advanced stage thymoma, the postoperative recurrence was much higher in non-MG group than MG

Table 2 The specific analysis of late Masaoka stage patients between two groups

Groups	MG, n=142 (%)	Non-MG, n=605 (%)	P
Masaoka stage			0.128
3	116 (81.7)	458 (75.7)	
4	26 (18.3)	147 (24.3)	
WHO classification			0.000
A	2 (1.4)	14 (2.3)	
AB	15 (10.6)	38 (6.3)	
B1	19 (13.4)	29 (4.8)	
B2	39 (27.5)	71 (11.7)	
B3	54 (38.0)	154 (25.5)	
C	13 (9.2)	273 (45.1)	
Carcinoid	0 (0.0)	26 (4.3)	
Complete thymectomy	122 (86.5)	434 (72.7)	0.001
Tumor size (cm)	6.4	7.9	0.000
Resectability	104 (73.2)	400 (66.4)	0.119
Recurrence	16 (15.7)	137 (31.7)	0.001

MG, myasthenia gravis.

Table 3 Univariate analyses in all patients

Factors	P
Sex (male/female)	0.088
Age (≥50/<50)	0.289
MG (yes/no)	0.038
Tumor size (≥5 cm/<5 cm)	0.459
WHO classification (A/AB or B1 or B2 or B3/C + NETT)	0.000
Masaoka's staging (1/2/3/4)	0.000
Approach of operation (thorascope/open)	0.043
Thymectomy (incompletely/completely)	0.041
Radiotherapy (no/yes)	0.000
Chemotherapy(no/yes)	0.000
Resectability (R0/R1 + R2)	0.000

MG, myasthenia gravis; NETT, neuroendocrine thymic tumor.

Table 4 Multivariate analyses in all patients

Factors	P	OR (95% CI)
MG (no/yes)	0.967	1.016 (0.479, 2.157)
Sex (female/male)	0.738	0.924 (0.580, 1.470)
WHO classification	0.012	
AB + B1 + B2 + B3	0.847	3,335.39 (0, 2.521E38)
C + NETT	0.827	7,582.361 (0, 5.732E38)
Masaoka stage (IV/III/II/I)	0.001	
II	0.050	3.046 (1.002, 9.254)
III	0.000	6.423 (2.489, 16.577)
IV	0.000	7.034 (2.416, 20.474)
Radiotherapy (yes/no)	0.138	0.656 (0.376, 1.145)
Chemotherapy (yes/no)	0.046	1.723 (1.009, 2.942)
Approach of operation (thorascope/open)	0.655	1.401 (0.319, 6.147)
Tumor size (≥5 cm/<5 cm)	0.448	0.780 (0.411, 1.481)
Resectability (R0/R1 + R2)	0.003	0.457 (0.273, 0.766)
Thymectomy (completely/incompletely)	0.593	1.148 (0.692, 1.906)

MG, myasthenia gravis; NETT, neuroendocrine thymic tumor.

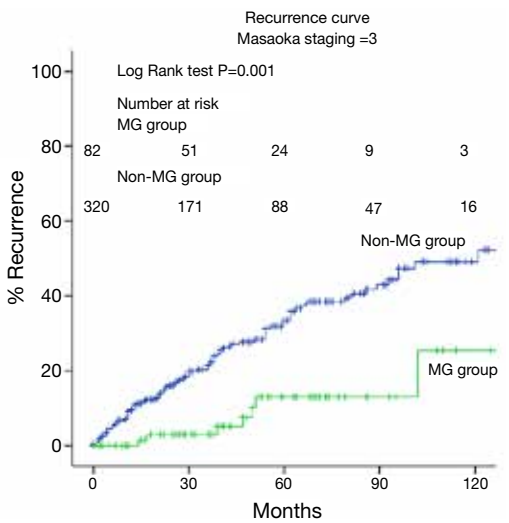

Figure 5 Comparison of tumor recurrence between MG group and non-MG group in advanced stage. MG, myasthenia gravis.

group (*Figures 5,6*).

Discussion

The appearance of MG in patients with thymoma makes them stand out from the population not only because of the fact the perioperative management has become more complicated, but the postoperative outcome is somewhat different. Results of earlier studies on postoperative prognosis of thymoma are quite different from those of recent studies (2,3,5). Anyway, MG does have an impact on patients with thymoma, as is shown in this multicenter study. Patients in MG group were at earlier stage of the disease and there were more proportion of type AB and B in this group, while patients with thymoma only were at quite advanced stage and their pathologic classification tended to be worse. The onset of MG is a good reason for the timely diagnosis and attention for the thymic tumor. The overall R0 resection rate, an independent prognostic factor according to the multivariate analysis of this study, was also higher in patients with MG. All these might account for the positive influence of MG on the long term outcome of subjects with thymoma.

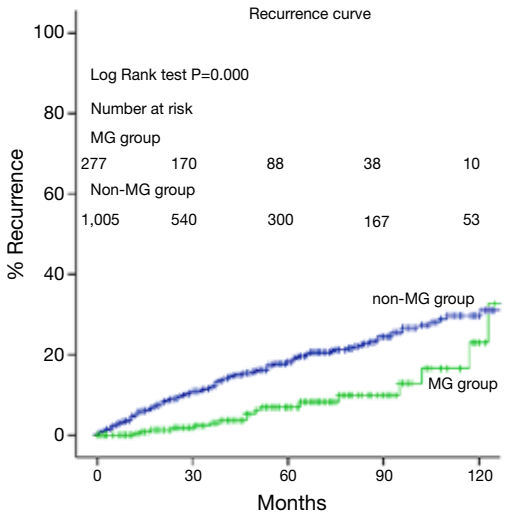

Figure 6 Comparison of tumor recurrence between MG group and non-MG group. MG, myasthenia gravis.

The inter-relations among MG, tumor histology and Masaoka staging have been under the study of quite a few physicians (6,7). Ruffini *et al.* proposed that two models, early Masaoka stage A/AB WHO type and high Masaoka stage/B WHO type, were most frequently seen in MG patients. He noted the influence of MG on Masaoka staging and histology, and his study showed only Masaoka stage had a prognostic significance on OS and disease free survival (DFS) (6). His conclusions could be well applied to the results of this multicenter study except that in the ChART database the independent prognostic factors included histology, tumor resectability besides Masaoka stage, and

MG seemed to have a positive impact on all three elements.

MG affects patients with thymoma in quite an interesting way. Although multivariate analysis indicated that MG was not an independent prognostic factor for a superior survival status, univariate study showed that on the whole patients with MG actually lived longer. Further investigation found MG had a different influence on the patients' survival in different Masaoka stages. Theoretically MG is usually not fatal and adds no mortality to thymoma providing adequate medical care is given. However, perioperative death from myasthenic crisis or pulmonary complications is possible if importance is not fully attached. In this study the worse survival status of MG group in early stages might result from the increased death contributed by MG related complications. Dramatically, the survival advantage of MG group became extremely obvious when thymoma was in quite advanced stage. This might be explained by the better pathologic classification and lower recurrence rate of thymoma in the MG group. Although this advantage was to some extent offset by the increased mortality of MG group in early stages, the positive effect of MG on the OS of thymoma patients still came into sight as shown by the single variant analysis. Hopefully, as the understanding and intervention for MG has developed rapidly, which minimizes death caused by MG, and multidisciplinary collaboration for thymoma patients with MG has become much tighter, an even better prognosis of thymoma patients with MG will be expected in future studies.

As a retrospective study, loss of patients' information in the ChART database caused quite a lot of cases to be excluded from the analysis. Bias hence produced seemed inevitable. In addition, patients included in the data base spanned 20 years during which medical progression was rapid, especially for MG. Therefore medical care received by these patients was not homogeneous. A prospective study may be needed to prove the results of this analysis.

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Footnote

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Editorial on "Postoperative survival for patients with thymoma complicating myasthenia gravis—preliminary retrospective results of the ChART database"

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Provenance: This is an invited Editorial commissioned by the Guest Editor Wentao Fang (Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

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This article by Wang and coauthors analyzes the *preliminary retrospective results of the ChART database* on '*Postoperative survival for patients with thymoma complicating myasthenia gravis*' (1). The Chinese Alliance for Research in Thymomas (ChART) registry recruited 2,306 patients with thymoma from 18 centers over the country in 20 (from 1992 to 2012) years with the intention to compare the postoperative survival between patients with thymoma only and those with both thymoma and myasthenia gravis (MG) so as to have a preliminary understanding of how MG affects the prognosis of patients with thymoma.

Staging and histology are described as the most important prognostic factors for thymic tumors (2). The completeness of the resection is also certainly another important prognostic factor even in advanced stages (3). Tumor diameter is also a reliable prognostic factor (3). These findings has been shown again in this study with multivariate analyzes. Almost half a century ago, MG was believed to affect the prognosis adversely. This impact disappeared by advances in medical management of MG. At least, presence of MG is no longer considered as a negative prognostic factor, and even most of the recent reports have suggested significantly better survival (4-6).

Conversely, other paraneoplastic syndromes are believed to affect the outcome of thymoma patients. In particular, acquired hypogammaglobulinemia, pure red cell aplasia cause significant morbidity (2). These syndromes include dermatopolymyositis, inflammatory bowel disease, pernicious anemia, rheumatoid arthritis, scleroderma and amyloidosis (2).

This study demonstrates 5- and 10-year OS rates were both higher in MG group (93% *vs.* 88% and 83% *vs.* 81%, P=0.034, respectively). However, the survival rate was significantly higher in non-MG group when the Masaoka staging was 1 (P=0.000), and the result was opposite when the Masaoka staging was 3/4 (P=0.003). Only this analyze may show that the disease itself may not have an impact in survival of thymoma patients. But majority of difference may be coming from the histology and the size of the thymoma. There were significantly more proportion of patients with AB/B1/B2/B3 histology in the MG group while there were more patients with thymoma C in the non-MG group (P=0.000). Tumor size of MG group was also significantly smaller (6.4 *vs.* 7.9 cm, P=0.000) and the two groups were comparable in resectability.

MG does have an impact on patients with thymoma. However, the onset of MG is a good reason for the timely diagnosis (smaller thymomas, early stage) which increases the possibility of overall R0 resection rate, which is an independent prognostic factor according to the multivariate analysis of this study. On the other hand, occurrence of Type C thymoma is an exceptional condition in MG patients. As shown recently, Type C has a tendency to develop more distant and lymph node metastases. All these might account for the positive influence of MG on the long term outcome of subjects with thymoma. I believe the secret of MG stays in the prevention of the patients from type C thymoma.

The molecular studies in near future may clarify why MG protects the patients from developing thymic carcinoma.

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Footnote

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Thymectomy versus tumor resection for early-stage thymic malignancies: a Chinese Alliance for Research in Thymomas retrospective database analysis

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Background: To evaluate the surgical outcomes of tumor resection with or without total thymectomy for thymic epithelial tumors (TETs) using the Chinese Alliance for Research in Thymomas (ChART) retrospective database.

Methods: Patients without preoperative therapy, who underwent surgery for early-stage (Masaoka-Koga stage I and II) tumors, were enrolled for the study. They were divided into thymectomy and thymomectomy groups according to the resection extent of the thymus. Demographic and surgical outcomes were compared between the two patients groups.

Results: A total of 1,047 patients were enrolled, with 796 cases in the thymectomy group and 251 cases in the thymomectomy group. Improvement rate of myasthenia gravis (MG) was higher after thymectomy than after thymomectomy (91.6% *vs*. 50.0%, P<0.001). Ten-year overall survival was similar between the two groups (90.9% after thymectomy and 89.4% after thymomectomy, P=0.732). Overall, recurrence rate was 3.1% after thymectomy and 5.4% after thymomectomy, with no significant difference between the two groups (P=0.149). Stratified analysis revealed no significant difference in recurrence rates in Masaoka–Koga stage I tumors (3.2% *vs*. 1.4%, P=0.259). However in patients with Masaoka-Koga stage II tumors, recurrence was significantly less after thymectomy group than after thymomectomy (2.9% *vs*. 14.5%, P=0.001).

Conclusions: Thymectomy, instead of tumor resection alone, should still be recommended as the surgical standard for thymic malignancies, especially for stage II tumors and those with concomitant MG.

Keywords: Thymic epithelial tumors (TETs); myasthenia gravis (MG); thymectomy; thymomectomy

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Introduction

Thymic epithelial tumors (TETs) should be resected together with the surrounding thymus and fatty tissue rather than shelled out because all TETs are considered malignant and transcapsular invasion is difficult to detect intraoperatively (1). However, there is no consensus on the appropriate extent of thymic resection (2-4). Although thymectomy may help prevent potential risks of postoperative myasthenia gravis (MG) and intrathymic or locoregional recurrence (5,6), some consider that tumor resection alone (thymomectomy) may be enough for noninvasive thymomas without MG (2,3). Also, increased use of CT screening for lung cancer has led to more cases of incidentally detected small lesions at early stage. And advent of minimally invasive surgery in recent years also contributed to increased interest in video-assisted thoracoscopic surgery (VATS) thymomectomy (7). Although some single-center studies have shown no statistical differences in disease-free survival between thymectomy and thymomectomy, the follow-up durations were relatively short despite of the rarity and the indolent nature of thymomas (2,3). Thus, it is important to compare long-term outcomes on a larger patient population base so as to determine the appropriate extent of resection for the disease.

The objective of this study was to evaluate the surgical outcomes of tumor resection with or without total thymectomy for TETs using a retrospective database of thymoma cases constructed by the Chinese Alliance for Research in Thymomas (ChART).

Materials and methods

The ChART, initiated by 18 tertiary referral centers in China, retrospectively collected the clinical data of 2,104 patients with thymic tumors from 1994 to 2012. The present study enrolled only 1,047 patients with early-stage tumors (Masaoka-Koga stage I and II) with no pretreatment. The study was proved by the hospital IRB. The following clinical data were collected: general information, presence of MG and other autoimmune diseases, surgical approach, postoperative histological type, postoperative clinic-pathological stage, and follow-up data. Because only de-identified data were used for the study, informed consent was waived by IRB. Preoperative classification and surgical treatment evaluation were performed in patients with MG according to both the Myasthenia Gravis Foundation of America Clinical Classification and Post-Intervention Status (8). Histological typing of tumors was classified according to the World Health Organization 2004 Classification of Thymoma. Clinic-pathological staging was performed according to the Masaoka-Koga staging system (9).

Surgical approaches included sternotomy, thoracotomy, and video-assisted thoracoscopic surgery (VATS). In this multi-center retrospective study, there was no uniform standard for the selection of the surgical approach; the surgeons chose the approach according to their preference. Likewise, there was no uniform standard for the selection of adjuvant therapy among the patients; decisions on adjuvant therapy were mostly based on the physicians' subjective evaluation.

Patients were divided into thymectomy and thymomectomy groups based on the resection extent of the thymus. In the thymectomy group, 796 patients underwent total or subtotal thymectomy to remove all thymic tissue, including the anterior mediastinal fat, on the basis of complete tumor resection. In the thymomectomy group, 251 patients underwent complete tumor resection, including some surrounding thymic tissue, or resection of the ipsilateral lobe of the thymus.

The follow-up completed in October 2013, with a median follow-up time of 38 months, and the follow-up rate was 78.4%.

Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Patients' characteristics

Table 1 Comparison of patient characteristics between thymectomy and thymomectomy

Variables	Thymectomy (n=796, %)	Thymomectomy (n=251, %)	P value
Gender			0.371
Male	377 (47.4)	127 (50.6%)	
Female	419 (52.6)	124 (49.4%)	
Age (yr, mean ± SD)	50.9±12.2	52.3±11.9	0.628
Tumor size (cm, mean ± SD)	6.67±2.90	6.68±3.40	0.902
Preoperative MG	247 (31.0)	15 (6.0)	<0.001
Masaoka staging			0.126
Stage I	523 (65.7)	178 (70.9)	
Stage II	273 (34.3)	73 (29.1)	
WHO histological types			0.001
A + AB	348 (43.7)	100 (39.8)	
B1 + B2 + B3	397 (49.9)	108 (43.1)	
Carcinoid + Ca	51 (6.4)	43 (17.1)	
Resection state			0.267
R0	786 (98.7)	247 (98.4)	
R1	10 (1.3)	4 (1.6)	
Surgical approach			<0.001
Sternotomy	498 (62.6)	23 (9.2)	
Thoracotomy	78 (9.8)	170 (68.0)	
VATS	220 (27.6)	57 (22.8)	
Adjuvant therapy			0.007
Surgery only	554 (71.5)	154 (62.3)	
Adjuvant therapy	217 (28.5)	93 (37.7)	

MG, myasthenia gravis; VATS, video-assisted thoracoscopic surgery.

were compared between the two groups using the *t*-test and χ^2 test. Survival analysis was performed using the Kaplan-Meier method and log-rank test. Differences were considered statistically significant when P<0.05.

Results

There were 504 male and 543 female in this series, with an average age of 51.3±12.1 (range, 15–83) years. A total of 1,033 patients (98.7%) underwent complete tumor resection (R0), with only 14 (1.1%) had microscopic residual disease (R1). A total of 310 patients (29.6%) received postoperative adjuvant therapies (radiotherapy and/or chemotherapy). Patients' characteristics are shown in *Table 1*. No significant differences were observed in gender, age, or tumor size between the two groups. There were more stage I tumors in the thymomectomy group (70.9%) than in the thymectomy group (65.7%), but without statistical significant difference (P=0.126). However, significantly higher proportion of thymic carcinoma was seen in the thymomectomy group than in the thymectomy group (17.1% *vs.* 6.4%, P=0.007).

In terms of surgical approach, sternotomy was mainly used in the thymectomy group and thoracotomy was more frequently chosen in the thymomectomy group, with a significant difference (P<0.001). There was no significant difference in minimally invasive approach. And complete resection rate (R0) between the two groups were also similar (P=0.267). However, a higher proportion of patients received adjuvant therapy after thymomectomy than after thymectomy (37.7% *vs.* 28.5%, P=0.007).

In total, 262 patients had MG before surgery. The majority of them (247, 94%) underwent thymectomy and only 15 patients (6%) underwent thymomectomy. The proportion of patients with MG was significantly different

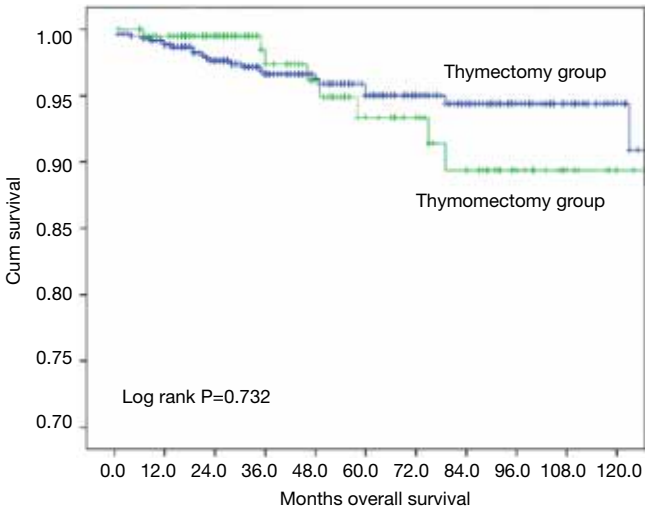

Figure 1 Comparison of overall survival between thymectomy and thymomectomy (P=0.732).

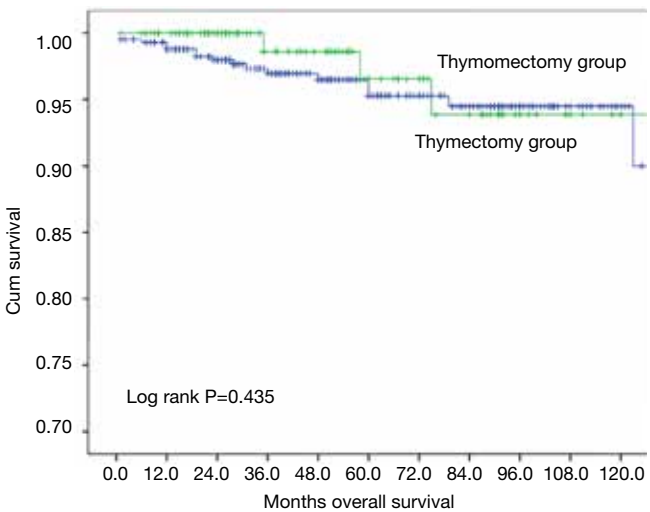

Figure 2 Comparison of overall survival between thymectomy and thymomectomy among patients with Masaoka-Koga stage I tumors (P=0.435).

between the two groups (P<0.001). MG remission rate was significantly higher after thymectomy than after thymomectomy (91.6% *vs.* 50.0%, respectively, P<0.001). Postoperative MG was found in only two patients (0.81%), both in the thymectomy group.

Ten-year overall survival was similar between the two groups (*Figure 1*, 90.9% after thymectomy and 89.4% after thymomectomy, P=0.732). Stratified

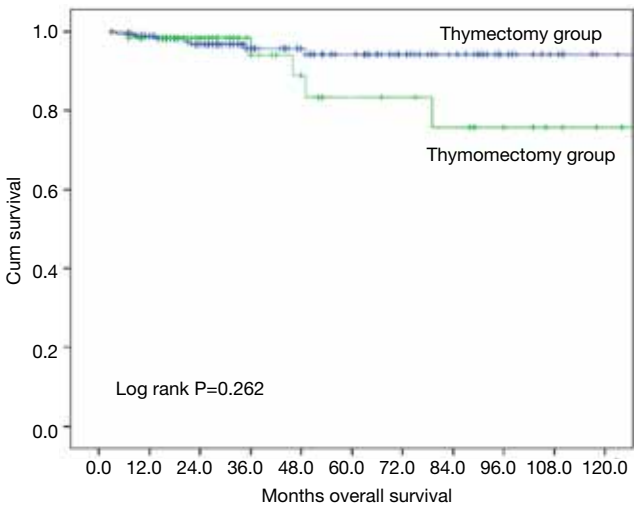

Figure 3 Comparison of overall survival between thymectomy and thymomectomy among patients with Masaoka-Koga stage II tumors (P=0.262).

analysis by Masaoka-Koga stage also did not show any significant difference in overall survival between the thymectomy and thymomectomy groups (*Figures 2,3*). Recurrence rate was 3.1% after thymectomy and 5.4% after thymomectomy, with no significant difference between the two groups (P=0.149). Stratified analysis did not find any significant difference in recurrence rates in Masaoka-Koga stage I tumors (3.2% *vs.* 1.4%, P=0.259). However in patients with Masaoka-Koga stage II tumors, recurrence was significantly less after thymectomy than after thymomectomy group (2.9% *vs.* 14.5%, P=0.001)

Discussion

Thymectomy through a median sternotomy has long been the gold standard for surgical treatment of TETs. In particular, when patients have concomitant autoimmune diseases such as MG before surgery, it is deemed necessary to remove all mediastinal fat on both sides during thymectomy (1). However, surgery through a median sternotomy causes marked injury, and there is a 1% to 5% risk of mediastinal infection after surgery (4). To reduce the surgical trauma, many surgeons choose to operate through intercostal thoracotomy, VATS, or transcervical incision (5-7). Although these approaches may enable resection of early-stage thymic tumors, it is technically demanding to perform a total thymectomy especially in case of intercostal

thoracotomy. With improvements in imaging and surgical techniques, a growing number of small-diameter thymomas have been detected incidentally and resected through various minimally invasive approaches, especially VATS, in the clinical setting. And some surgeons tend to perform thymomectomy under VATS to avoid the risk of bleeding from the brachiocephalic vein (3). Therefore, it is necessary to evaluate the effect of the extent of thymectomy on the prognosis of early-stage TETs.

Prognosis of TETs is closely associated with tumor stage, histological type, completeness of surgical resection, and effective adjuvant therapy (10). Early-stage thymic tumors have good prognosis with low recurrence and mortality rates (11). In the current study, 10-year overall survival was as high as 90% for stage I and II tumors. Several studies comparing the extent of thymectomy for thymomas found no significant difference in postoperative recurrence rate or survival between thymectomy and thymomectomy (2-4). In the current study with stage I and II tumors, 10-year survivals after these two procedures were also similar (90.9% *vs.* 89.4%). However, this does not support the similar efficacy of thymomectomy to thymectomy. Adjuvant therapies were used more frequently after thymomectomy than after thymectomy in our patients. Besides, thymomas are relatively indolent tumors and long-term survival could still be expected even after tumor recurrence. In this concern, recurrence status is often considered a better index for evaluation of management outcome. In the current study, although postoperative recurrence rates were also similar after these two procedures (3.1% *vs.* 5.4%, P=0.149), stratified analysis revealed a significantly increased risk of tumor recurrence after thymomectomy in Masaoka-Koga stage II tumors (2.9% *vs.* 14.5%, P=0.001). Masaoka-Koga stage II refers to tumors infiltrating the thymus or surrounding adipose tissue. For well encapsulated Masaoka-Koga stage I tumors, complete tumor removal may be readily achieved by either thymomectomy or thymectomy. For Masaoka-Koga stage II tumors, it is basically impossible to determine the extent of tumor invasion during surgery. Then without an accurate judgment of tumor margin, there is potentially an increased risk of tumor spillage during thymomectomy. And tumor implantation in the pleural cavity is the most often encountered recurrence pattern in thymic tumors. This may also help explain the higher recurrence rate in the thymomectomy group for Masaoka-Koga stage II tumors in our study.

Theoretically, either thymomectomy or thymectomy can be desirable procedure for stage I tumors which are confined to a complete capsule without any invasion into the surrounding structures. And there was no significant difference between the two groups in overall survival or recurrence rates for Masaoka-Koga stage I tumors. However, it is extremely difficult to accurately define a stage I tumor before operation or during. Computed tomography (CT) is the most widely used imaging technique for the diagnosis of thymic tumors. The International Thymic Malignancy Interest Group (ITMIG) has also recommended the use of CT as a standard examination for preoperative staging (12). Yet, few studies have focused its usefulness and accuracy (13). Overall, CT scan has relatively low sensitivity and specificity for early-stage TETs, and there is no way to accurately identify Masaoka-Koga stage I tumors from stage II diseases (14). Although positron emission tomography scan may help distinguish thymomas from more malignant thymic carcinomas, its staging accuracy is not high enough in lesions without obvious invasion into the neighboring structures, especially in small-diameter tumors (15). Similar to the management for most other malignancies, the goal of surgery lies not only in complete removal but also accurate staging of the disease. Therefore even for clinically stage I tumors, thymectomy should still be recommended.

Thymectomy has been shown to be effective in treating TETs with concomitant MG before surgery, with an improvement rate of 73% to 89%, and a complete remission rate ranging from 28% to 52% (8,15-18). Studies to date mainly compared the therapeutic effects of surgery with medical treatment (cholinesterase inhibitors and immunosuppressive agents), with favorable results showing higher improvement rates in patients who received thymectomy than medical treatment (16,17). Up till now, no study has ever compared the effect of the extent of thymectomy on the outcome of surgical treatment for MG with concomitant thymomas. In the present study, most MG patients received thymectomy and only 15 patients had thymomectomy. And the postoperative improvement rate of MG was 50% in these 15 patients, far below that in patients in the thymectomy group (91.8%). This is in accordance with the reports from Sonett *et al.* (19) showing that increased extent of clearance of the thymus and mediastinal fat might help improve the remission rate for MG. Our finding suggests that at least for those thymoma patients concomitant with MG, thymectomy, instead of tumor resection alone, should be chosen to ensure a satisfactory outcome.

Another concern is that thymoma patients without MG before surgery still carry the risk of developing MG after

tumor resection at a reported rate of 1.5% to 28.0% (5,6). Whether the extent of thymectomy affects the development of MG after surgery remains unclear. Ito *et al.* (18) reported that the incidence of postoperative MG was 5.0% in the thymectomy group and 4.2% in the thymomectomy group, with no significant difference between the two groups. Similar results were reported by Tseng *et al.* (3) and Onuki *et al.* (2). In the present study, only two patients (0.81%) without preoperative MG developed MG after surgery, both in the thymectomy group. This seems to indicate that postoperative MG is very rare and total thymectomy does not help prevent the risk of newly onset MG in patients without preoperative MG.

Limitations of our study include its retrospective nature and the associated inherent selection biases. Extent of resection and selection of postoperative adjuvant therapy were mostly based on the surgeons' own preferences without uniformed standards. And the dropout rate was also relatively high. Although stratified analysis was used to rule out potential confounding biases to the greatest extent, prospective randomized controlled studies are still necessary to further validate our findings.

Conclusions

Although overall survival appeared to be similar after tumor resection alone and thymectomy, there is no sufficient evidence to support the routine application of thymomectomy for thymic malignancies, even in early stage tumors. The higher recurrence rate after thymomectomy in stage II tumors, along with the difficulty in accurate clinical staging, indicate that thymectomy should still be recommended to ensure radical resection and accurate staging. And this is particularly true for thymoma patients with concomitant MG.

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Footnote

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Thymomectomy in early stage thymomas—case closed?

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Thymic epithelial tumors (TET) are rare tumors with an annual incidence ranging from 1.3 to 3.2 per million (1). Histologically TETs can be divided in thymomas and thymic carcinomas. A third of all patients with a thymoma will also be affected by an autoimmune disease, of which myasthenia gravis (MG) is most commonly found (2). Thymomas should be considered malignant because of their potential invasiveness. Incomplete surgical resection is one of the predictors of recurrence after resection of a thymoma. Therefore, it has been suggested that a total thymectomy should be the gold standard in all thymoma patients for oncological reasons and possibly to prevent the development of MG (post-thymectomy MG). However, some consider a resection of the thymoma alone (thymomectomy) sufficient in non-MG non-invasive thymomas. The reason for this is that some data suggested that a thymomectomy results in lower morbidity with the same early oncological outcome (3).

In this issue of the *Journal of Thoracic Disease* (*JTD*) Gu and colleagues report the outcome of the evaluation of tumor resection with or without total thymectomy for early stage thymomas (Masaoka-Koga stage I and II) using the Chinese Alliance for Research in Thymomas (ChART) retrospective database (4). The ChART retrospectively collected clinical data of 18 tertiary referral centers in China. Gu and colleagues analyzed 1,047 patients with early stage thymoma without pretreatment. A thymectomy was performed in 796 patients and a thymomectomy in 251 patients. Follow-up data with a median of 38 months was available for 78.4% of patients. Ten-year overall survival was similar between the thymectomy and thymomectomy group (91.6% *vs.* 89.4%). Patients who underwent thymomectomy underwent significant more adjuvant therapy (28.5% *vs.* 37.7%, P=0.007).

The overall recurrence rate was also similar in both groups (3.1% after thymectomy and 5.4% after thymomectomy). However, a stratified analysis showed a significant increased risk (2.9% after thymectomy *vs.* 14.5% after thymomectomy, P=0.001) of tumor recurrence in patients with Masaoka-Koga stage II thymomas undergoing thymomectomy. These high recurrence rates are worrisome after a follow-up of only 38 months since thymomas are known for their indolent nature and can give recurrences even after a follow-up of 10 years. One might conclude that a thymomectomy is acceptable in Masaoka-Koga stage I thymomas. However, differentiating between Masaoka-Koga stage I or II on pre-operative imaging and during surgery is almost impossible. Therefore, in our opinion, a total thymectomy should be performed in patients with a clinically stage I thymoma as well.

Another large study addressing the thymectomy *vs.* thymomectomy discussion was a retrospective analysis of the Japanese Association for Research on the Thymus (JART), where 1,286 patients were analyzed. (5) The 5-year overall survival was similar between both groups (96.9% after thymectomy *vs.* 97.3% after thymomectomy). Nevertheless, there was a trend towards more local recurrences in the thymomectomy group (2.2% *vs.* 0.4%, P=0.0613). Postoperative complications were seen more frequently after a thymectomy. However, these were non-

life threatening with a 30 days mortality rate of 0%. This trend towards more local recurrences confirms our opinion to perform a total thymectomy in all thymoma patients.

Post-thymectomy MG is a phenomenon that is not clearly understood with a wide variety of incidence (0.9% to 20%) reported in the literature (6,7). Post-thymectomy MG has been reported in patients with tumor recurrence (8). However, it can also occur in patients without a tumor recurrence (9). Whether the extent of the thymectomy influences the incidence of post-thymectomy MG remains under debate.

Gu and colleagues did not find any difference regarding the frequency of post-thymectomy MG. This is in line with results reported in two retrospective studies including smaller cohorts of thymoma patients (3,10). The analysis of 299 thymoma patients by Yamada *et al.* showed that serum anti-acetylcholine receptor antibodies (AChR-Ab) positivity, type B1/B2/B3 thymoma histology and incomplete resection were risk factors for the development of post-thymectomy MG (11). Nakajima *et al.* found that patients with post-thymectomy MG all showed high titers of AChR-Ab at the onset of MG (12). Although there were no differences seen in the frequency of post-thymectomy MG, these findings should be investigated in prospective trials.

As the authors acknowledge, the study suffers from limitations due to the retrospective design. First, the data were collected from many different institutions over a long period of time. Second, there was no uniform standard for the selection of the surgical approach, probably resulting in allocation-bias, an unavoidable but important drawback of non-randomized studies: the surgeon chose the approach according to his or her preference or specific baseline characteristics. If patients were receiving adjuvant therapy, this decision was based on the physicians' subjective evaluation as well. Propensity-matched analysis could have been performed to overcome the allocation-bias partially. Third, follow-up information was available in 78.4%, and although it is known that thymomas can reoccur after several years the median follow-up was only 38 months. Therefore, the study results should be interpreted with some caution.

Taken together, Gu and colleagues should be congratulated on the accomplishment of this study. These results offer important knowledge and they are doing tremendous work by collecting their data in the retrospective database and by building a prospective database. Only by the collaboration of the regional thymic groups and International Thymic Malignancy Interest Group our knowledge about the management of this orphan disease will improve. However, this case is not closed yet; we should yet be careful drawing firm conclusions. Analyses from prospective data with longer follow-up are needed. For the time being, in non-MG patients a total thymectomy should be recommended for early stage thymomas.

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Footnote

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Standardized definitions and policies of minimally invasive thymoma resection

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A wide range of technical approaches for the minimally invasive resection of thymus have been described. Most of the time, the benefits are superior cosmetic outcome and shorter duration of postoperative stay. Other demonstrable differences that have been reported include shorter duration of surgery, less intraoperative blood loss and less postoperative pleural drainage. Robotic surgery and video-assisted surgery (VATS) may become routinely used procedures in the treatment of stage I and II thymomas.

Keywords: Thymoma; video-assisted thoracoscopic surgery (VATS); robotics

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Surgical treatment of thymoma has been a controversial topic in the field of mediastinal surgery, due to the lack of proper definitions and standardization. However, the development of terms, definitions and policies for minimally invasive thymoma by the International Thymic Malignancy Interest Group (ITMIG), a worldwide collaborative organization of individuals interested in mediastinal tumors, has been able to change perspectives towards this procedure (1). Surgeons with experience in minimally invasive thymic resections were assembled to recommend standardized definitions, terms and procedures in the existing literature for minimally invasive thymoma resections. These recommendations were then discussed with a larger working group consisting of a diverse range of specialists in ITMIG, which was supported by the International Association for the Study of Lung Cancer, until an overall consensus was reached. This agreement has led to improved outcomes of both minimally invasive and open thymic resections.

There is a wide variety of technical approaches for minimally invasive thymic resections (2-5). Many types of incisions, methods of exposure, visualization, equipment via transcervical, extended transcervical, video-assisted thoracoscopy and robotic approaches (right and/or left, right and cervical, left and cervical, subxiphoid and right and left, cervical and subxiphoid) are currently considered as minimally invasive thymic resections (1). Some techniques may involve sternal lifting or rib spreading via soft tissue retractors. However, in the near future, only approaches that do not involve sternotomies (including partial sternotomy) or thoracotomy with rib spreading will be considered to be minimally invasive thymic resection (1).

Why minimally invasive thymoma resection?

The major benefits of minimally invasive thymic resections are improved cosmesis and shorter postoperative stays. However, other benefits include: shorter duration of surgery, less intraoperative blood loss and reduced postoperative pleural drainage (6). A study comparing outcomes of transsternal and video-assisted thoracoscopic surgery (VATS) thymectomy for thymoma demonstrated that patients undergoing VATS thymectomy have shorter hospital stays and potentially fewer complications compared to transsternal thymectomy. In addition, mid-term follow-up revealed that VATS thymectomy had comparable oncological outcomes with transsternal thymectomy in terms of adjuvant therapy received, disease progression, and

survival (7). Finally, there is a lack of complications from sternotomy in patients with corticosteroid dependency, due to the medications for myasthenia gravis (MG) and the need to have adjuvant radiotherapy.

Standard resection of a thymoma

A standard thymoma resection is defined as a complete en bloc resection of the tumor and complete thymectomy with removal of the upper cervical poles and the surrounding mediastinal fat (8). Resection also extends to structures invaded by the thymoma, which may include the pericardium, lung, phrenic nerve, superior vena cava, aorta and its main branches. However, there are reports that do not follow these recommendations, whereby only the thymic mass was resected, and not the thymus or mediastinal fat. A study showed that in early-stage nonmyasthenic thymoma patients, thymomectomy without thymectomy via thoracotomy or VATS is associated with lower morbidity and shorter hospitalization compared to thymomectomy with extended thymectomy (9). It also reported that MG did not develop in any of the patients enrolled in a study postoperatively, over a median follow-up of 57 months. Overall tumor recurrence rates were not significantly different between these two patient groups. Thymomectomy without thymectomy through thoracotomy or VATS is justified for early-stage nonmyasthenic thymoma patients, and further studies with longer follow-up periods are required to investigate the role of thymectomy in these patients (9).

Should lymph node resection be routine at the time of thymoma resection with minimally invasive surgery?

Until recently, it has been shown that the rate of lymph node metastases is 1.8% in patients with thymic epithelial tumors (10,11). Kondo and Monden's paper is the only publication to have reported the incidence and prognostic relevance of nodal metastases in patients with thymoma. However, a large database of patients from the United States was recently presented to demonstrate the incidence and prognostic significance of nodal metastases in patients with thymoma (12). According to this study, 2,227 patients with thymoma were entered into the Surveillance, Epidemiology and End-Result (SEER) database. Of these, 442 patients had lymph node resection in addition to thymoma resection. The median number of resected nodes was two. There were 59 patients (13.3%) found to have lymph node involvement. These patients were younger and tended to have smaller thymomas. Given that nodal metastases may occur more frequently than is currently recognized, evaluation of anterior mediastinal lymph nodes and pathologic analysis and reporting should be included in the routine investigation for a thymoma. In addition, younger and smaller thymoma patients are typically suitable candidates for minimally invasive thymoma resection. This study demonstrated a clinical need for mediastinal lymph node dissection or sampling in order to determine the proper staging and treatment of thymoma. The technical recommendations for this development have yet to be defined for minimally invasive resection of thymoma. Authors of this paper suggested the removal or sampling of at least the anterior mediastinal lymph nodes routinely.

In 2013, Park *et al.* (13) recommended routine resection of all mediastinal lymph nodes in patients with thymic resection. Furthermore, the ITMIG and International Association for the Study of Lung Cancer has produced a new TNM staging classification emphasizing the importance of lymph node status (14,15).

Minimum requirements of minimally invasive thymoma resection

Minimally invasive resection does not equate to minimal resection of the thymoma and mediastinal tissues. The actual resection should be the same as what is deemed appropriate for an open approach. Incomplete resection and debulking should not be considered acceptable in a minimally invasive procedure, and in such situations, conversion to open surgery is required (1). During the dissection, the innominate vein and both phrenic nerves should be visualized. Opening and resection of the contralateral pleura must be performed using a 30 degree or greater scope in order to visualize the contralateral phrenic nerve. Pulling the tissue towards the surgeon may further assist in identifying the phrenic nerve. Conversion to open surgery is required if oncologic principles are being compromised or violated: e.g., perforation of the capsule, incomplete resection possibility, risk of a discontinuous (not en bloc) resection, or disruption of the tissues exposing the tumor. The access incision for retrieval of the thymoma should be large enough to prevent specimen disruption. Trans-capsular invasion can be subtle and not be detected by the surgeon; therefore, the tumor should be resected with the surrounding thymus and fatty tissue rather than be shelled out. If the tumor projects into the

pleural space, pleural metastases may be present, and the entire pleural space should be subsequently searched for possible parietal and visceral metastases, which should be resected accordingly if present. Inspection of the pleural space may not be performed for a tumor that is completely contained within the thymus. The suggested procedure is a complete thymectomy for patients without MG, including nodes close to the tumor, and an extended thymectomy for patients with MG (removal of the contiguous right and left mediastinal pleura, mediastinal and pericardiophrenic fatty tissues, and dissection of aorta-pulmonary window in addition to complete thymectomy) (1). A maximal thymectomy may be performed with a neck dissection and sternal lifting methods (4). If the surgeon chooses to do so, the authors recommend removing all lymph nodes for documentation purposes. Lesions with a preoperative diagnosis such as thymic carcinoid tumour or thymic carcinoma may benefit from such a procedure, as a more aggressive lymph node dissection may be required in these circumstances. All tissue retrievals must be contained in the bag.

Upper limits of minimally invasive thymoma resection

According to our report, Masaoka stage 1 and 2 tumors may be resected safely and efficiently (16). It is well known that the learning curve in learning the technique is steep, and a level of expertise is essential in minimally invasive resection of a thymoma (17).

Clinical and radiographic findings can be used to select patients for a VATS thymoma resection; markers of invasion such as phrenic or recurrent laryngeal nerve palsy or major vessel invasion may be considered as reasons for open surgery. It has been proposed that involvement of the phrenic nerve, innominate vein or other major vessels is a contraindication to a minimally invasive approach when diagnosed preoperatively or intraoperatively. The ITMIG paper recommends avoiding minimally invasive resections of the phrenic nerve. However, I believe that phrenic nerve invasion, if diagnosed intraoperatively, can be evaluated and managed with a minimally invasive approach, taking appropriate steps to preserve the nerve if possible. I also recommend diaphragmatic plication in the same operation.

Experienced surgeons have demonstrated the feasibility of VATS resection in Masaoka stage 3 and 4a (18). Agasthian and colleagues [2011] selected patients with tumors smaller than 5 cm without major invasion on preoperative computed tomography. Out of 77 patients, there were 13 invasive thymomas (Masaoka stage III and IV). Limited resection of the phrenic nerve, pericardium, perithymic fat and a wedge of lung was performed en bloc with the tumor. Median hospital stay was 3.6 days. There was one case of wound infection and no operative mortality. The mean size of the thymomas was 34 mm (range, 23-55 mm). All patients had adjuvant radiotherapy. During follow-up of 4.9 years (range, 1-10 years), there was one local recurrence. Evidently, selected invasive thymomas detected during surgery can be removed safely without requiring open conversion (18). It must be understood that the invasiveness of thymoma may not necessarily correlate with thymoma size, as documented in our previous publication. Rather, it is the stage that indicates the feasibility of minimally invasive resection (16).

According to our experience, surgeons with expertise in VATS thymectomies can perform resection of Masaoka stage 3 thymomas. However, our study clearly demonstrated that patients with Masaoka stage 3 and higher did not benefit from the advantages of VATS resection (16). Conversion to open surgery is necessary if any pathological or surgical issue would be potentially compromised or inadequately managed by minimally invasive techniques (1).

In patients with thymoma resection, recurrences may occur many years later. We must be careful in firmly establishing outcomes of minimally invasive approaches first in straightforward cases before expanding the technical boundaries too rapidly.

Does robotic surgery provide any additional benefit?

In a recent study, 79 patients operated in four European centers for early-stage thymoma with robot-assisted thoracoscopic surgery (RATS) thymectomy were evaluated (19). In this study, one patient needed open conversion, one patient required a standard thoracoscopy following a robotic system breakdown, and five patients required an additional access incision. No vascular and neural injuries were recorded, and no perioperative mortality occurred. Median hospital stay was three days (range, 2-15 days). Median diameter of tumor resected was 3 cm (range, 1-12 cm), and Masaoka stage was stage I in 30 patients (38%) and stage II in 49 patients (62%). At a median follow-up of 40 months, 74 patients were alive and five had died (four patients from nonthymoma-related causes and one from a diffuse intrathoracic recurrence), with

a five-year survival rate of 90%. This report indicated that RATS thymectomy for early-stage thymoma is a technically sound and safe procedure with a low complication rate and a short hospital stay. While the oncologic outcomes appear acceptable, longer follow-up is needed to definitively consider this as a standard approach (19).

The short-term outcomes of 46 patients who underwent surgery for Masaoka stage I thymoma without MG were evaluated in another recent study (20). Of these patients, 25 received unilateral VATS, while the remaining 21 received unilateral RATS thymectomy. The duration of surgery and intraoperative blood loss did not significantly differ between the two groups. The postoperative hospital stay, however, was significantly shorter in the RATS group (3.7 *vs.* 6.7 days; P<0.01), and the postoperative pleural drainage duration of the RATS group was also significantly lower (1.1 *vs.* 3.6 days; P<0.01). No patients in the RATS group required conversion to open surgery, compared to one case of conversion in the VATS series. No surgical complications were observed except for one case of pulmonary atelectasis in the RATS group, and one patient who developed pneumonia after surgery. The use of robotics is more expensive than VATS (20). No early recurrence was observed in both groups. According to this study, the minor benefits of robotic surgery may be promising (20).

What is new after the proposals made by the ITMIG?

There are several points to be discussed in redefining minimally invasive thymoma resections, as follows:

(I) Could Masaoka stage 3 and 4a patients be candidates for minimally invasive resections? Resection of thymomas with invasion of lung, pericardium and phrenic nerve may be performed in experienced hands. However, our data did not show any functional benefit to parameters such as duration of hospital stay and duration of drainage. Nonetheless, the minimally invasive approach does provide a cosmetic benefit;

(II) Should a lymph node dissection be performed with a minimally invasive approach, considering the most recent proposals of ITMIG? Not yet, as we do not have a solid evidence-base. However, recent reports demonstrate that lymph node invasion is more common than has been reported. According to our personal experience with a long period of patient follow-up, we see more and more lymph node recurrences in the mediastinum after resection of thymomas. Subsequently, we believe that at least the anterior mediastinal nodes should be resected using minimally invasive techniques;

(III) Does robotic surgery have additional benefits? As the developments in minimally invasive surgery techniques, indications and capabilities continue, there will be a higher patient demand for minimally invasive surgery. Certainly, robotic surgery may be an attractive option, although there are very few reports showing its superiority to other minimally invasive approaches. However, as a surgeon performing an equal number of VATS and robotic surgeries, I still prefer VATS over robotic surgery for three main reasons. Firstly, most patients in this group are myasthenic, and in my experience, robotic surgery is more time-consuming in the resection of a thymoma, compared to VATS. Duration of surgery is extremely important in myasthenic patients. Secondly, most of the experience that I have gained in thymoma resections was during the pre-robotic era. Surgeons should operate with the technique that they are most comfortable with. Thirdly, VATS thymoma resection could be performed at the same cost as open surgery, whereas robotic surgery is more expensive.

Conclusions

Over the past few years, perceived benefits of shortened hospital stays and reduced pain have shifted the favor to minimally invasive surgery. However, the superiority of these approaches compared with open techniques has yet to be properly documented. Prospective collaborative data collection was provided in several platforms. The ITMIG and European Society of Thoracic Surgeons (ESTS) databases may assist in defining the future value of these techniques.

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Footnote

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

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Video-assisted thoracoscopic surgery versus open thymectomy for thymoma: a systematic review

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Background: Video-assisted thoracoscopic surgery (VATS) thymectomy is an increasingly utilized alternative to traditional open approaches for the resection of thymomas. Recent studies have suggested comparable survival and oncological efficacy as well as reduced perioperative morbidity when using the VATS approach. This current systematic review thus aimed to critically evaluate existing evidence for the efficacy and safety of VATS versus open (transsternal or transthoracic) thymectomy for thymomas.

Methods: Six electronic databases were searched from their date of inception to April 2015. Relevant studies were identified using specific eligibility criteria and data were extracted and analyzed based on predefined primary and secondary endpoints.

Results: Fourteen comparative observational studies with a total of 1,061 patients were obtained for qualitative assessment, data extraction and analysis. Five-year overall survival and 10-year recurrence-free survival was similar or higher in patients undergoing VATS compared to open thymectomy. On average, the VATS group also demonstrated reduced intraoperative blood loss (131.8 *vs.* 340.5 mL), shorter hospital stays (7.0 *vs.* 9.8 days), and lower rates of postoperative pneumonia (1.9% *vs.* 4.1%). The mean rate of conversion from VATS to open thymectomy was relatively low (3.1%), while 30-day mortality remained low in both the VATS and open groups (0% *vs.* 0.3%).

Conclusions: The current evidence suggests that VATS thymectomy for thymoma has at least equal if not superior oncological efficacy and survival outcomes, as well as reduced perioperative complications, compared to open surgery. Further adequately powered studies and future randomized trials are required to confirm these findings.

Keywords: Video-assisted thoracoscopic surgery (VATS); thymectomy; thymoma

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Introduction

While thymoma is a rare disease, it remains the most common primary mediastinal neoplasm in adults, with an estimated incidence of 0.15 cases per 100,000 (1). The overwhelming majority of thymic neoplasms are benign and slow-growing, and metastases are typically limited to the pleura, pericardium and/or diaphragm (1). Therefore, complete surgical resection is accepted as the mainstay of therapy, with median sternotomy currently considered to be the gold standard for resection approaches (2,3). However, interest has grown in minimally invasive surgical approaches, most notably video-assisted thoracoscopic surgery (VATS) thymectomy, as a means of reducing perioperative morbidity and mortality (3).

Recent institutional studies have associated VATS thymectomy with improved outcomes, including reduced postoperative pain, fewer complications such as bleeding and pneumonia, shorter hospital stays, better preservation of baseline pulmonary function, and superior cosmesis with the use of smaller surgical incisions (2,4). Furthermore, similar

survival and recurrence rates have been demonstrated for VATS thymectomy compared to open thymectomy patients, reinforcing the rising popularity of the VATS approach as it continues to become increasingly used in centers worldwide (2,4).

Nonetheless, evidence for the efficacy, particularly long-term oncological outcomes, of VATS thymectomy compared to open surgery remains limited, with a current paucity of randomized controlled trials. The present systematic review thus aimed to summarize existing studies comparing VATS thymectomy to open thymectomy (transsternal or transthoracic). The primary outcomes of interest were overall and recurrence-free survival, while secondary endpoints included the incidence of postoperative complications and length of hospital stay.

Methods

Literature search

The present systematic review was performed according to recommended PRISMA guidelines (5,6). Six electronic databases, including MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Reviews of Effects (DARE), were searched from their dates of inception to April 2015. To maximize the sensitivity of the search strategy, the following terms were combined: (VATS OR thoracoscopic OR thoracoscopy) AND (open OR sternotomy OR transsternal OR transthoracic) AND (thymus or thymoma or thymic or thymectomy) as either keywords or MeSH terms. The reference lists of articles retrieved were also reviewed in order to identify additional related studies.

Eligibility criteria

Comparative studies that reported any postoperative outcome of VATS thymectomy versus open (transsternal or transthoracic) thymectomy for thymoma were eligible for analysis. At least ten adult patients aged 18 years and over were required to be in each arm of the study. When institutions published duplicate studies with overlapping sample populations, only the most recent reports were included. Only studies published in the English language were selected. Case reports, conference abstracts, editorials, commentaries, pediatric or adolescent studies, and review articles were excluded.

Data extraction and critical appraisal

All data were extracted from article texts, tables and figures. Two independent investigators (A.X., R.T.) reviewed each article retrieved. Inter-reviewer discrepancies were resolved by discussion and consensus (A.X., R.T., K.P.). If the study reported medians and ranges we calculated the equivalent means and standard deviations (SDs) using the conversion method described by Hozo, Djulbegovic & Hozo [2005] (7). The studies were also qualitatively assessed using the critical review checklist formulated by the Dutch Cochrane Group and MOOSE guidelines (8) (*Table S1*). These checklist criteria included the clear definition of study population, outcomes and outcomes assessment; independent outcomes evaluation; adequate follow-up duration; no selective losses to follow-up; and identification of key confounders. The final results were reviewed by the senior investigator (T.D.Y.).

Statistical analysis

Conventional descriptive statistics were used to summarize the baseline demographics of included patients. Data were presented as raw numbers, percentages, or means with standard deviations unless otherwise indicated. Pooled averages were calculated for outcomes reported in at least three of the included studies. When not explicitly reported in the article text, rates of overall survival and recurrence-free survival were reconstructed for specific time points on digitized Kaplan-Meier curves using the software program, DigitizeIt v2.0.

Results

Quantity and quality of evidence

A total of 414 records were identified through the database searches. After eliminating duplicates and screening the studies based on abstracts 33 full-text articles were assessed using the eligibility criteria. Fourteen relevant studies were selected for analysis, all of which were observational, though two of these trials also used propensity score-matched groups (9,10) (*Figure S1*, *Table 1*).

A total of 1,061 patients were included in the analysis, with 540 undergoing VATS and 521 for open thymectomy. Individual sample sizes varied across the studies, with a median of 23.5 [12-125] for VATS and 22 [10-137] for open thymectomy. The mean length of follow-up similarly varied but was generally longer for open surgery, with a range of 24.4±8.8 to 99.4±27 months for VATS, and

Table 1 Characteristics of studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Year	Institution	Study period	Type of study	Sample size (n)	VATS (n)	Open (n)	Mean follow-up, entire cohort (months)	Mean follow-up, VATS (months)	Mean follow-up, open (months)
Chao	2015	Chang Gung Memorial Hospital, Taoyuan City, Taiwan	1991-2007	PSM	140 (96^{P})	61 (48^{P})	58^{TS} (48^{P}), 21^{TC}	53^{M}	66^{M}	95^{M}
Cheng	2005	Kaohsiung Medical University Hospital, Kaohsiung, Taiwan	1999-2004	OS	22	12	10	33.9±19.7	NR	NR
Chung	2012	Asan Medical Centre, Seoul, Korea	2002-2008	OS	70	25	45	NR	78.0±21.9	70.0±23.6
He	2013	First Affiliated Hospital of Nanjing Medical University, Nanjing, China	2006-2011	OS	33	15	18	12-61^{R}	NR	NR
Kimura	2013	Osaka University Hospital, Osaka, Japan	2002-2009	OS	74	45	29	NR	53.7±24.5	49.6±25.3
Liu	2014	National Taiwan University Hospital, Taipei City, Taiwan	1991-2010	OS	120	76	44	NR	61.9±52.0	69.71±68.4
Maniscalco	2015	Sant'anna Hospital of Ferrara, Ferrara, Italy	1995-2007	OS	27	13	14	123^{M}	101^{M}	129^{M}
Manoly	2014	Southampton General Hospital, Southampton, UK	2004-2010	OS	39	17	22	NR	30.5±14.3	35.0±20.2
Odaka	2010	Jikei University School of Medicine Tokyo, Japan	2000-2008	OS	40	22	18	NR	24.4±8.8^{C}	56.2±20.3^{C}
Pennathur	2011	University of Pittsburgh Medical Center, Pittsburgh, USA	1996-2008	PSM	40	18	22	36^{M}	27^{M}	58^{M}
Sakamaki	2014	Osaka Police Hospital, Osaka, Japan	1998-2011	OS	82	71	11	49^{M}	63.0±38.0^{C}	57.5±30.0^{C}
Tagawa	2014	Nagasaki University Hospital, Nagasaki; Oita Prefectural Hospital, Oita, Japan	1995-2007	OS	27	15	12	NR	99.4±27^{C}	106.1±32.8^{C}
Ye	2014	Shanghai Chest Hospital, Shanghai, China	2008-2012	OS	262	125	137	NR	35.8±14.8^{C}	36.3±14.8^{C}
Yuan	2014	Cancer Institute and Hospital of Chinese Academy of Medical Sciences, Beijing, China	2007-2013	OS	129	38	44^{TS}, 47^{TC}	NR	NR	NR

PSM, propensity-matched study; OS, observational study; ^{P}, propensity-matched number; VATS, video-assisted thoracoscopic surgery; ^{TS}, transsternal; ^{TC}, thoracotomy; ^{M}, median; MN, mean; ^{R}, range; ^{C}, converted from median and range to mean and standard deviation; NR, not reported.

35.0±20.2 to 106.1±32.8 months for the open approach. One study used a historical open thymectomy group (from 2000 to 2005) for comparison with VATS outcomes (2005-2008) (11).

Of the seven studies (9,11-17) that reported their eligibility criteria for either surgical approach, the majority limited their use of the VATS approach to those patients with a tumor diameter of less than 5 cm (12,14,16,17) or 6 cm (13), tumors located inferior and separate to the innominate vein (12,13,16), and/or little or no evidence of invasion or close proximity to vital organs including the heart and great vessels (9,11-16). Exceptions to these criteria, particularly tumors measuring over 5 cm that were still accessible through thoracoscopy, were reported by at least two studies (12,14). The first included study that used propensity-scores matched the VATS and open surgery groups for thymoma Masaoka stage and tumor size (9). The second such study matched for variables of tumor size, presence of myasthenia gravis (MG), and date of surgery (10).

Baseline characteristics

The baseline demographics are summarized in *Table 2*. The weighted mean age, proportion of male patients, and body mass index (BMI) were similar between VATS and open groups. The percentage of tumors classified as Masaoka stage I (60.2% *vs.* 58.6%) and II (39.6% *vs.* 40.1%) was also similar between VATS and open thymectomy patients, respectively. Only one study included thymomas in Stage III (VATS, n=0; open, n=5) and IV (VATS, n=1; open, n=1) (12). Histological grading (A-B3) according to World Health Organization guidelines was additionally comparable between the two groups, with only one study including one open thymectomy patient classified as grade C (17). Mean tumor size, as determined by either computed tomography or histopathology, was slightly larger at 5.6 cm (3.4-7.7 cm) in the open surgery group compared to 4.5 cm in the VATS group (3.2-6.6 cm).

Furthermore, a higher proportion of VATS patients had MG (24.9%) compared to open thymectomy patients (18.7%), although the range for both groups was large (0%-100%), due to several studies incorporating MG into their inclusion (18) or exclusion criteria (11,12,17). The perioperative use of adjuvant therapy (radiotherapy and/or chemotherapy) appeared to be comparable in both groups (34.1% for VATS *vs.* 31.2% for open), although the range was similarly large (0%-100%) across the studies.

Intraoperative characteristics

Differences were noted in the operative approaches and strategies for both VATS and open thymectomy across included studies (*Table 3*). Based on weighted means the majority of patients underwent a total or extended thymectomy with a higher proportion in the open thymectomy group (98.5%, range, 63.6%-100%) than in the VATS group (79.9%, 40.8%-100%). Correspondingly, a greater percentage of VATS patients underwent a 'partial' thymectomy (20.8%, 0%-59.2%) compared to open thymectomy patients (1.5%, 0%-36.4%). In the two studies that performed hemithymectomy or partial thymectomies for selected patients, the extent of resections was not clearly defined (9,15).

Most of the unilateral VATS thymectomy patients underwent a right-sided procedure (74%, 64%-100%) rather than left-sided (26%, 0%-36%). Four studies specified their surgical approach as always being from the side of the tumor (9,11,17,19), while an additional two studies preferred the right-sided approach except in cases of obvious left-sided thymoma (18,20). Maniscalco *et al.* [2015] reported that their VATS approach was mostly left-sided, although specific rates of use were not included (21). Eight studies included bilateral VATS approaches (9-11,13-16,19), while Tagawa utilized a cervico-xyphoidal-thoracic approach in an unspecified proportion of their patients (16). All open surgery groups utilized a midline sternotomy (n=474) except for a small proportion from the study by Yuan *et al.* [2014], which utilized a thoracotomy (n=47) (19).

The mean operative duration was similar between VATS (172 minutes, 117.0-249.8) and open thymectomy (173.6 minutes, 131.0-227.9) patients. The conversion rate for VATS was relatively low (3.1%), though this ranged from 0% to up to 11.8% in one study (22). Mean intraoperative blood loss was observed to be markedly higher in the open surgery group (340.5 mL, 75.0-484.8) compared to the VATS group (131.8 mL, 40.0-214.9). There were no cases of intraoperative mortality reported.

Postoperative characteristics

The postoperative outcomes are summarized in *Tables 4-6*. The length of hospital stay was, on average, longer for open surgery patients (9.8 days, 5.4-19.0) compared to VATS patients (7.0 days, 2.6-14.0). The length of intensive care unit (ICU) stay was similar between the two groups (1.4 days for VATS *vs.* 1.5 days for open), though this value should be

Table 2 Baseline demographics of participants in studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Approach	Age (years)	Male (%)	BMI	Masaoka stage I (%)	Masaoka stage II (%)	WHO histology (%)	Tumour size (CT)	Myasthenia gravis (%)	Adjuvant therapy (%)
Chao	VATS	50.7±0.4	50.0	24.9±3.6	35.4	64.6	A 8.3, AB 33.3, B1 10.4, B2 37.5, B3 10.4	5.8±1.8	26.0	37.5
	Open	50.8±1.4	54.2	24±3.8	35.4	64.6	A 6.3, AB 25, B1 8.3, B2 45.8, B3 14.6	5.7±1.7	26.0	33.3
Cheng	VATS	40.2±16.3	58.3	NR	0.0	100.0	NR	NR	50.0	100.0
	Open	47.7±8.5	40.0	NR	0.0	100.0	NR	NR	60.0	100.0
Chung	VATS	45.8±12.3	52.0	NR	72.0	24.0	A 16, AB 16, B1 44, B2 24	5.2±2.0×4.2±1.6×2.7±1.0^{PT}	0.0	NR
	Open	51.7±12.5	46.7	NR	66.7	20.00	A 11.1, AB 46.7, B1 31.1, B2 11.1	7.7±2.6×5.8±1.7×3.9±1.2^{PT}	0.0	17.8
He	VATS	54.2±11.9	46.7	24.5±2.4	NR	NR	NR	NR	100.0	33.3
	Open	48.6±8.9	61.1	23.7±3.4	NR	NR	NR	NR	100.0	50.0
Kimura	VATS	55±12	42.2	NR	91.1	8.90	A 11.1, AB 35.6, B1 31.1, B2 31.1, B3 4.4	4.8±2.1	31.1	NR
	Open	57±12	34.5	NR	58.6	41.4	A 3.4, AB 37.9, B1 44.8, B2 6.9, B3 6.9	6.5±2.5	31.0	NR
Liu	VATS	50.5±14.6	46.1	23.2±3.3	75.0	25.0	A 11.3, AB 49.3, B1 11.3, B2 18.3, B3 9.9	4.6±1.9^{PT}	46.1	NR
	Open	51.8±14.5	40.9	22.3±3.4	84.1	15.9	A 4.9, AB 51.2, B1 22, B2 14.6, B3 7.3	6.1±2.9^{PT}	31.8	NR
Maniscalco	VATS	59.4^{M}	53.8	NR	61.5	38.5	NR	3.5^{M}	38.5	100.0
	Open	64^{M}	50.0	NR	71.4	28.6	NR	6^{M}	35.7	0.0
Manoly	VATS	63.1±15.7	35.3	29.1±5.1	NR	NR	NR	NR	47.1	47.1
	Open	65.4±11.0	59.1	26.9±4.9	NR	NR	NR	NR	18.2	NR
Odaka	VATS	51.9±14.2	63.6	NR	68.2	31.8	NR	4.4±1.9	0.0	NR
	Open	51.1±13.2	38.9	NR	61.1	38.9	NR	4.9±2.2	0.0	NR
Pennathur	VATS	64^{M}	55.6	NR	27.8	72.2	NR	3.5±1.1	38.9	38.9
	Open	64^{M}	40.9	NR	40.9	59.1	NR	5.8±2.0	18.2	54.5
Sakamaki	VATS	56.0±17.5^{C}	38.0	NR	56.3	43.7	B2-B3 23.9	4.8±2.5^{C}	36.6	9.9
	Open	59.0 ±14.8^{C}	45.5	NR	36.4	63.6	B2-B3 27.3	7.2±3.2^{C}	27.3	9.1
Tagawa	VATS	51.4±16.0	46.7	NR	53.3	46.7	NR	3.6±1.0	6.7	26.7
	Open	50.9±15.0	25.0	NR	66.7	33.3	NR	3.8±1.3	66.7	16.7

Table 2 (*continued*)

Table 2 (*continued*)

First author	Approach	Age (years)	Male (%)	BMI	Masaoka stage I (%)	Masaoka stage II (%)	WHO histology (%)	Tumour size (CT)	Myasthenia gravis (%)	Adjuvant therapy (%)
Ye	VATS	51.9±13.0	52.0	NR	64.0	36.0	A 12.8, AB 68, B1 13.6, B2 3.2, B3 2.4, C 0	3.2±0.9	0.0	32.0
	Open	50.0±15.6	54.0	NR	65.7	34.3	A 10.4, AB 56.1, B1 14, B2 1.8, B3 0.6, C 0.6	3.4±0.7	0.0	29.9
Yuan	VATS	49.3±11.8[C]	50.0	25.4±4.0[C]	44.7	55.3	NR	6.6±2.6[C]	13.2	NR
	Open	47.6±15.3[C]	50.5	25.6±4.0[C]	53.8	46.2	NR	7.3±2.6[C]	15.4	NR
Weighted Mean	VATS	52.1	48.2	24.7	60.2	39.6	A 9.8, AB 46.8, B1 11.8, B2 9.3, B3 3.8, C 0	4.5	24.9	34.1
	Open	51.2	48.7	24.6	58.6	40.1	A 9.4, AB 51, B1 15.7, B2 6.7, B3 2.2, C 0.6	5.6	18.7	31.2
Range	VATS	40.2-63.1	35.3-63.6	23.2-29.1	0-91.1	8.90-100.0	A 8.3-16, AB 16-68, B1 10.4-44, B2 3.2-37.5, B3 2.4-10.4, C 0	3.2-6.6	0.0-100.0	9.9-100.0
	Open	47.6-65.4	25.0-61.1	22.3-26.9	0-84.1	15.9-100.0	A 3.4-11.3, AB 25-56.1, B1 8.3-44.8, B2 1.8-45.8, B3 0.6-14.6, C 0.6	3.4-7.7	0.0-100.0	0.0-100.0

VATS, video-assisted thoracoscopic surgery; [M], median; BMI, body mass index; [C], converted from median and range to mean and standard deviation; NR, not reported; WHO, World Health Organization; [CT], computed tomography; [PT], measured from histopathology specimens.

Table 3 Intraoperative outcomes in studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Approach	Full thymectomy (%)	Partial thymectomy (%)	VATS right-sided (%)	VATS left-sided (%)	Operation duration (min)	Conversion rate (%)	Blood loss (mL)	Operative mortality (%)
Chao	VATS	62.5	37.5	77.1	22.9	153±60	2.1	40±66	0.0
	Open	100.0	0.0	–	–	173±56	–	75±96	0.0
Cheng	VATS	NR	NR	NR	NR	193.3±79.6	0.00	119.2±70.6	0.0
	Open	NR	NR	–	–	207.5±85.8	–	238.5±110.2	0.0
Chung	VATS	100.0	0.0	64.0	36.0	117±48	7.1	NR	0.0
	Open	100.0	0.0	–	–	131±43	–	NR	0.0
He	VATS	100.0	0.0	100.0	0.0	202.3 ± 53.1	0.0	98.7±62.8	0.0
	Open	100.0	0.0	–	–	141.8±30.7	–	225.0±101.8	0.0
Kimura	VATS	NR	NR	NR	NR	197±102	NR	105±133	0.0
	Open	NR	NR	–	–	167±42	–	262±205	0.0
Liu	VATS	NR	NR	NR	NR	141.7±62.8	1.3	105.1±142.2	0.0
	Open	NR	NR	–	–	149.9±33.3	–	159.7±109.6	0.0
Maniscalco	VATS	NR	NR	NR	NR	138.0	0.0	NR	0.0
	Open	NR	NR	–	–	162.0	–	NR	0.0
Manoly	VATS	NR	NR	NR	NR	177.1±70.2	11.8	NR	0.0
	Open	NR	NR	–	–	151.7±63.3	–	NR	0.0
Odaka	VATS	NR	NR	72.7	27.3	194.0±61.8	0.0	100.6±76.5	0.0
	Open	NR	NR	–	–	180.9±43.3	–	208.1±236.4	0.0
Pennathur	VATS	NR	NR	NR	NR	NR	NR	NR	0.0
	Open	NR	NR	–	–	NR	–	NR	0.0
Sakamaki	VATS	40.8	59.2	NR	NR	208±58^{TT}, 136±65^{PT}	5.6	NR	0.0
	Open	63.6	36.4	–	–	191±29^{TT}, 176±96	–	NR	0.0
Tagawa	VATS	100.0	0.0	NR	NR	249.8±52.9	0.0	92.3±67.6	0.0
	Open	100.0	0.0	–	–	227.9±52.6	–	225.1±133.6	0.0
Ye	VATS	100.0	0.0	72.0	28.0	171±31.1	3.2	183.1±98.2	0.0
	Open	100.0	0.0	–	–	216±41.2	–	462.4±95.6	0.0
Yuan	VATS	NR	NR	NR	NR	146.8±67.5^{C}	NR	214.9±145^{C}	0.0
	Open	NR	NR	–	–	143.6±53.8^{C}	–	484.8±362.5^{C}	0.0
Weighted mean	VATS	79.9	20.8	74.0	26.0	172.0	3.1	131.8	0.0
	Open	98.5	1.5	–	–	173.6	–	340.5	0.0
Range	VATS	40.8-100.0	0.0-59.2	64.0-100.0	0.0-36.0	117.0-249.8	0.0-11.8	40.0-214.9	0.0
	Open	63.6-100.0	0.0-36.4	–	–	131.0-227.9	–	75.0-484.8	0.0

VATS, video-assisted thoracoscopic surgery; ^{TT}, total thymectomy; ^{PT}, partial thymectomy; ^{C}, converted from median and range to mean and standard deviation; NR, not reported.

Table 4 Postoperative outcomes in studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Approach	Length of hospital stay (days)	Length of ICU stay (days)	Chest drain duration (days)	Chest drain volume (mL)	30 day mortality (%)	Pneumonia (%)	Phrenic nerve injury (%)	Margin positive (%)	Reoperation (%)
Chao	VATS	5.8±2	NR	4.4±1.5	NR	NR	NR	NR	NR	NR
	Open	7.0±2.2	NR	4.9±1.9	NR	NR	NR	NR	NR	NR
Cheng	VATS	6.8±2.3	NR	4.2±2.1	NR	0.0	NR	NR	NR	NR
	Open	8.9±4.4	NR	4.6±2.1	NR	0.0	NR	NR	NR	NR
Chung	VATS	3.4±1.3	NR	1.8±0.9	NR	0.0	NR	NR	NR	NR
	Open	6.4±2.5	NR	3.6±2.0	NR	0.0	NR	NR	NR	NR
He	VATS	10.6±5.1	1.2±1.0	3.5±0.9	394.0±151.9	0.00	13.3	0.0	NR	NR
	Open	12.2±3.6	0.8±0.8	3.6±1.2	409.7±159.0	0.00	16.7	0.0	NR	NR
Kimura	VATS	14±9	NR	NR	NR	0.00	NR	NR	NR	8.9
	Open	19±13	NR	NR	NR	0.00	NR	NR	NR	NR
Liu	VATS	7.1±3.6	1.7±1.9	4.1±2.5	NR	0.00	NR	NR	0.0	NR
	Open	9.1±3.8	2.1±2.6	5.2±2.6	NR	2.30	NR	NR	0.0	NR
Maniscalco	VATS	2.6	NR	NR	NR	0.00	NR	7.7	7.7	NR
	Open	5.4	NR	NR	NR	0.00	NR	0.0	0.0	NR
Manoly	VATS	4.4±1.8	1.1±0.4	NR	NR	0.00	0.0	11.8	NR	0.0
	Open	6.4±4.6	2.0±1.2	NR	NR	0.00	0.0	0.0	NR	4.5
Odaka	VATS	4.6±1.7	NR	2±1	NR	NR	NR	NR	0.0	NR
	Open	11.2±3.6	NR	4.1±1.3	NR	NR	11.1	NR	0.0	NR
Pennathur	VATS	2.9±1.6	NR	NR	NR	NR	NR	NR	5.9	NR
	Open	6.2±4.2	NR	NR	NR	NR	NR	NR	0.0	NR
Sakamaki	VATS	NR	NR	NR	NR	0.00	NR	NR	NR	NR
	Open	NR	NR	NR	NR	0.00	NR	NR	NR	NR
Tagawa	VATS	NR	NR	NR	NR	0.00	NR	6.7	NR	NR
	Open	NR	NR	NR	NR	0.00	NR	NR	NR	NR
Ye	VATS	7.3±1.5	NR	3.2±0.8	311.8±122.0	NR	0.8	NR	0.0	13.6
	Open	12.4±7.6	NR	4.9±0.9	496.6±112.7	NR	2.2	NR	0.0	13.9
Yuan	VATS	6.4±2.8[C]	1.1±0.9[C]	4.9±2.0[C]	731.8±370.0[C]	NR	NR	NR	NR	NR
	Open	8.0±2.3[C]	1.2±1[C]	5.2±1.8[C]	1150.5±655[C]	NR	NR	NR	NR	NR
Weighted mean	VATS	7.0	1.4	3.6	408.4	0.0	1.9	6.7	0.8	11.2
	Open	9.8	1.5	4.8	732.1	0.3	4.1	0.0	0.0	NR
Range	VATS	2.6-14.0	1.1-1.7	1.8-4.9	311.8-731.8	0.0-0.0	0.0-13.3	0.0-11.8	0.0-7.7	0.0-13.6
	Open	5.4-19.0	0.8-2.1	3.6-5.2	409.7-1150.5	0.0-2.3	0.0-16.7	0.0-0.0	0.0-0.0	NR

VATS, video-assisted thoracoscopic surgery; [C], converted from median and range to mean and standard deviation; ICU, intensive care unit; NR, not reported.

Table 5 Overall survival outcomes in studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Year published	Approach	6 months	9 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Chao	2015	NR												
Cheng	2005	NR												
Chung	2012	VATS	NR	NR	NR	100	NR	NR	100.0	NR	100.0	NR		
		Open	NR	NR	NR	98	NR	NR	98	NR	77	NR		
He	2013	VATS	NR											
		Open	NR	NR	94.4	NR								
Kimura	2013	VATS	100.0	100.0	100.0	100.0	100.0	NR						
		Open	100.0	100.0	100.0	100.0	100.0	NR						
Liu	2014	VATS	100.0	100.0	100.0	100.0	100.0	100.0	100.0	NR				
		Open	NR	NR	NR	NR	NR	NR	96.8	NR				
Maniscalco	2015	NR												
Manoly	2014	VATS	NR	NR	100	NR	83.3	NR	83.3	NR				
		Open	NR	NR	100	NR	93.8	NR	93.8	NR				
Odaka	2010	NR												
Pennathur	2011	NR												
Sakamaki	2014	VATS	98.1	98.1	98.1	96.8	96.8	96.8	96.8	96.8	96.8	96.8	96.8	96.8
		Open	90.7	90.7	90.7	90.7	90.7	79.1	79.1	79.1	79.1	79.1	79.1	79.1
Tagawa	2014	NR												
Ye	2014	NR												
Yuan	2014	NR												
	Range	VATS	90.7-100.0	98.1-100.0	98.1-100.0	96.8-100.0	83.3-100.0	NR	83.3-100.0	NR	NR			
		Open	NR	NR	94.4-100.0	90.7-100.0	NR	NR	79.1-98.0	NR	NR			

VATS, video-assisted thoracoscopic surgery; NR, not reported.

Table 6 Recurrence-free survival outcomes in studies reporting on video-assisted thoracoscopic surgery versus open thymectomy for thymoma

First author	Year published	Approach	6 months	9 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Chao	2015	VATS	100.0	100.0	100.0	100.0	100.0	100.0	100.0	95.1	88.9	88.9	88.9	88.9
		Open	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	92.8	92.8	92.8	92.8
Cheng	2005	NR												
Chung	2012	VATS	100.0	100.0	100.0	100.0	NR	NR	96.0	96.0	96.0	NR		
		Open	NR	NR	NR	98.0	NR	NR	87.0	NR	77.0	NR		
He	2013	NR												
Kimura	2013	NR												
Liu	2014	VATS	NR	NR	NR	NR	NR	NR	96.9	NR				
		Open	NR	NR	NR	NR	NR	NR	92.2	NR				
Maniscalco	2015	VATS	100.0	100.0	100.0	100.0	100.0	100.0	100.0	NR				
		Open	100.0	100.0	100.0	100.0	100.0	100.0	100.0	NR				
Manoly	2014	VATS	100.0	100.0	100.0	NR	83.3	83.3	83.3	NR				
		Open	100.0	100.0	100.0	NR	85.2	NR	71.0	NR				
Odaka	2010	NR												
Pennathur	2011	VATS	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
		Open	100.0	100.0	100.0	100.0	100.0	83.0	83.0	83.0	83.0	83.0	83.0	83.0
Sakamaki	2014	VATS	98.5	98.5	98.5	96.9	95.0	95.0	92.4	92.4	92.4	92.4	92.4	92.4
		Open	90.5	90.5	90.5	90.5	90.5	79.5	79.5	79.5	79.5	79.5	79.5	79.5
Tagawa	2014	NR												
Ye	2014	NR												
Yuan	2014	NR												
	Range	VATS	98.5-100.0	98.5-100.0	98.5-100.0	96.9-100.0	83.3-100.0	83.3-100.0	83.3-100.0	92.4-100.0	88.9-100.0	88.9-100.0	88.9-100.0	88.9-100.0
		Open	90.5-100.0	90.5-100.0	90.5-100.0	90.5-100.0	85.2-100.0	79.5-100.0	79.5-100.0	79.5-100.0	77.0-92.8	79.5-92.8	79.5-92.8	79.5-92.8

VATS, video-assisted thoracoscopic surgery; NR, not reported.

interpreted with caution due to the large variation reported in individual studies. Both the duration of chest drainage and volume drained were lower in VATS patients compared to open thymectomy patients (3.6 *vs.* 4.8 days, and 408.4 *vs.* 732.1 mL respectively). Thirty-day mortality was low, at 0% for VATS, and 0.3% for open surgery.

Complications were variably reported, but higher rates of pneumonia were observed in the open group (4.1% *vs.* 1.9%), while the incidence of phrenic nerve injury was higher in VATS (6.7% *vs.* 0% in open surgery). A small proportion (0.8%) of VATS patients also demonstrated positive margins in resected specimens in contrast to none in the open surgery group. Other complications were insufficiently reported and thus not included in the analysis. The rate of reoperation for the VATS group was variable (0%-13.6%) with an average of 11.2%, whilst it was inadequately documented for open surgery and therefore not reported.

The ranges of overall survival at 1, 2, and 5 years were similar or higher in VATS patients compared to open thymectomy patients (98.1%-100%, 96.8%-100%, and 83.3%-100% in VATS *vs.* 94.4%-100%, 90.7%-100%, and 79.1%-98.0% in open surgery, respectively) (*Table 5*). Small variations in survival rates are most likely attributable to inconsistent reporting and different time points documented across studies, with only four trials that examined 5-year survival (12,14,15,22). Recurrence-free survival at 6 months, 9 months, and yearly for up to 10 years was also predominantly similar or higher for VATS compared to the open surgery group (*Table 6*). In addition, this outcome was better reported in the studies analyzed, with seven trials that included recurrence-free survival up to at least 5 years (9,10,12,14,15,21,22). Only three studies reported recurrence-free survival at 10 years postoperatively (88.9%-100% in VATS *vs.* 79.5%-92.8% in open thymectomy) (9,10,15).

Discussion

Our results suggest that VATS thymectomy may be associated with similar, if not superior, overall and recurrence-free survival rates compared to open surgery. The VATS approach was also shown to potentially result in fewer complications such as bleeding and pneumonia, and shorter hospital stays. Furthermore, the average conversion rate was relatively low, at 3.1%. Subsequently, these findings reinforce those of existing reviews of the literature, though no previous publications have specifically focused on comparing VATS with open thymectomy for thymoma (1,2).

The majority of baseline characteristics, including demographics, use of adjuvant radiotherapy and/or chemotherapy, and tumor stage and grade were similar between the VATS and open groups. However, a key issue with comparing the two surgical approaches did arise from the non-random case selection in the studies. Although the criteria varied slightly across different trials, patients were generally reported as eligible for VATS if their tumor was less than 5 cm (12,14,16,17) or 6 cm (13) in diameter. Furthermore, most studies required the tumor to be sufficiently separate from the innominate vein and other vital organs, including the great vessels, heart, and trachea, with no evidence of local invasion (9,11-16). As a result, tumor size was on average greater in the open thymectomy patients compared to VATS (5.6 *vs.* 4.5 cm, respectively). This difference may have resulted in selection bias and potentially skewed results towards more positive outcomes for the VATS group.

It should be noted that two of the included studies used propensity-matching to adjust for the possible confounding effect of tumor size (10) and additionally, Masaoka stage (9), and still demonstrated similar or superior disease-free survival in VATS compared to open thymectomy patients at 5 years. Furthermore, exceptions to the VATS selection criteria were reported. A small proportion of patients with tumors over 5 cm in diameter still underwent VATS in at least three of the studies (11,12,14). The potential feasibility and safety of the VATS approach for bulky intrathoracic benign lesions over 5 cm size was moreover demonstrated by Gossot *et al.* [2007], albeit in a single-arm (23). Agasthian [2011] further showed that VATS thymectomy could be performed for 13 invasive Masaoka stage III and IV thymomas <5 cm in size, with only one recurrence over a median follow-up of 4.9 years (24). Evidently however, adequately powered randomized controlled trials are required to confirm the efficacy of VATS thymectomy compared to open surgery for a broader range of thymic tumor types (22).

Variations in surgical techniques were also observed across the studies. A greater proportion of VATS patients received a 'partial-' or 'hemi-' thymectomy (20.8%, range, 0.0-59.2) compared to open surgery patients (1.5%, range, 0.0-36.4). Although partial thymectomy may raise concerns about tumor recurrence in the remaining thymic tissue, proponents argue that this is extremely rare and that an unnecessarily wide resection for an early-stage lesion in a non-myaesthenic patient may increase the risk of operative complications (11,25,26). Moreover, in the

current review, disease-free survival was still similar or superior in VATS patients compared to open thymectomy patients, despite variations in resection extent. This result also eventuated despite a small percentage of the VATS group demonstrating positive resection margins (0.8%) (10,11,14,21). Another concern with partial thymectomy has been that of post-thymectomy myasthenia gravis (PTMG); however, this complication was insufficiently reported in the studies included and therefore not presented in our analysis. Nonetheless, PTMG, which has an estimated incidence of 1%-3%, has been shown to occur even after cases of extended thymectomy, suggesting that full resection is not necessarily more protective compared to partial thymectomy (27). Future studies comparing different extents of resection for thymoma are required to determine their respective efficacy and safety.

Inter-study variations in the approach to open thymectomy were likewise observed. Although the majority of studies exclusively utilized a midline sternotomy (n=474) a small proportion of patients (n=47) in the trial by Yuan *et al.* [2014] underwent a thoracotomy instead (19). Subgroup analysis in this trial revealed similar outcomes for the sternotomy versus thoracotomy patients, with the exception of greater blood loss and longer operation times for a sternotomy. Thoracotomy, conversely, was shown to have shorter operating times than for VATS. When the two open techniques were combined in a comparative analysis against VATS thymectomy, operative times were subsequently similar, although blood loss and length of hospital stay remained greater for open thymectomy (19). Although these subgroup differences may have influenced the results of the current review, their effect is likely to be minimal given the relatively small proportion of patients who underwent a thoracotomy.

Other factors to consider include potential complications of VATS, which, although inconsistently reported across the studies, included phrenic nerve injury (6.7% in VATS *vs.* 0% in open). The risk of these complications may well be increased in the initial stages of the learning curve associated with VATS thymectomy (21,22,28). In addition, VATS has been suggested to increase the risk of pleural dissemination and recurrence. Proposed mechanisms for this increased risk have included excessive manipulation of the thymoma in the restricted working space of the anterior mediastinum, making the tumor capsule more prone to tearing, as well as incision of the mediastinal pleura, which may facilitate seeding of tumor cells (29). Although lower rates of recurrence for VATS compared to open thymectomy were demonstrated in the current review, longer follow-up to at least 5 years in future studies is required to confirm this demonstration of equal, or potentially superior, oncological efficacy.

Limitations

This review had several limitations inherent to the studies analyzed. These included their non-randomized, observational nature, small sample sizes, and insufficient and/or inconsistent reporting of outcomes including long-term survival, recurrence rates, and postoperative complications. There was a particular paucity of data reported after 5 years of follow-up, restricting the types of statistical comparisons that could be made. As pooled averages could not be calculated, meta-analysis was not performed. As previously discussed, variations in study protocols, including eligibility criteria for VATS and surgical techniques for VATS and open thymectomy, may have also contributed to selection bias and heterogeneity in results. Qualitative evaluation using MOOSE criteria further demonstrated an apparent paucity of independent assessment of outcome parameters by at least two investigators and specification of trial inclusion and exclusion criteria, based on lack of reporting by their respective studies.

Conclusions and recommendations

VATS thymectomy is emerging as an increasingly feasible and efficacious alternative to open surgery for resection of thymomas. The present systematic review reaffirmed several potential benefits of VATS compared to open thymectomy, which included similar, if not superior, overall and disease-free survival, reduced blood loss, lower rates of complications such as pneumonia, and shorter hospital stays. However, given the limitations inherent in retrospective observational studies with small sample sizes, further adequately powered trials with longer-term follow-up and future randomized controlled trials are required to confirm the comparative safety and efficacy of VATS thymectomy for thymoma.

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Footnote

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

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Minimally invasive versus open thymectomy: a systematic review of surgical techniques, patient demographics, and perioperative outcomes

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Background: Thymectomy is the mainstay of treatment for thymoma and other anterior mediastinal tumors, and is often utilized in the management of patients with myasthenia gravis (MG). While traditionally approached through a median sternotomy, minimally invasive approaches to thymectomy have increasingly emerged. The present systematic review was conducted to compare perioperative and clinical outcomes following minimally invasive thymectomy (MIT) and open thymectomy (OT).

Methods: Articles were obtained through a PubMed literature search. Comparative studies reporting clinical outcomes following MIT and OT were eligible for inclusion. We selected studies with full text availability, written in the English language, published after 2005 and with at least 15 patients in each arm. A descriptive analysis was performed.

Results: Twenty studies were included, involving a total of 2,068 patients undergoing either MIT (n=838) or OT (n=1,230). Within individual studies, MIT and OT cohorts were well matched with regards to patient age and gender, but there was considerable variation across studies. Resected thymomas were consistently larger in OT groups, with mean diameter significantly larger in five studies (MIT, 29–52 mm; OT, 31–77 mm). MIT was consistently associated with a lower estimated blood loss (MIT, 20–200 mL; OT, 86–466 mL), chest tube duration (MIT, 1.3–4.1 days; OT, 2.4–5.3 days), and hospital length of stay (MIT, 1–10.6 days; OT, 4–14.6 days). There were no consistent differences in rates of perioperative complications, thymoma recurrence, MG complete stable remission, or 5-year survival.

Conclusions: In appropriately selected patients, MIT may reduce blood loss, chest tube duration, and hospital length of stay, with comparable clinical outcomes compared to OT via median sternotomy.

Keywords: Thymectomy; transsternal; minimally invasive; outcomes

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Introduction

Thymectomy is most commonly indicated and performed for myasthenia gravis (MG), thymoma, and other anterior mediastinal tumors (1-6). While median sternotomy has long been the accepted standard approach, minimally invasive methods have emerged over recent decades including transcervical, video-assisted thoracoscopic (VATS), and robotic video-assisted thoracoscopic (R-VATS) approaches (7-11). While maintaining safety and surgical veracity remain the first priority, in appropriately selected patients, minimally invasive approaches aim to lower postoperative morbidity and improve post-operative quality

of life. However, there remains debate regarding the indications, selection, and outcomes of patients undergoing these procedures versus open resections (12-31).

The purpose of this systematic review was to synthesize the current literature comparing minimally invasive thymectomy (MIT) versus open thymectomy (OT) approaches. We sought to identify patient demographics and surgical strategies employed, and describe key perioperative and long-term outcomes associated with each approach.

Methods

Literature search strategy

An electronic search of the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) was conducted from June 2015 to August 2015, employing English language and full-text availability restrictions. The following search terms were employed: "thymectomy AND (robot OR robotic)" OR "thymectomy AND thoracoscopic". Results for these searches were then combined and duplicates were sequentially removed.

Eligibility criteria

Comparative studies reporting clinical outcomes of patients who underwent MIT and OT were eligible for inclusion. To be included, studies were required to have at least 15 patients in each surgical arm.

Data extraction and analysis

The listed authors extracted data for this review, and quality of evidence was assessed through examination of the design, analysis and sample size of each study. Relevant data from selected studies were tabulated, sorted by characteristics and outcomes of interest. We then performed a descriptive analysis by evaluating the overall trends in studies comparing MIT versus OT.

Results

Literature search

Literature search of the PubMed database using the proposed filters produced a total of 177 articles suitable for screening. Articles were subsequently evaluated for relevancy to this review topic, with 53 meeting eligibility criteria. Of these 53 articles, 20 were found to include a comparison of MIT and OT, and have at least 15 subjects in each surgical arm. These 20 studies were included in this review (*Figure 1*).

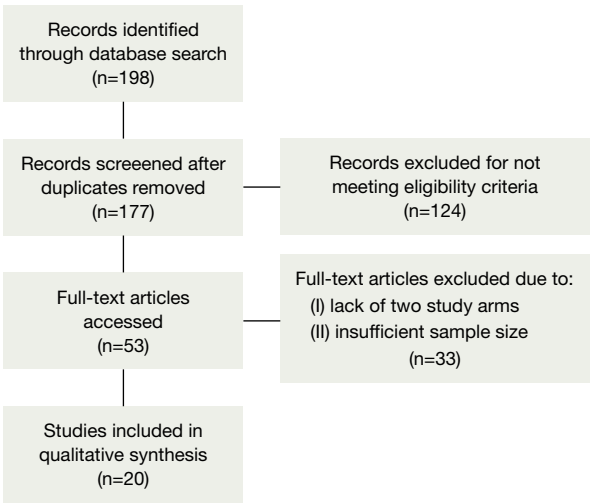

Figure 1 Flow diagram of literature search and study selection.

Patient demographics

A total of 2,068 patients were reported in the identified studies, including 838 (40.5%) who underwent MIT and 1,230 (59.5%) who underwent OT procedures. Overall, surgical cohorts within individual studies were well matched, with only one study identifying a statistically younger median age in the MIT group versus the OT group (46 *vs.* 52 years; P=0.02) (20). There was considerable variation of age and gender across studies. Patient age ranged from a mean 20.5 to a median of 64 years in the MIT groups, and a mean of 25.5 to a mean of 65.4 years in the OT groups. Gender distribution ranged from 18% to 64% male in MIT groups, and 29% to 61% male in OT groups (*Table 1*).

The most common indications for thymectomy in the included studies were thymoma [1,046, (51%)] and/or MG [1,132, (55%)]. Overall, 469 (56%) of MIT patients and 577 (47%) of OT patients had thymoma. Similarly, 430 (51%) of MIT and 702 (57%) of OT patients had MG. Patients with thymoma were selected by either clinical or pathological Masaoka staging, and in one instance, World Health Organization (WHO) pathological staging (19). Patients with MG were selected by either thymoma status or Osserman classification. Two studies included all

Table 1 Study characteristics and demographic information

Studies	Year	Study population	Minimally invasive approach [%]	Case number, n		Mean age, years		Male gender [%]		Presence of MG, n [%]		Presence of thymoma, n [%]		Mean thymoma diameter, mm	
				MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT
Mineo	2015	nonthymomatous MG	VATS: right, 15 [32] or left, 32 [68]	47	194	37	–	34	–	47 [100]	194 [100]	0 [0]	0 [0]	–	–
Gu	2015	c-Masaoka stage I, II thymoma	VATS : right or left	49	44	51.3	50.9	57	52	4 [8]	5 [11]	49 [100]	44 [100]	43#	54#
Chen	2014	nonthymomatous MG	VATS : right, 54 [100]	54	73	20.5	25.5	60	52	54 [100]	73 [100]	0 [0]	0 [0]	–	–
Ye	2014	p-Masaoka stage I,II thymoma	VATS: right, 90 [72] or left 35 [28]	125	137	51.9	50.0	52	54	0 [0]	0 [0]	125 [100]	137 [100]	32	34
Ye	2014	p-Masaoka stage I, II thymoma	R-VATS: right, 15 [65] or left, 8 [35]	23	51	52.5	50.1	52	61	0 [0]	0 [0]	23 [100]	51 [100]	30	33
Seong	2014	anterior mediastinal mass	R-VATS- right, left or bilateral	34	34	53.7	52.4	44	52	2 [6]	1 [3]	11 [32]	13 [38]	29	31
Manoly	2014	p-Masaoka stage I, II, III thymoma	VATS: right or left	17	22	63.1	65.4	35	59	8 [47]	4 [18]	17 [100]	22 [100]	–	–
Liu	2014	p-Masaoka stage I, II thymoma	VATS: right, left, or bilateral	76	44	50.5	51.8	46	41	35 [46]	14 [32]	76 [100]	44 [100]	46#	61#
Kimura	2013	c-Masaoka stage I, II thymoma	VATS: side not indicated	45	29	55	57	42	34	14 [31]	9 [31]	45 [100]	29 [100]	48#	65#
He	2013	MG + p-Masaoka stage I, II thymoma	VATS: right, 15 [100]	15	18	54.2	48.6	47	61	15 [100]	18 [100]	15 [100]	18 [100]	–	–
Weksler	2012	all thymectomy procedures	R-VATS: right, 13 [87] or left, 2 [13]	15	35	56.8	50.7	47	51	5 [33]	6 [17]	10 [67]	14 [40]	45	44
Jurado	2012	all thymectomy procedures	R-VATS, 2 [3] or VATS, 75 [97]: right, 2 [3] or bilateral 75 [97]	77	186	46*#	52*#	31	37	43 [56]	96 [52]	10 [13]	62 [33]	45*	65*
Chung	2012	thymoma (excluding WHO B3 and C subtypes)	VATS: right, 16 [64] or left, 9 [36]	25	45	45.8	51.7	52	47	0 [0]	0 [0]	25 [100]	45 [100]	52#	77#
Pennathur	2011	c-Masaoka stage I, II thymoma	VATS: right, left, or bilateral	18	22	64*	64*	56	41	7 [39]	4 [18]	18 [100]	22 [100]	36*#	61*#
Lee	2011	MG	VATS: bilateral, 55 [100]	55	59	35.6	37.4	18	29	55 [100]	59 [100]	11 [20]#	25 [42]#	–	–
Huang	2011	MG	VATS – right, 33 [100]	33	66	36.5	37.3	27	30	33 [100]	66 [100]	2 [6]	6 [9]	–	–
Odaka	2010	p-Masaoka stage I, II thymoma	VATS: right, 16 [73] or left, 6 [27]	22	18	51.9	51.1	64	39	0 [0]	0 [0]	22 [100]	18 [100]	44	50
Lin	2010	nonthymomatous MG	VATS: right, 38 [100]	38	22	33.1	30.4	26	32	38 [100]	22 [100]	0 [0]	0 [0]	–	–
Meyer	2009	MG	VATS: right, 48 [100]	48	47	39.8	34.4	48	33	48 [100]	47 [100]	4 [8]	6 [13]	–	–
Bachmann	2008	MG (Osserman 2-4)	VATS: side not specified	22	84	Combined: 38.2*		27	33	22 [100]	84 [100]	6 [27]	21 [25]	–	–

*, denote data presented as a median value; #, values were reported as statistically significant with $P<0.05$. MIT, minimally invasive thymectomy; OT, open thymectomy; MG, myasthenia gravis; VATS, video-assisted thoracoscopy; R-VATS, robotic video-assisted thoracoscopy; p-Masaoka, pathologic Masaoka stage; c-Masaoka, clinical Masaoka stage.

thymectomy procedures for any indication (20,21). Seong *et al*. included thymectomy performed for all anterior mediastinal masses (*Table 1*).

Operative technique

MIT was most commonly performed via VATS [764, (91%)] or R-VATS [74, (9%)]. Across the included studies, MIT was conducted through a right-sided [355, (62%)], bilateral [130, (23%)], or left-sided [92, (16%)] approach. OT was universally performed via median sternotomy with or without an accompanying cervical incision.

Thymoma size and staging

Of studies reporting histological Masaoka staging, 216 (62%) of thymomas resected by MIT were stage I, while 124 (36%) and 6 (2%) were stages II and III respectively. Likewise, 239 (58%) of thymomas resected by OT were stage I, and 156 (38%) and 20 (5%) were stages II and III respectively (data not shown). One study reported a significant difference in clinical tumor staging; 91% were stage I in the MIT group and 59% were stage I in the OT group (P=0.0025) (23). Thirteen studies did not show significant difference in thymoma staging (15-22,25,26,28-30). Thymomas resected by OT were consistently larger, with significantly greater tumor diameter reported in five studies (18,19,23,25,30). Reported thymoma diameter ranged from 29 to 52 mm in MIT groups and 31 to 77 mm in OT groups (*Table 1*).

Perioperative and post-operative outcomes

There was no consistent trend in operative times among studies (*Table 2*). Three studies reported statistically shorter operative times in the MIT groups (28-30), while another three-demonstrated statistically shorter times in the OT groups (16,22,31). Estimated blood loss in the MIT groups ranged from a median of 20 mL to a median of 200 mL. OT blood loss ranged from a mean of 86 mL to a mean of 466 mL. Twelve of 14 studies reported significantly less blood loss during MIT versus OT (15-17,20-24,28-31).

There was no significant difference in resection margins between MIT and OT. Reported rates of R0 resection of thymoma ranged from 59.1% to 100% during MIT versus 52.9% to 100% during OT. Chung *et al*. reported a higher incidence of local thymoma invasion in their OT arm [4 (8.9%) *vs*. 0 (0%); P=0.044]. Four studies provided rates of en bloc resection of adjacent structures necessary to complete the operation (20,26,27,30). Manoly *et al*. reported phrenic nerve resection in two (11.8%) of MIT patients in order to obtain complete thymoma resection (0% in OT). Diaphragmatic plication was not performed in either case. Other structures included lung parenchyma removed via wedge resection (MIT, 2%–6%; OT, 2%–10%), pericardium (MIT, 2%–9%; OT, 3%–10%), and innominate vein (MIT, 0%; OT, 1%–4%). Some structures were resected en bloc and in combination with others. No studies reported a significant difference in rates of additional resection (*Table 2*). It was not possible to determine from these studies the rates of R0 resection following en bloc additional resections.

There were 23 reported open conversions to either sternotomy or thoracotomy in this series. Rates of conversion ranged from 0% to 11.8% (*Table 2*). Eight were performed for bleeding, three for pleural adhesions, and four for invasion of vascular structures and/or phrenic nerve. Other reasons included local tumor invasion of pericardium, lack of experience with MIT, or no indication was provided.

Mean chest tube drainage time ranged from 1.3 to 4.1 days in the MIT groups and 2.4 to 5.3 days in the OT groups. Seven studies reported significantly shorter drainage times following MIT (15,17,19,25,27-29). MIT patients also experienced shorter stays in the intensive care unit (ICU), with three studies reporting significance. Lastly, the MIT groups experienced a significantly shorter hospital length of stay (LOS) in 16 studies (12-15,17-21,25-31). Hospital LOS ranged from 1 to 10.6 days following MIT, and 4 to 14.6 days following OT (*Table 3*).

There was no consistent trend in postoperative morbidity. Complication rates ranged from 0% to 22.7% following MIT and 0% to 57% for OT, with one study reporting significantly fewer complications following MIT (6.7% *vs*. 57.1%; P=0.001) (21). There were a total of 46 postoperative complications reported for MIT and 118 for OT. The most commonly reported complications for MIT were respiratory infection/pneumonia (10), atelectasis (4), pleural effusion (3), atrial fibrillation (2), brachial plexus injury (2), and pneumothorax (2). There was one reported iatrogenic phrenic nerve injury, one transient phrenic nerve palsy, and one study reporting a single "phrenic nerve lesion" (12). The most common complications following OT were respiratory infection/pneumonia (26), atrial fibrillation (16), pleural effusion (12), and wound infection (5). One study reported six "phrenic nerve

Table 2 Study characteristics and intraoperative outcomes

Study	Year	Mean operating time (min)		Mean blood loss (mL)		R0 resection rate (%)		Lung resection, n [%]		Pericardial resection, n [%]		Phrenic nerve resection, n [%]		Innominate vein resection, n [%]		Open conversion, n [%]
		MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT
Mineo	2015	150#	138#	180#	240#	–	–	–	–	–	–	–	–	–	–	4 [8.5]
Gu	2015	65#	88#	126#	177#	100	100	1 [2]	1 [2]	1 [2]	2 [4]	0 [0]	1 [2]	0 [0]	2 [4]	3 [6.1]
Chen	2014	119	112	35#	86#	–	–	–	–	–	–	–	–	–	–	–
Ye	2014	170*#	210*#	200*#	450*#	–	–	–	–	–	–	–	–	–	–	4 [3.2]
Ye	2014	97#	215#	61#	466#	100	100									0 [0]
Seong	2014	157	139	–	–	–	–	2 [6]	1 [3]	2 [6]	1 [3]	–	–	–	–	1 [2.9]
Manoly	2014	177	152	–	–	52.9	59.1	–	–	–	–	2 [11.8]	0 [0]	–	–	2 [11.8]
Liu	2014	142	150	105	160	100	100	–	–	–	–	–	–	–	–	1 [1.3]
Kimura	2013	197	167	105#	262#	–	–	–	–	–	–	–	–	–	–	–
He	2013	202#	142#	99#	225#	–	–	–	–	–	–	–	–	–	–	0 [0]
Weksler	2012	130	–	42#	151#	100	100	–	–	–	–	–	–	–	–	–
Jurado	2012	167*	144*	20*#	100*#	100	91.9	3 [4]	18 [10]	7 [9]	18 [10]	–	–	0 [0]	2 [1]	6 [7.8]
Chung	2012	117	131	–	–	–	–	–	–	–	–	–	–	–	–	2 [8.0]
Pennathur	2011	–	–	–	–	94.4	100	–	–	–	–	–	–	–	–	–
Lee	2011	112	131	34#	124#	98.2	96.6	–	–	–	–	–	–	–	–	0 [0]
Huang	2011	207#	173#	89#	227#	–	–	–	–	–	–	–	–	–	–	0 [0]
Odaka	2010	194	181	101#	208#	100	100	–	–	–	–	–	–	–	–	0 [0]
Lin	2010	169	177	126	187	–	–	–	–	–	–	–	–	–	–	0 [0]
Meyer	2009	128	119	–	–	–	–	–	–	–	–	–	–	–	–	0 [0]
Bachmann	2008	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

*, denote data presented as a median value; #, values were reported as statistically significant with $P<0.05$. MIT, minimally invasive thymectomy; OT, open thymectomy.

Table 3 Perioperative and long-term outcomes

Study	Year	Mean pleural drainage (days)		Mean ICU LOS (days)		Mean hospital LOS (days)		Morbidity (%)		Transfusion (%)		30-day mortality (%)		5-year overall survival (%)		Thymoma recurrence (%)		MG complete stable remission (%)		Mean follow-up time (years)	
		MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT	MIT	OT
Mineo	2015	–	–	–	–	3.8#	4.5#	2.1	2.5	–	–	–	–	–	–	–	–	40	45	12.4	–
Gu	2015	2.5	2.7	0.8#	2.2#	5.7#	8.4#	–	–	0	0	–	–	–	–	0	0	–	–	Combined: 2.25*	
Chen	2014	2.6	2.4	1.4	1.6	7.8	6.9	3.7	6.8	–	–	–	–	–	–	–	–	20.4	27.4	–	–
Ye	2014	3*#	5*#	–	–	8*#	10*#	4.8	3.6	2.4	1.5	–	–	–	–	0.8	0.7	–	–	3.4*	3.5*
Ye	2014	1.3#	4.8#	–	–	3.7#	11.6#	4.3	3.9	0	0	–	–	–	–	0	0	–	–	1.4	1.5
Seong	2014	1.5#	3.1#	–	–	2.7#	5.5#	0	14.7	–	–	–	–	–	–	0	0	–	–	1.1	1.9
Manoly	2014	–	–	1.1	2.0	4.4#	6.4#	17.6	45.5	0	18.2	0	0	83.3	93.8	5.9	9.1	–	–	2.5	2.9
Liu	2014	4.1#	5.2#	1.7	2.1	7.1#	9.1#	0	0	–	–	–	–	100	96.8	2.6	2.3	–	–	3.7*	4.1*
Kimura	2013	–	–	–	–	11*	15*	–	–	–	–	–	–	–	–	6.7	0	–	–	–	–
He	2013	3.5	3.6	1.2	0.8	10.6	12.2	26.7	33.3	13.3	27.8	0	0	–	–	0	0	26.7	–	–	–
Weksler	2012	–	–	–	–	1*#	4*#	6.7#	57.1#	0	0	0	2.9	–	–	–	–	–	–	–	–
Jurado	2012	–	–	0*#	1*#	3*#	5*#	9.1	13.4	–	–	0	0.5	–	–	0	8	–	–	2.4*	6.7*
Chung	2012	1.8#	3.6#	–	–	3.4#	6.4#	0	6.7	–	–	0	0	100#	87#	0	4.4	–	–	6.5	5.8
Pennathur	2011	–	–	–	–	3*#	5*#	–	–	–	–	–	–	100	88	0	4.5	–	–	2.3*	4.8*
Lee	2011	2.4#	5.3#	0.3#	3.1#	6.8#	14.6#	2	5	0	3	0	0	–	–	–	–	–	–	–	–
Huang	2011	–	–	–	–	–	–	24.2	15.1	–	–	–	–	–	–	–	–	42.4	60.6	6.4#	9.8#
Odaka	2010	2.0#	4.1#	–	–	4.6#	11.2#	0	22.2	0	5.6	–	–	–	–	0	0	–	–	1.8	4.9
Lin	2010	–	–	2.1	2.0	5.6#	8.1#	5	5	8	0	0	0	–	–	–	–	32	36	3.2	7.2
Meyer	2009	–	–	–	–	1.9#	4.6#	–	–	–	–	–	–	–	–	–	–	34.9	15.8	6.1*#	4.2*#
Bachmann	2008	–	–	–	–	10.5*#	19*#	22.7	19.0	–	–	–	–	–	–	–	–	47.6	35.1	Combined: 8*	

*, denote data presented as a median value; #, values were reported as statistically significant with P<0.05. MIT, minimally invasive thymectomy; OT, open thymectomy; LOS, length of stay; ICU, intensive care unit; MG, myasthenia gravis.

lesions" following OT (12).

Thirty-day mortality did not differ between groups. Chung *et al*. published a significantly higher 5-year survival rate in the MIT versus OT group (100% *vs*. 87%; P=0.033). Three other studies reported no difference in 5-year survival (18,25,26). Additionally, no significant differences in thymoma recurrence were reported between MIT and OT. Pleural recurrence/dissemination was more commonly reported than local recurrence for both MIT and OT. There were six cases of pleural recurrence/dissemination and one case of local recurrence following MIT. Similarly, there were four cases of pleural recurrence/dissemination and one case of local recurrence following OT. Lastly, none of the included studies reported a significant difference in MG complete stable remission (CSR) rate between MIT and OT groups. CSR rates ranged from 20.4% to 47.6% for MIT and 15.8% to 60.6% for OT (*Table 3*).

Cost analysis

Ye and colleagues reported mean hospitalization costs of 53,886 versus 43,798 Chinese Yuan for R-VATS and transsternal thymectomy, respectively. These findings were not found to be statistically significant (P=0.174) (data not shown).

Discussion

Thymectomy is an important component in the treatment of early stage thymoma and anterior mediastinal tumors, as well as MG. Selection of surgical technique has been a long debated topic since its initial development. The current debate is focused on the determination of which surgical approach minimizes perioperative morbidity, while also offering acceptable long-term outcomes associated with a complete resection. The aim of this study was to investigate and summarize the current literature comparing minimally invasive and open approaches for thymectomy. We were particularly interested in perioperative and long-term outcomes, as well as any key differences in patient demographics between the surgical groups.

Surgical cohorts within each study were well matched with regards to age and gender, with one exception (20). However, we found considerable variation across studies, which can likely be attributed to differences in patient selection. This variation was likely due to differences between the two most common indications for thymectomy: (I) MG, which classically affects younger populations; and (II) thymoma, which presents at later ages. In studies investigating nonthymomatous MG, mean age ranged from 20.5 to 33.1 years in MIT groups and 25.5 to 30.4 in OT arms. In comparison, studies listing thymoma as an inclusion criterion had a mean age ranging from 45.8 to 64.0 years for MIT and 50.0 to 65.4 years for OT arms. This heterogeneity in populations may have contributed to the variation in reported outcomes across studies.

OT was consistently utilized for larger thymomas, while MIT was implemented for smaller tumors. Several studies reported a thymoma diameter cutoff for MIT at 5 cm (19,23,25,28,29), 6 cm (23) or 8 cm (20), which in turn selected for smaller tumors to be resected by MIT. It is difficult to determine the effect that this uneven matching may have had on perioperative and long-term outcomes. It is likely that larger tumors are associated with higher rates of additional en bloc resection of adjacent structures, and carry a different prognosis than smaller tumors. However, due to the paucity of available data, the present systematic review was not able to adequately investigate these differences.

MIT was associated with decreased blood loss, shorter chest tube duration, and shorter hospital LOS (12-31). The incidence of post-operative complications and long-term outcomes were comparable between the two surgical groups. Moreover, there were no reported significant differences in phrenic nerve injury. In patients with resectable disease, MIT may be a superior option for minimization of bleeding and hospitalization time, while offering long-term disease control comparable to OT. However, there is evidence to suggest a role for OT when MIT cannot be safely completed (19,20,26,27,29-31). Such instances include resection of large invasive tumors, dense adhesive disease, and high risk of significant bleeding unable to be controlled by MIT.

Robotic-assisted thymectomy

This review included three studies that used robotic-assisted platforms as their sole method of minimally invasive thymic resection (21,27,28). These articles reported significantly lower blood loss (range, 42–61 mL), chest intubation times (range, 1.3–1.5 days), and hospital LOS (range, 1.0–3.7 days) when compared to OT. These authors suggest that robotic assisted approaches may achieve outcomes comparable to conventional video-assisted techniques. Ruckert *et al*. reported similar rates of postoperative

complication between R-VATS and VATS thymectomy, and a higher rate of MG CSR in patients undergoing R-VATS (CSR, 39.3% *vs.* 20.3%; P=0.01) (32).

In our own experience of 17 patients undergoing R-VATS thymectomy, we have seen acceptable perioperative and short-term outcomes. Mean estimated blood loss in our cohort was 39 mL, and median chest tube and hospital LOS were 1 and 2 days, respectively. Robotic assisted MIT may show promise in development of safe and effective strategies for obtaining complete thymic resections, and potentially offer advantages of better visualization and instrument control over non-robotic MIT approaches.

Study limitations

The present study had several limitations. As with any systematic review, the process of literature search is prone to publication bias and the non-differential selection of studies with positive findings. To date, there have been no randomized trials comparing MIT and OT. As a result, this review was composed of non-randomized observational reports with significant and inherent selection bias. Another limitation was the degree of variability across studies with regards to study design, patient selection criteria, clinical versus pathologic staging, follow-up time, and presentation of findings. Additional limitations include effects of surgeon experience and learning curves associated with the various procedures, which were largely unreported or difficult to quantify in the included studies.

In appropriately selected patients with MG, or with moderate to small sized thymoma, therapeutic outcomes of MIT are comparable to OT, and may result in shorter hospital length of stay, decreased blood loss, and potentially fewer post-operative complications. Right or left VATS approaches appear to be comparable in outcome and a matter of surgeon preference. While robotic assisted approaches may afford the surgeon improved control and visualization during the conduct of operation, clinical outcomes appear to be similar to VATS. Cost analyses remain indeterminate, with MIT likely incurring higher operational costs than OT, but with potentially overall lower cost due to decreased length of hospital stay. The impact of robotic assisted approaches on cost remain a significant unknown, with “common” wisdom suggesting higher costs due to the high capital costs of these platforms, but with few formal analyses investigating this assumption. Prospective, randomized, controlled trials will likely be necessary to better delineate the differential outcomes and costs between open and minimally invasive approaches in these patients.

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Footnote

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

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Endoscopic thymectomy: a neurologist's perspective

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Myasthenia gravis (MG) is an autoimmune neuromuscular disease characterized by the presence of antibodies interacting at the neuromuscular junction (NMJ), resulting in loss of strength and severe exhaustibility of striated muscles. The abnormal production of these antibodies is triggered mainly in the thymus, and hence thymectomy in MG is considered a universally recommended treatment in order to improve the symptomatologic condition of this pathology. Currently, minimally invasive thymectomy using the Da Vinci robot system is certainly one of the most innovative techniques, performed in Pisa since 2001. This approach provides a valuable alternative to the traditional thymectomy through median sternotomy. The contribution of a neurologist is fundamental for preoperative patient selection and for the peri-operative clinical assistance in both approaches. We believe that in the robotic approach, the multidisciplinary collaboration between the neurologist, thoracic surgeon and anesthetist is important in reducing perioperative complications and ensuring a higher rate of complete remission or stable clinical improvement of MG.

Keywords: Myasthenia gravis (MG); acetylcholine receptor antibodies (AchRAb); thymic hyperplasia; thymoma; robotic thymectomy

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Introduction

Myasthenia gravis (MG) is a neuromuscular disease characterized in most of the cases by the presence of antibodies interacting at the neuromuscular junction (NMJ) that results in loss of strength and severe exhaustibility of striated muscles which can even reach a point of impairment of vital functions (1).

The abnormal antibody production is triggered mainly in the thymus. In these categories of patients, the thymus presents morphological abnormalities as: hyperplasia (65% cases), tumors (thymoma) in 10%–15% or atrophy (1%–2%).

Thymectomy in MG is a universally recommended procedure, especially in MG with positive anti-acetylcholine receptor antibodies (AchRAb) (2,3) with the intent to improve symptoms and, in many cases, to achieve the complete remission of MG (4).

Our centre has dedicated a particular interest in MG and thymic-related pathologies, and has performed 730 thymectomies in patients with MG since 1990.

This great case volume necessitated development of a dedicated multidisciplinary team with collaboration between neurologists, thoracic surgeons and anesthetists (5).

We believe that this multidisciplinary approach is paramount in reducing perioperative complications, as well as optimizing the possibility of complete remission or a stable clinical improvement of the patient's condition.

Minimally-invasive thymectomy, using the da Vinci robot system, is one of the most innovative approaches for this type of operation. Despite of the fact that this technique was adopted since 2001 in Pisa for the treatment of lung tumors, its application for the treatment of thymic disease was only

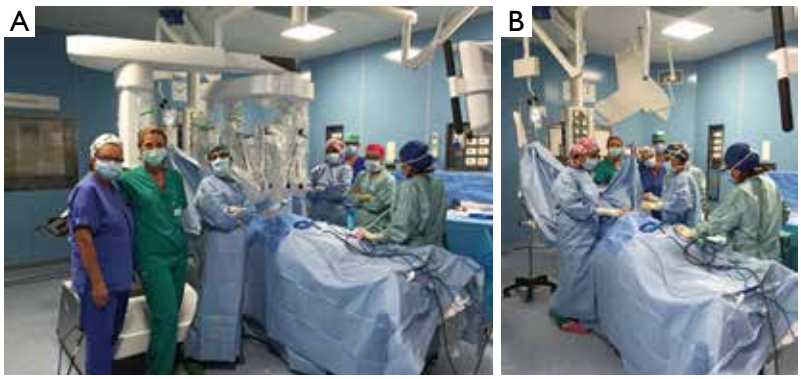

Figure 1 Setting of the operating theatre for robotic surgery in myasthenia gravis patient with the multidisciplinary team in Pisa (in *Figure 1A*, from left to right neurologist, anesthetist, thoracic surgeon and collaborators).

Figure 2 Operating theatre for robotic surgery during a thymectomy case in Pisa.

initiated in 2011, due to the excellent results achieved with thymectomy via sternotomy approach and also because an aesthetic skin access did not seem to justify the use of the da Vinci system.

Since 2011, 66 patients have undergone robotic thymectomy in our center. Within this group, our experience in 36 patients with MG suggests that thymectomy was a valid alternative for the treatment of their disease (6). The same team of the neurologist, thoracic surgeon and anesthetist who took care of thymectomy patients through the median sternotomy approach also managed patients through this minimally invasive approach (5) (*Figures 1*,*2*).

MG and thymic pathology: therapy

MG is an autoimmune neurological disease of multifactorial etiology in which genetic predisposition plays an important role (7,8). Furthermore, specific genetic polymorphisms has been linked to the incidence of thymoma in MG patients (9).

Knowledge of the pathogenesis of MG has enabled the development of different therapeutic approaches on a symptomatic and etiologic basis.

Symptomatic treatment through anticholinesterase drugs, mainly pyridostigmine bromide, is the most traditional therapy of the disease (10), and also the most commonly used as the initial approach (11). These are generally administered orally in chronic MG, but can be administered via intramuscular or intravenous, in cases of emergency or in the immediate postoperative phase. Other alternative ways of rapid administration, such as intranasally, have been studied (12).

The anticholinesterase drugs are efficacious in those MG forms with positive anti-acetylcholine receptors (AChR) antibodies, but are rarely efficacious and are responsible for the important cholinergic side effects in the seronegative forms and even more so in those MG patients with positive Anti-MuSK antibodies (13,14).

The use of anticholinesterases is also limited in that they are purely used for symptomatic relief and in order to act, need some residual function of the NMJ. With disease progression, and the reduction of the number of AChR, anticholinesterase therapy alone can become insufficient to control the myasthenic symptoms.

Once this occurs, it becomes necessary to use the etiologic treatments that act upon the pathologic autoimmune mechanisms responsible for the disease, particularly corticosteroids, which, according to our experience, often represent the immediate choice after the use of anticholinesterase drugs. Corticosteroids have been used since 1970 to treat MG (15), as they have the advantage to act rapidly and effectively in most forms of

the disease. When steroid treatment is not sufficiently effective or when it is contraindicated, a number of cytotoxic immunosuppressive drugs, monoclonal antibodies, intravenous immunoglobulins (IVIG), plasma exchange and thymectomy are used. The use of IVIG in treating MG dates back to 1984 (16-19), and in our centre, this sort of treatment is considered a better option than the plasma exchange in all those cases that require rapid improvement of the patient's clinical condition (17,19).

In the overarching management of these patients, thymectomy is the only strategic intervention capable of modifying the natural history of the disease. Thymectomy increases significantly the possibility of success in the treatment of MG: only 10% of the non-thymectomized patients achieve remission from the disease while the percentage increases significantly in those patients that undergo thymectomy (4,20), particularly young individuals with a recent onset of MG.

Thymectomy in MG has been universally used for many years (20-22), even though nowadays, based on our experience, we recommend this procedure exclusively for AChRAb-positive MG patients, which represent the majority of subjects affected by MG (2,3).

We also believe that patients with ocular AChRAb-positive MG and thymic hyperplasia can be good candidates for surgery, as in these cases, the ocular symptoms often represent the early phase of a form of generalized MG. The minimally invasive nature of robotic thymectomy is an additional reason to also recommend this surgical technique in patients younger than 50 years with ocular AChRAb positive-MG.

In conjunction with the thymectomy, it is important to assign specific pre- and postoperative neurological therapy, which, according to our experience, should primary be based on the use of steroids, combined with anticholinesterase drugs when useful. Corticosteroids seem to increase the therapeutic effect of the surgery, allowing a rapid improvement of the clinical condition that can even reach a complete remission from the disease (5).

Our experience and numerous scientific publications highlight the importance of the radical thymectomy, with the intent to excise not only the thymus but also the surrounding adipose and ectopic tissue that could be responsible for perseverance of MG (5,23-25).

A particularly attentive analysis of the chest computed tomography (CT) scan of the thymic region is essential in order to choose the most appropriate surgical approach; chest CT scan detection of a thymoma sized >5 cm with infiltration of the capsule or surrounding structures is the main exclusion criteria for the robotic approach.

Role of the neurologist

The neurologist manages the MG patient starting from arrival in the outpatient clinic, and is aware of all the clinical information for each individual. The role of the neurologist is to use all the most appropriate medical and surgical tools in order to achieve a stable clinical improvement or complete remission of the condition.

MG is a disease characterized by a huge clinical diversity, both from the symptoms as well as the pharmacological response point of view. For this reason, the constant presence of the neurologist is necessary throughout the surgical management of these patients.

Preoperatively, the aim of the neurologist is to optimize symptom control, using all the appropriate specific therapies for each individual patient. The primary treatment, in our experience, is generally the use of steroids in combination with anticholinesterases, in personalized doses based on disease severity in individual patient. In this situation, prednisone offers the possibility of a faster and better control of myasthenic symptoms than the other immunosuppressive drugs and with a minor risk of side effects. In our experience, we did not encounter any additional infectious complications or delay in the healing of the surgical wound.

Steroids should be associated to a hyposodic and hypocaloric diet, plus potassium supplements in order to avoid hypokalaemia. In addition, calcium supplements and calcitriol are given to prevent osteoporosis.

During the whole perioperative period, the anticholinesterase and steroid treatment are usually maintained at the same dosages as those given preoperatively. On the day of the operation, oral prednisone is replaced by an equivalent dosage of intramuscular dexamethasone.

We are not in favor of the use of immunosuppressants before the thymectomy, but if the patient has ongoing treatment with azathioprine or cyclosporine A, it is advisable to suspend these medications for approximately 10 days during the perioperative period with the intent to reduce the possibility of infectious complications.

Based on the collaboration between the neurologist and the anaesthetist in the operating theatre, general anesthesia is performed according to the patient's characteristics and severity of MG. The use of low-dose latest generation curare, such as rocuronium, has significantly reduced the

rate of postoperative respiratory complications.

Through this multidisciplinary approach, our patients do not need to stay in the intensive care unit following surgery. Instead, they are directly transferred to the ward or stay for 24 hours in the high dependency unit before being brought to the ward.

The collaboration between the neurologist and anesthetist is also valuable in determining an appropriate post-surgical pain therapy. In our experience, intra-venous non-steroidal anti-inflammatory drugs, paracetamol and tramadol therapy are favoured over other types of therapies. The use of low dosage morphine and opiates is reserved in those cases with the best clinical MG offset. Following robotic thymectomy the average hospital stay is of three to four days.

The use of steroids, based on our experience, seems to be beneficial not only for the induction and maintenance of clinical pre- and postoperative improvements, but also in achieving complete remission from the disease or on its long-term consistent improvement. These key clinical outcomes of MG can be obtained in a few months after the surgical procedure, but usually they can occur after an average period of three years or more (5,26).

Our methods

Multidisciplinary collaboration

From 1976 to 2015, our centre in Pisa has performed extended thymectomies through the median sternotomy approach, which have allowed almost half of the cases to reach complete remission of the disease (5,27).

Over 4,950 MG patients have been treated in our centre, and 730 have undergone thymectomy in the Hospital of Pisa Thoracic Surgery Department.

Since 1993, in conjunction with the surgical approach, a multidisciplinary system was activated (*Figures 1,2*). Based on a close collaboration with the neurologist, the patients with MG were inserted into a diagnostic therapeutic pathway, characterized also by an attentive pharmacological control of the MG during the perioperative period.

Robotic system

In 2001, the robotic surgery utilizing the "da Vinci" system was introduced in Pisa as well; this is considered a natural evolution of the video-assisted thoracoscopic surgery (VATS) approach. This method has the advantage of having a three-dimensional high definition vision of the operating field and better articulation of surgical instruments within the chest cavity. These features allow precise isolation of anatomical structures, safe manipulation of the tissues, and also guarantee a complete radical excision with the operation (6,28-31).

This innovative tool has been used also in thymectomy for MG patients in Pisa since 2011, showing that this approach can guarantee in selected cases a radical excision of the thymic gland and the entire perithymic adipose tissue with a comparable surgical outcome and clinical effects of the median sternotomy approach.

Robotic thymectomy offers a number of advantages compared to thymectomy through median sternotomy. The main advantage is reduced invasiveness of surgery, that according to our experience in Pisa, requires only one thoracoscopic camera access and two accesses for the robotic arms (29,30).

This method offers a better aesthetic result and is therefore preferred by young and mostly female patients, who are the predominant demographic affected by MG. In addition, in most cases, this surgical approach offers a rapid postoperative course making it a more appealing option than median sternotomy. The aesthetic result and the rapid functional recovery are also important elements to convince those patients concerned about the thymectomy through median sternotomy.

Selection criteria

The principal elements used by the neurologist to select patients to undergo a minimally invasive approach include: the type of thymic pathology, the patient body habitus, comorbidities, the ongoing medical therapy, and symptom severity according to Myasthenia Foundation of American Clinical Classification (MGFA).

The neurologist makes a diagnosis of MG through accurate anamnesis, a complete neurological examination and through the presence of the anti-AChRAb. Positivity for AChRAb represents a clear diagnostic indicator in these patients, making unnecessary the use of electromyography and pharmacological tests, which sometimes may also be confounding factors for diagnosis. The presence of anti-MuSK antibodies represents a contraindication for thymectomy; indeed, numerous publications confirm its therapeutic inefficacy in this form of myasthenia (32,33).

In patients seronegative for both AChRAb and anti-MuSK, we have noticed no improvement in the clinical

conditions following thymectomy; therefore, we have stopped various years ago to operate these patients.

Patients with MG and positive dosage of AChRAb should always undergo a chest CT to evaluate the presence of a thymic pathology. Thymectomy is indicated in patients with radiologic evidence of thymoma and those with thymic hyperplasia associated with positivity for AChRAb and, in most cases, with an age less than 50 years. Robotic thymectomy can be an option in those patients older than 50 years with AChRAb positivity, associated with thymic hyperplasia or thymic residue, MG poorly responsive to medical therapy and without major comorbidities.

The full inclusion and exclusion criteria for robotic thymectomy in MG patients are as follows:

(I) Inclusion criteria
- (i) Patients with AChRAb-positive, mild-moderate MG according to the MGFA classification (including ocular forms of MG) and generally aged less than 50 years;
- (ii) Chest CT scan detection of thymic hyperplasia or thymic residue associated with AChRAb-positive MG in patients generally aged less than 50 years;
- (iii) Chest CT scan detection of a thymoma sized <5 cm without capsular infiltration or of the surrounding structures (29,30).

(II) Exclusion criteria
- (i) Severe MG based on the MGFA classification;
- (ii) AchRAb-negative MG patients (including ocular forms);
- (iii) Anti-MuSK positive MG patients;
- (iv) Severe obesity;
- (v) Presence of important comorbidities, mainly cardiac and respiratory;
- (vi) Chest CT scan detection of a thymoma >5 cm in size with capsular infiltration or surrounding structures;
- (vii) Patients older than 50 years with MG responsive to medical therapy.

Possible neurological complications

In MG patients, it is always appropriate to consider the possible complications related to this disease, particularly those resulting from reduced muscular strength that may lead to altered respiratory function.

Thanks to our multidisciplinary approach, postoperative myasthenic crisis is considered a very rare complication in our centre. Despite the 10%–20% incidence of post-thymectomy myasthenic crisis described in the literature, this complication only occurred in our centre after extended operations that required prolonged general anesthesia in patients with myasthenia not well controlled by specific medical therapy (34,35).

Our experience

A total of 728 MG patients have undergone thymectomy in our centre since 1993. We retrospectively studied 36 patients who underwent robotic thymectomy between 2011 and 2015 (9 males and 27 females, mean age 36±12 years, mean age of onset of MG 34±12 years). Eleven patients were included in class 1, 11 patients in class 2A, 18 patients in class 2B, and two patients in class 3B according to MGFA classification. The mean operating time was 166±64 minutes.

In all cases, thymus excision was complete with perithymic adipose tissue removal, and in a patient with associated hyperthyroidism, the thyroid gland was also removed. All patients were given steroids throughout the entire perioperative period, and one patient required additional treatment with a cycle of IVIG for five days prior to the thymectomy in order to optimise the patient preoperative conditions. One patient was on azathioprine, which was suspended during the perioperative period for 10 days. No significant intra- or postoperative complications occurred, aside from transient recurrent laryngeal nerve irritation (n=1) and pleural effusion (n=1). The mean postoperative hospital stay was three days (ranging between two to five days).

Histologically, four patients were affected by thymoma (two thymoma A, one thymoma AB, and one patient thymoma B1) while 32 patients were shown to have thymic hyperplasia (*Figure 3*).

During this brief period of follow-up, complete stable remission (CSR) from the disease were observed in four patients who underwent thymectomy for hyperplasia and in two for thymoma. Eleven patients achieved pharmacologic remission after a mean period of seven months; five patients presented significant clinical improvement with minimal signs of the disease; and two patients showed marginal improvement. Three patients, however, did not show any significant clinical changes. None of the patients had worsened symptoms. There was no appropriate follow-up available for nine patients operated on in 2015; however, we can already point out that one patient has suspended medical therapy, two are controlled exclusively with

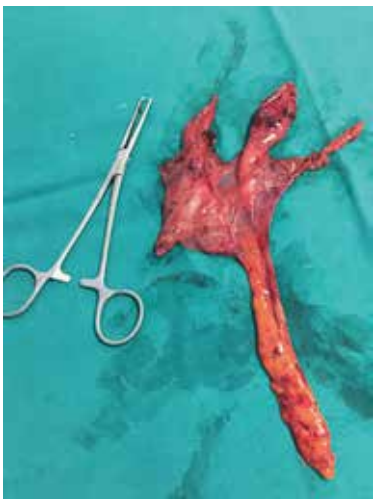

Figure 3 Thymic hyperplasia excised with robotic technique.

anticholinesterases, and six are treated with a combination therapy of anticholinesterases and low-dose prednisone.

Conclusions

The minimally invasive robotic thymectomy is a safe alternative to the median sternotomy approach in those forms of MG associated with thymic hyperplasia or non-invasive thymoma. Our encouraging results also derive from a multidisciplinary approach, personalized preoperative therapy, meticulous patient selection, and the use of steroids in the entire perioperative phase.

These particular measures were not only used to reduce the postoperative complications but also to guarantee a better chance for improvement of the clinical condition. The robotic technique is a valid alternative to the invasive surgery, particularly for clinically well-compensated young patients in whom the mini-invasive approach and the rapid postoperative recovery could represent an important additional factor for the achievement of an optimal therapeutic result.

According to this analysis, an appropriate neurological treatment prior to thymectomy and a correct anesthetic approach represent a safety factor during the whole surgical pathway minimizing the risk of complications.

These results were also achieved thanks to an integrated approach between the neurologist, thoracic surgeon and anaesthetist, using experience acquired from numerous sternotomies performed in Pisa.

We would also like to highlight that the association between radical thymectomy and appropriate neurological treatment during the postoperative years may be an additional factor for the achievement of CSR or the clinical improvement of myasthenic patients.

Myasthenia gravis is a disease where emotional stress can lead to exacerbation of symptoms, and in which the diagnosis and the search for right therapy could be very difficult and be an additional cause of prolonged suffering. These negative experiences could worsen the severity of the disease. We believe that it is therefore paramount to achieve a compassionate approach between doctor and patient; this empathy can contribute to obtaining the best therapeutic result. We consider this element a further fundamental pillar of our model of cure of MG (26).

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Footnote

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Perioperative outcomes and long-term survival in clinically early-stage thymic malignancies: video-assisted thoracoscopic thymectomy versus open approaches

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Background: Video-assisted thoracoscopic surgery (VATS) theoretically offers advantages over open thymectomy for clinically early-stage (Masaoka-Koga stage I and II) thymic malignancies. However, long-term outcomes have not been well studied. We compared the postoperative outcomes and survival from a cohort study based on the database of the Chinese Alliance for Research in Thymomas (ChART).

Methods: Between 1994 and 2012, data of 1,117 patients having surgery for clinically early-stage (Masaoka-Koga stage I and II) tumors were enrolled for the study. Among them, 241 cases underwent VATS thymectomy (VATS group), while 876 cases underwent open thymectomy (Open group). Univariate analyses were used to compare the clinical character and perioperative outcomes between the two groups. And multivariate analysis was performed to determine the independent predictive factors for long-term survival.

Results: Compared with the Open group, the VATS group had higher percentage of total thymectomy (80.5% *vs.* 73.9%, P=0.028), resection rate (98.8% *vs.* 88.7%, P=0.000) and less recurrence (2.9% *vs.* 16.0%, P=0.000). Five-year overall survival was 92% after VATS and 92% after open thymectomy, with no significant difference between the two groups (P=0.15). However, 5-year disease free survival were 92% in VATS group and 83% in Open group (P=0.011). Cox proportional hazards model revealed that WHO classification, Masaoka-Koga stage and adjuvant therapy were independent predictive factors for overall

survival, while surgical approach had no significant impact on long-term outcome.

Conclusions: This study suggests that VATS thymectomy is an effective approach for clinically early-stage thymic malignancies. And it may offer better perioperative outcomes, as well as equal oncological survival.

Keywords: Thymic malignancies; thymectomy; video-assisted thoracoscopic surgery (VATS); open surgery

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Introduction

Minimally invasive surgery has gained increasing interest in the management of thymic tumors. Recently, several studies have reported that video-assisted thoracoscopic surgery (VATS) could yield better short-term clinical outcomes than open thymectomy (1-4). However, the sample size in these studies were not powered enough to reach any definite conclusion, mainly due to the low incidence of the disease. In the meantime, impact of different surgical approaches on long-term survival has not yet been well studied, as most reported series did not have long-term follow-up. Therefore, current available evidence regarding the pros and cons of VATS for the treatment of thymic malignancies remains insufficient (5). We thus compared both the peri-operative outcomes and survival from a large patient cohort based on the Chinese Alliance for Research in Thymomas (ChART) retrospective database, trying to shed some new light into the problem.

Materials and methods

The ChART retrospectively database collected 2,370 patients treated at 18 tertiary referral centers in China between years 1994 to 2012. Because only de-identified data were used for the study, informed consent was waived by IRB. Inclusion criteria for the current study were clinically early-stage (Masaoka-Koga stage I and II) thymic malignancies surgically resected without any pretreatment. Exclusion criteria were cases receiving neoadjuvant therapy or none-surgical treatment. Also cases lacking detailed information on histology, staging, or surgical approach were removed from the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. And the ethics committee of all hospitals approved the study protocol. All patients provided written informed consent for surgery.

In this multi-center retrospective study, there was no uniformed standard for the selection of surgical approach; the surgeons chose the approach according to the tumor characteristics and their own preference. These included video-assisted thoracoscopic surgery (the VATS group), median sternotomy, clam-shell incision, and lateral thoracotomy (the Open group).

Statistical analysis was undertaken using the SPSS 22.0 software. Continuous variables were compared using Student *t* test, and categorical data using Chi-square test or Fisher exact test when appropriate. Survival curves were estimated using the Kaplan-Meier method, and the significance of differences was assessed with Log-rank test. Cox proportional hazard model was applied for multivariate analysis to explore the independent predictive factors for long-term survival. A 2-sided P value less than 0.05 was considered to be statistically significant.

Results

A total of 1,117 eligible cases were finally entered into the study. Among them, 241 cases underwent VATS thymectomy and 876 underwent open thymectomy. VATS thymectomy was first used in 2004, as shown in *Figure 1*. A sharp increase could be seen in the later three years to over 40% by the end of the study cohort (*Figure 2*).

Demographic characteristics of the VATS and the Open groups were listed in *Table 1*. Compared with the Open group, there were more female but less myasthenia patients in the VATS group. The Open group had significantly larger and more cStage II tumors than the VATS group. Upon histological examination, there were significantly more high-grade tumors (thymic carcinoma *vs.* thymomas) and advanced-stage lesions. Otherwise, the two groups were comparable in patient age.

Overall, both the percentage of total thymectomy (80.5% *vs.* 73.9%, P=0.028) and complete resection rate (98.8% *vs.* 88.7%, P=0.000) was significantly higher in the VATS

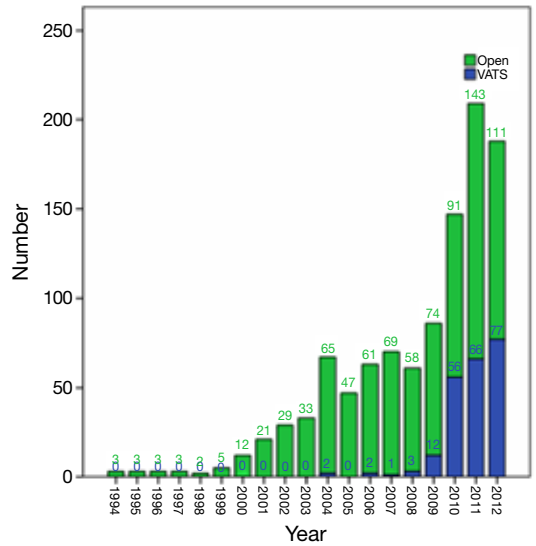

Figure 1 Annual numbers of patients undergoing thymectomy via open or VATS approach from 1994 to 2012. VATS, video-assisted thoracoscopic surgery.

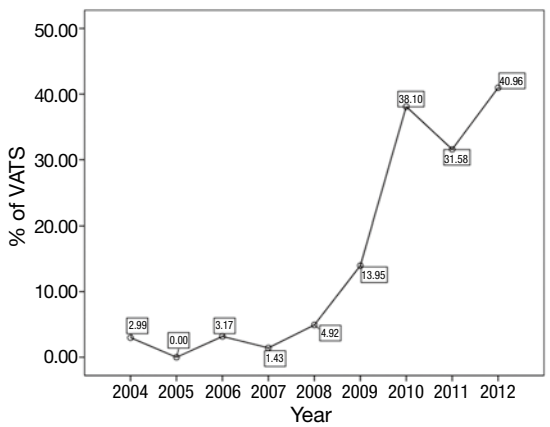

Figure 2 Annual percentages of VATS thymectomy from 2004 to 2012. VATS, video-assisted thoracoscopic surgery.

group than the Open group. Three patients died after open surgery within 30 days, while there was no mortality in the VATS group. But the difference was not statistically significant (*Table 2*).

At a median following up of 33.5 months, the 5-year overall survival rates were 92% in VATS group and 92% in Open group (P=0.15). However, less recurrence (2.9% *vs.* 16.0%, P=0.000) was observed in the VATS group than in the Open group. Accordingly, 5-year disease free survival of the VATS group was significantly higher than the Open group (92% *vs.* 83%, P=0.011) (*Figures 3,4*). Upon multivariate analysis for overall survival, only WHO classification (type C over type B, and type B over types A/AB), Masaoka-Koga stage (stage IV over stage III, and stage III over stage II), and adjuvant therapy were revealed as independent predictive factors for worse prognosis (*Table 3*).

Table 1 Patient demographics

Variable	VATS group (N=241)	Open group (N=876)	P
Gender			0.027
Male	108 (44.8%)	463 (52.9%)	
Female	133 (55.2%)	413 (47.1%)	
Age (y)	51.79	50.62	0.201
Myasthenia gravis			0.000
Yes	82 (34.3%)	191 (21.9%)	
No	157 (65.7%)	682 (78.1%)	
Clinical stage			0.008
1	183 (75.9%)	587 (67.0%)	
2	58 (24.1%)	289 (33.0%)	
WHO classification			0.000
A + AB	100 (41.5%)	282 (32.2%)	
B1 + B2 + B3	127 (52.7%)	406 (46.3%)	
C	14 (5.8%)	188 (21.5%)	
Tumor size (cm)	4.65	7.17	0.000
Pathological stage			0.000
1	168 (71.5%)	386 (44.2%)	
2	61 (26.0%)	224 (25.6%)	
3	3 (1.3%)	213 (24.4%)	
4	3 (1.3%)	51 (5.8%)	

VATS, video-assisted thoracoscopic surgery.

Table 2 Perioperative outcomes

Variable	VATS group (N=241) (%)	Open group (N=876) (%)	P
Extent of resection			0.028
Partial thymectomy	46 (19.1)	229 (26.1)	
Total thymectomy	195 (80.5)	647 (73.9)	
Resection status			0.000
R0	238 (98.8)	776 (88.7)	
R1	3 (1.2)	32 (3.7)	
R2	0 (0.0)	67 (7.7)	
30-day mortality	0 (0.0)	3 (0.34)	1.000

VATS, video-assisted thoracoscopic surgery.

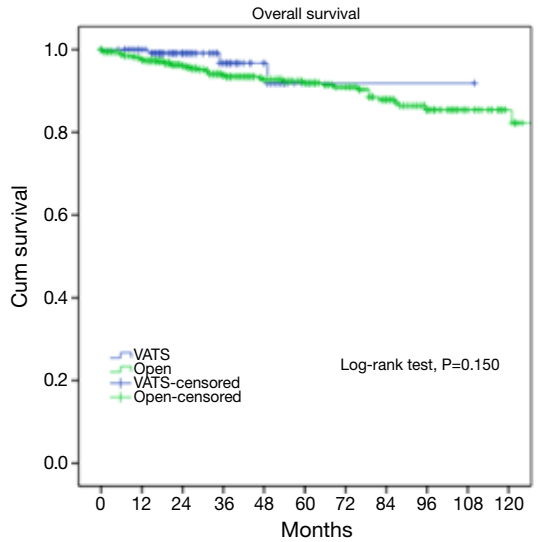

Figure 3 Overall survivals of the VATS and the Open groups. VATS, video-assisted thoracoscopic surgery.

Table 3 Multivariate analyses for survival (Cox proportional hazards model)

Factor	P	HR
Myasthenia gravis (no *vs.* yes)	0.307	0.617
WHO classification	0.001	
B1 + B2 + B3 *vs.* A + AB	0.006	17.064
C *vs.* B1 + B2 + B3	0.001	31.283
Masaoka stage	0.005	
II *vs.* I	0.082	2.165
III *vs.* II	0.002	3.421
IV *vs.* III	0.001	5.886
Adjuvant therapy (yes *vs.* no)	0.010	2.984
Surgical approach (VATS/Open)	0.374	1.956
Tumor size (≤5 *vs.* >5 cm)	0.721	1.124
Resection status (R1 + R2 *vs.* R0)	0.397	0.767

VATS, video-assisted thoracoscopic surgery; HR, hazard ratio.

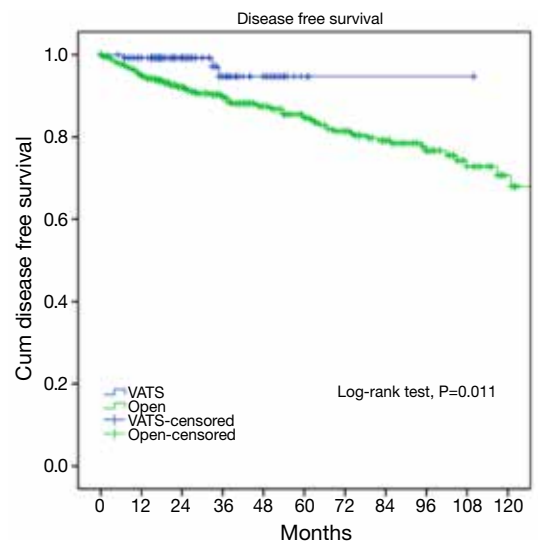

Figure 4 Disease-free survivals of the VATS and the Open groups. VATS, video-assisted thoracoscopic surgery.

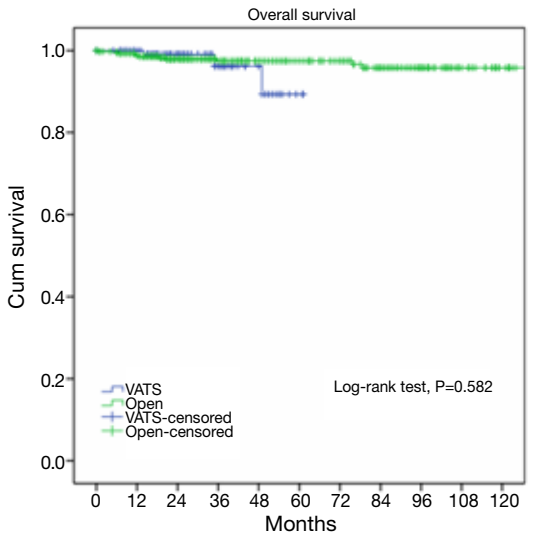

Figure 5 Five-year overall survivals of the VATS and the Open groups (89.4% *vs.* 96.7%, P=0.582) in Masaoka-Koga pStage I-II tumors. VATS, video-assisted thoracoscopic surgery.

And surgical approach had no significant impact on long-term overall survival.

As the two groups were quite heterogeneous in clinico-pathological features, we further select only those patients who turned out to have pathologically early-stage tumors and compared their long-term outcomes. Two hundred and twenty nine patients from the VATS group and 610 patients from the Open group were confirmed of having Masaoka-Koga pStage I-II tumors. For these patients, both the 5-year overall survival (89.4% *vs.* 96.7%, P=0.582) and the recurrence rate (3.3% *vs.* 4.7%, P=0.579) were similar between the two groups (*Figures 5,6*).

Discussion

Median sternotomy has traditionally been regarded as

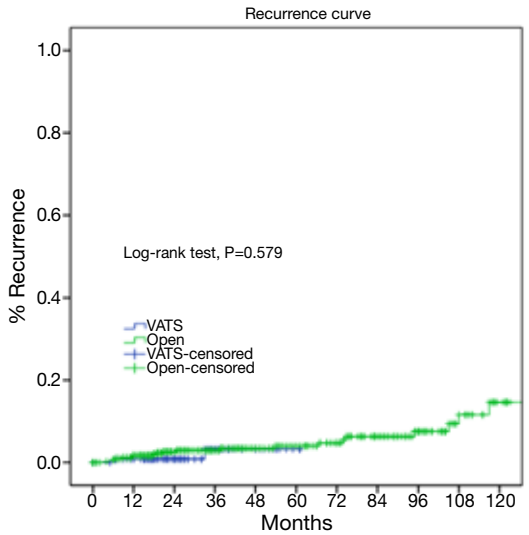

Figure 6 Cumulative incidence of recurrence of the VATS and the Open groups (3.3% *vs.* 4.7%, P=0.579) in Masaoka-Koga pStage I-II tumors. VATS, video-assisted thoracoscopic surgery.

the standard approach for surgical treatment of thymic malignancies, while open lateral thoracotomy is sometimes used as an alternative for special cases such as large tumors that deviates into the pleural cavity (6,7). Minimally invasive approaches, typically VATS thymectomy, were introduced only recently but have been gaining popularity very rapidly (8-10). Similarly in China, a continuously increased proportion of patients with early-stage thymic tumors have been treated with VATS thymectomy. As could be seen in the current study from 18 high-volume tertiary centers, there was a sharp boost of interest in VATS thymectomy in recent years.

Comparing with open procedures, VATS thymectomy has the potential advantage of providing an excellent view of the anterior mediastinum, allowing the surgeon to explore the ipsilateral pleural cavity and perform total thymectomy with resection of the tumor along with surrounding mediastinal fat. This means that thymectomy could be safely performed under VATS as well as via open approaches, as suggested in previous reports (11,12). In the current study, percentage of total thymectomy was even higher in the VATS group than the Open group (80.5% *vs.* 73.9%, P=0.028). What is more, we once reported that comparing with median sternotomy, there was decreased operative time, blood loss during operation, and length of hospital stay after VATS thymectomy. The results were in accordance with existing publications (13). The ChART database was a joint effort with the International Thymic Malignancy Interest Group (ITMIG) worldwide retrospective data collection. Unfortunately peri-operative results were not collected in detail, except 30-day mortality. Although there was no statistically significant difference between the two groups, all three patients died in peri-operative period were in the Open group. And there was no mortality in the VATS group.

It is yet to be proved whether long-term outcomes after VATS thymectomy are comparable to open resections for thymic malignancies. There have been sporadic reports documenting tumor spread to the pleural cavity after VATS thymectomy (14,15). However, a comparative study of 40 patients by Pennathur and colleagues suggested no significant differences in disease recurrence or overall survival after VATS or open surgery with a mean follow-up of 36 months (16). In the current study, less recurrence was observed in the VATS group than in Open group. However, long-term survival could still be expected even after recurrence, owing to the relatively indolent nature of thymic tumors (17). This may explain for the statistically significant difference in disease-free survival between VATS and Open groups (92% *vs.* 83%, P=0.011), but no significant difference in overall survival (92% *vs.* 92%, P=0.15). To rule out potential selection bias in our study, we further compared long-term outcomes in pathologically proven early-stage patients. It turned out there was no longer any difference either in incidence of recurrence (89.4% *vs.* 96.7%, P=0.582) or overall survival (3.3% *vs.* 4.7%, P=0.579). This again indicates that VATS thymectomy could offer comparable oncological results to patients who truly have early-stage thymic tumors.

In keeping with previous studies (18-21), Masaoka-Koga stage and WHO histological classification were again revealed as independent prognostic factors for long-term prognosis in thymic malignancy. In the current study, Masaoka-Koga stage III and IV tumors showed increased risk of worse prognosis as compared to early-stage lesions. But there was no significant difference between stage I and II tumors. In fact both Masaoka-Koga stage I and II tumors could be readily resected completely either by VATS or via open approaches. Upon multivariate analysis, surgical approach did not show up as a risk factor for prognosis. This again indicates the feasibility of minimally invasive approach in surgical management of early-stage thymic tumors. Apart from that, a decreased survival was observed with the use of adjuvant therapies in the current study. The role of adjuvant therapy after completely resected early stage thymic tumors remains controversial (22). The worse prognosis associated

with adjuvant therapies deserves further analysis. But it is beyond the scope of the current study.

The current study was based on the largest number of cases ever published. However, it still has certain limitations. The surgical procedures were not randomized, resulting in unavoidable selection bias. Although no difference in survival or recurrence when pathologically proven early stage patients were selected for further comparison, the retrospective nature of the study makes it impossible to rule out inherent biases. A case-matched study or a prospective score matched study may be necessary to solve this problem. Besides, the follow-up period was not long enough. Thymic malignancies are relatively indolent tumors and requires longer than usual follow-up to reveal the true outcome. Ten-year survival would be necessary for full evaluation of results in future studies.

Conclusions

The results of this study suggest that VATS thymectomy is a safe and effective approach for early stage thymic malignancies. Comparing to open thymectomy, minimally invasive procedures may offer better peri-operative outcomes, as well as equivalent oncological results.

Acknowledgements

None.

Footnote

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Early stage thymoma: is VATS the new standard of care?

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VATS has become the standard of care in early stage lung cancer over the last decade. Improvement in technology in terms of energy devices, staplers and visualization has enabled thoracic surgeons to perform the most complex procedures using VATS approach.

However the adoption of VATS thymectomy for thymic malignancies has progressed slowly, mainly due to the limitations and concerns related with the disease itself and its anatomic location. Open resection of early stage thymoma results in excellent long term survival (90%) and very low rate (<5%) of recurrence (1). The technical difficulty of the VATS approach for anterior mediastinum, especially in the presence of a fragile mass, stimulated thoracic surgeons for varieties such as bilateral VATS and additional subxiphoid and/or cervical incisions. Conversion rates of VATS for thymic tumors is in single digit numbers (3%–8%) (1-5).

The current study is a multi-institutional collection of patients spanning a period of almost two decades [1994–2012] and is comparing the results of open and VATS approaches in clinically early stage (Masaoka-Koga I and II) thymomas (6). The number of patients collected is substantial (n=1,117) for this rare thoracic malignancy and the authors should be congratulated for undertaking such a difficult task. Straightforward comparison of 241 VATS cases with 876 open cases shows that VATS results in a higher percentage of total thymectomy, complete resection rate and less recurrence, but with an identical long-term survival rate (92% at 5 years). Is this result enough to recommend VATS thymectomy as a standard technique for early stage thymomas?

When we carefully look at the data presented in the paper, there are data supporting a "YES" and a "NO" answer.

(I) A total of 1,098 of 1,117 patients (98%) were operated on after 2000 and 233 of 241 (96%) VATS thymectomy patients were operated on after 2009. This certainly leads to a time and experience related bias. The surgeons gained significant experience in terms of patient evaluation and selection using contemporary tools during this time and also technical expertise with open procedures before shifting to VATS. Thus a comparison of patients operated either with VATS or open technique after 2009 would be interesting to see if these findings persist or not.

(II) The current study does not detail the VATS technique. Most typical approach is from the right side, but there are bilateral approaches as well and in some cases additional cervical and/or subxiphoid incisions. Whether the technique of VATS affects the operation time, complete resection and recurrence rates is to be investigated.

(III) The whole cohort shows that, open surgery group had higher number of males, less associated myasthenia gravis, significantly larger tumors (7.17 *vs*. 4.65 cm), more clinical stage 2 tumors. Pathologic stage was 3 and 4 in 264 (30%) patients in open surgery group, whereas only in 6 patients (2.5%) in VATS group. As a result

Table 1 Some of the studies published in literature comparing VATS and open technique in thymic malignancies

Author, year and country	Type of study	N (VATS/open)	Morbidity and mortality	Blood loss	Hospital stay	Recurrence rate	Survival
Friedant, 2016, USA (1)	Systematic review and meta-analysis	1,355/683	No difference	No difference	Shorter in VATS	No difference	No difference
Xie, 2015, Australia (2)	Systematic review	540/521	Less pneumonia, no difference in mortality	Less in VATS	Shorter in VATS	No difference	No difference
Manoly, 2014, UK (3)	Retrospective case series	17/22	Less pneumonia, no difference in mortality	Less need for transfusion in VATS	Shorter in VATS	No difference	No difference
Sakamaki, 2014, Japan (4)	Retrospective case series	71/11	No difference	No difference	NS	No difference	Lower in open group
Jurado, 2012, USA (5)	Retrospective case series	77/186	No difference	Less in VATS	Shorter in VATS	No difference	No difference

NS, not stated.

there was a 7.7% R2 resection rate in the open surgery group. This data obviously reflects a very significant selection bias in favor of VATS group. As expected, multivariate analysis reveals that it is not the surgical technique, but Masaoka and WHO classification, and adjuvant therapy are of prognostic importance.

(IV) And finally when techniques (VATS n=229 and open n=610) were compared according to pathologic stage (Masaoka-Koga stage I and II), there was no difference in terms of 5-year survival (89.4% *vs.* 96.7% respectively) and recurrence rate (3.3% *vs.* 4.7% respectively).

Some of the series comparing VATS and open approaches in thymic malignancies are presented in *Table 1* (1-5). The typical improvements that are gained with a VATS approach are shorter hospital stay and reduced blood loss, whereas overall and recurrence-free survival are same in almost all series.

So if we finally answer the question raised above, based on current large multi-institutional study and available literature data, a VATS approach for early stage thymic tumors in experienced centers is as safe as an open approach. It will most likely result in less intraoperative blood loss, less pneumonia and reduced hospital stay without having any impact on long term survival. However surgeons with limited experience in the evaluation and selection of these patients, should not be tempted with the lure of VATS, but rather play on the safe side.

My answer is a "conditional" YES.

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Footnote

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

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Minimally invasive thymectomy: the Mayo Clinic experience

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Background: The prevalence of minimally invasive thymectomy (MIT) is increasing and may have significant benefit to patients in terms of morbidity and post-operative recovery. Our aim was to review the Mayo Clinic experience of MIT.

Methods: We reviewed data from all MIT cases collected in a prospectively maintained database from January 1995 to February 2015. Data were collected regarding patient demographics, perioperative management and patient outcomes.

Results: A total of 510 thymectomies were performed in 20 years. Fifty-six patients underwent MIT (45 video-assisted thoracoscopy, 11 robotic-assisted). The median age was 55 years (range, 23-87 years) with male to female ratio of 25:31. Thymoma was the main pathologic diagnosis in 27/56 patients (48%), with 11/27 (41%) associated with myasthenia gravis (MG), and 16/27 (59%) non-MG. Other pathologies included 1/56 (2%) of each teratoma, lymphoma, lymphangioma, carcinoma and thymolipoma. There were 3/56 (5%) atrophic glands, 4/56 (7%) cysts, 6/56 (11%) benign glands and 11/56 (20%) hyperplastic. Mean blood loss (mL) and operative time (min) were significantly lower in the video-assisted thoracoscopic surgery (VATS) group compared to robotic (65±41 *vs.* 160±205 mL, P=0.04 and 102±39 *vs.* 178±53 min, P=0.001, respectively). There was no 30-day mortality. Post-operative morbidity occurred in 7/45 (16%) VATS patients (phrenic nerve palsy 7%, pericarditis 4%, atrial fibrillation 2%, pleural effusion 2%) and 1/11 (9%) robotic (urinary retention requiring self-catheterization). Reoperation was required in 1/3 of VATS patients with phrenic nerve palsy. There was no significant difference in length of hospital stay [VATS 1.5 days (range, 1-4 days) and robotic 2 days (range, 1-5 days) VATS; P=0.05]. Mean follow-up was 18.4 months (range, 1-50.4 months) with no tumor recurrences.

Conclusions: MIT can be performed with low morbidity and mortality. VATS is associated with reduced blood loss, operative times and earlier hospital discharge compared to robotic MIT.

Keywords: Thymus; thymectomy; mediastinum; minimally invasive; myasthenia gravis (MG)

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Introduction

Thymectomy is an acceptable therapy in the comprehensive care of myasthenia gravis (MG) and in undetermined lesions (not thought to be lymphoma) that are found within the anterior mediastinum by cross-sectional imaging (1-3). Primary epithelial thymic tumors are discovered in approximately 50% of all anterior mediastinal masses, of which thymoma is the most common (4,5). The efficacy of surgery in managing thymic diseases, including the ability to improve symptoms of inadequately controlled myasthenia, is contingent upon complete excision of all thymic and perithymic adipose tissue (6).

Video-assisted thoracoscopic surgery (VATS) and the da Vinci robotic system (Intuitive Surgical Inc., Sunnyvale, CA, USA) offer a minimally invasive approach to thymectomy

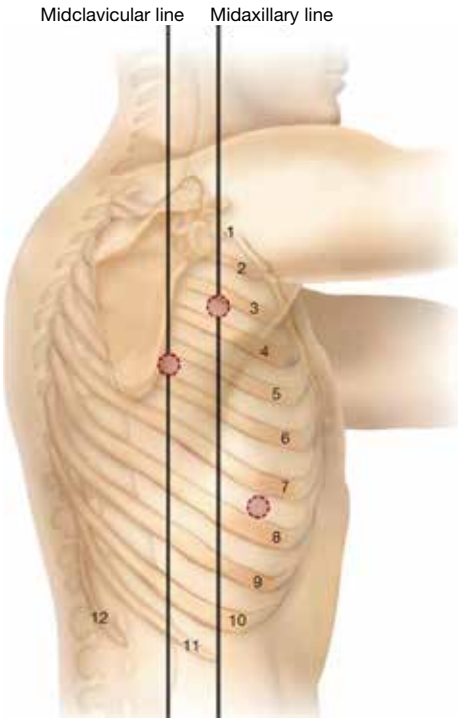

Figure 1 Right VATS port placement. VATS, video-assisted thoracoscopic surgery.

with potentially less morbidity. However, controversy exists regarding the appropriateness of minimally invasive thymectomy (MIT) when employed for surgical resection of thymoma and other malignant neoplasms. Although evidence substantiating MIT as an effective treatment with less operative trauma, shorter length of hospital stay, fewer pulmonary complications and more satisfactory cosmetic results without compromising surgical outcomes is available, few studies have compared the two MIT approaches (7,8). The primary objective of the present study is to analyze patient and surgical outcomes in our experience with VATS and robotic-assisted thymectomy.

Methods

All patients who underwent resection for a thymic lesion at our institution between January 1, 1995 and February 28, 2015 were identified from a prospectively maintained surgical database. The medical records were retrospectively reviewed for demographic data, presenting symptoms, operative procedures, complications, pathology, recurrence, and date of last follow-up or death. The revised Masaoka staging system was used for staging thymomatous neoplasms (9,10). Histologic type was classified according to the 2004 revision of the World Health Organization (WHO) classification of thymic epithelial tumors (11).

The Mayo Foundation Institutional Review Board approved the current study with waiver of informed consent. During the study period, 510 thymectomies were performed at Mayo Clinic Rochester. Of the 510 thymus glands removed, 56 (11%) were performed using a minimally invasive approach: 45 (80.4%) had a VATS resection whereas 11 (19.6%) had a robotic-assisted resection. There were 25 men (44.6%) and 31 women (55.4%) with a median age of 55 years (range, 23-87 years) at the initial thymectomy.

Descriptive statistics for categorical variables are reported as frequency and percentage; continuous variables are reported as mean (SD) or median (range) as appropriate. Patient characteristics in the VATS and robotic resection groups were compared using Fisher's exact test for categorical variables and the Wilcoxon test for continuous variables. A P value of less than 0.05 was considered statistically significant. The SAS software (JMP, Version 10., SAS Inc., Cary, NC, 1987-2007, USA) was used for statistical analysis.

Surgical technique

The right-sided approach to VATS thymectomy is often preferred given the physical constraint from the heart on the left. However, VATS thymectomy can be safely performed with solitary entry into either pleural space. Herein we present our technique of right-sided VATS thymectomy. The patient is positioned in the left lateral decubitus position supported with axillary roll and bean bag when necessary. The patient's anterior superior iliac spine should be positioned at the break in the bed with the bed flexed to at least 30 degrees to open the intercostal rib spaces, facilitate port positioning, and allow the lungs to fall away posteriorly. We prefer general anesthesia with a double-lumen endotracheal tube with confirmation of position via bronchoscopy. The right arm is positioned over the left arm and supported by a brace. All pressure points are padded. With a pause in ventilation, the first 5 mm port is placed between the 5th or 6th intercostal space (ICS) along the posterior axillary line (*Figure 1*). Once entry into the pleural space is confirmed with finger sweep, the thoracoscope is inserted to inspect the pleural cavity for any pathology (effusions or suspicious lesions). Any suspicious lesions are routinely biopsied. Under direct vision, a second 5 mm port is inserted at the 3rd or 4th ICS along the mid-

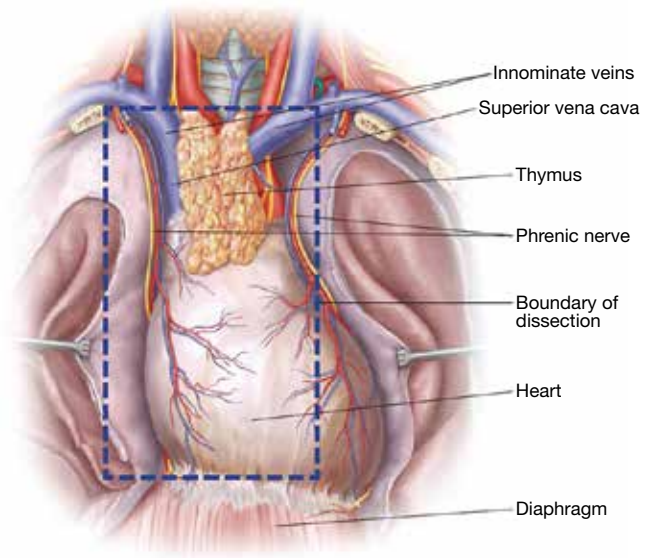

Figure 2 Extent of thymectomy.

axillary line (*Figure 1*). This will serve as the camera port for the remainder of dissection. The third port is then placed at the 5th or 6th ICS along the anterior axillary line (*Figure 1*). Port location can be varied according to surgeon preference and additional cannulae may be placed if visualization or dissection is not optimal. The boundaries of surgical resection should include all thymic and perithymic tissue between the phrenic nerves and from the innominate vein superiorly to the diaphragm inferiorly (*Figure 2*). The phrenic nerve should be identified prior to proceeding, with division of the right inferior pole of the thymus from the pericardial fat pad using an advanced vessel sealing device. With electrocautery on a low setting, the mediastinal pleura can be scored 1-2 cm medial to the phrenic nerve to facilitate lateral dissection as the surgeon proceeds cranially to the right superior pole. Medium to large-sized venous branches from the innominate vein may be encountered and are effectively controlled with clip placement followed by sharp or electrocautery division. A vessel sealing device is used to divide the attachments of the thyrothymic ligament. Dissection is carried to the contralateral side beyond the midline dividing superior and inferior attachments in similar fashion. Protecting the contralateral phrenic nerve and vascular bundle remains an essential step. If visualization of these structures is impaired, patient repositioning with contralateral VATS should be undertaken to avoid inadvertent injury and subsequent hemidiaphragm paralysis. The specimen is placed in a bag and removed through a protected port. The port incision may need to be lengthened for larger sized glands or neoplasms to allow extraction of the specimen. A small bore chest tube may be placed using the skin incision from the third port and placed to –20 cmH_2O suction. The intercostal muscle layers and skin are then closed.

Results

Demographic data

The patients' age, sex, functional status, history of MG, and presenting symptoms in both MG and non-MG at the time of thymectomy are shown in *Table 1*. There were no significant differences among patients selected for either VATS or robotic-assisted thymectomy.

A slight female preponderance (55.4%) existed in our cohort, with patients most commonly presenting in the fifth decade of life. Over 96% of patients were ethnically white and only 15 (27%) patients had a normal BMI (≥18.5 to 24.9 kg/m^2) at the time of operation. Nineteen (34%) were overweight (≥25.0 to 29.9 kg/m^2), and 23 (41%) were obese (≥30 kg/m^2) according to the National Institute of Health (NIH) and WHO classification of obesity (12,13).

MG was preoperatively diagnosed in 24 (42.9%) patients, all of who were seropositive for acetylcholine receptor antibodies and exhibited classic findings on electromyographic studies. Only one patient with MG was asymptomatic (Modified Osserman Stage 0) and was counseled to undergo thymectomy due to an enlarging thymic nodule on serial imaging with computed tomography (CT). All other MG patients underwent thymectomy for symptom improvement. The majority of MG patients 17 (71%) were either a Modified Osserman Stage 2 or 3 pre-operatively.

The most common presentation of non-MG patients with thymic lesions requiring resection was an incidentally discovered asymptomatic anterior mediastinal mass by CT imaging, found in 17 (53.1%) patients. Cough or dyspnea was observed in 11 (34%), and chest pain in three (9%) patients.

Perioperative outcomes

Pathologic analyses of the 56 resected thymic glands are shown in *Table 2*. A total of 32 tumors with six different histologic features were identified. Twenty-four thymic glands were benign with 11 (19.6%) containing hyperplastic

Table 1 Patient demographics

Variable	VATS	Robotic	P value
Gender			0.513*
Male	19	6	
Female	26	5	
Age (years)			0.749†
Median	50.6	52.2	
Range	23-87	23-74	
Ethnicity			1.00†
White	43	11	
American Indian/ Alaska Native	2	0	
BMI (kg/m^2)			0.256
Median	28.2	30.8	
Range	19.9-47.7	20.2-37.9	
Prior chest operations	0	0	
Preop ASA score			0.232*
1	2	0	
2	23	4	
3	20	7	
Pre-op diagnosis of MG			0.069†
Yes	22	2	
No	23	9	
Duration MG symptoms (min)			0.080*
Mean	9	5.7	
SD	17.6	18.6	
Osserman classification			
0	1	0	
1	2	2	
2	9	0	
3	8	0	
4	2	0	
Symptoms in non-MG patients [%]			
Asymptomatic	13 [56]	4 [44]	
Dyspnea/Cough	8 [35]	3 [33]	
Chest pain	1 [4]	2 [22]	
Early satiety	1 [4]	0	

VATS, video-assisted thoracoscopic surgery; MG, myasthenia gravis; BMI, body mass index; ASA, American Society of Anesthesiologists; SD, standard deviation; *, Fisher's exact test; †, Wilcoxon test (2 tailed).

Table 2 Thymus pathology

Characteristic	Number	Frequency (%)
Tumors		
Thymoma	27	48.2
Thymomatous MG	11	19.6
Nonthymomatous MG	16	28.6
Teratoma	1	1.8
Lymphoma	1	1.8
Lymphangioma	1	1.8
Thymolipoma	1	1.8
Thymic carcinoma	1	1.8
^WHO histologic type thymoma		
A	2	7.4
AB	11	40.7
B1	5	18.5
B2	5	18.5
B3	2	7.4
Not determined	2	7.4
Thymoma stage		
Stage I	18	66.7
Stage IIA	9	33.3
Non-tumorous thymic tissue		
Hyperplastic gland	11	19.0
Benign thymic tissue	6	10.7
Thymic cyst	4	7.1
Atrophic thymus	3	5.4
Thymus (grams)		
Median	60.8	
Range	3.0-330	
*Mean thymus size (cm^3)		
VATS	17.0×7.4×2.3	
Robotic	18.4×7.5×2.5	
†Mean tumor size (cm^3)		
VATS	2.6×2.0×1.3	
Robotic	3.5×2.5×1.8	

^WHO, World Health Organization; MG, myasthenia gravis; VATS, video-assisted thoracoscopic surgery; *, P=0.9; †, P=0.3.

Table 3 Technique comparison

Variable	VATS	Robotic	P value
Laterality			0.9*
Right	21	5	
Left	23	6	
Bilateral	1	0	
Mean blood loss (mL)	65±41	160±205	0.042†
Mean operative time (min)	102±39	178±53	0.001†
Intraoperative tube thoracostomy [%]	25 [55]	11 [100]	0.004*
Conversion to open	0	0	

*, Fisher's exact test; †, Wilcoxon test (2 tailed). VATS, video-assisted thoracoscopic surgery.

Table 4 Complications

Intraoperative	VATS	Robotic
Pericardiotomy (2-3 mm)	4	0
Injury to IMA	1	0
Trocar induced liver injury	0	1
Postoperative		
Phrenic nerve palsy	3	0
Ipsilateral	2	0
Contralateral	1	0
Temporary paresis	1	0
Permanent injury	2	0
Pericarditis	2	0
Atrial fibrillation	1	0
Urinary retention	0	1
Pleural effusion requiring drainage	1	0

VATS, video-assisted thoracoscopic surgery; IMA, internal mammary artery.

tissue. The most common tumor was a thymoma in 27 (84.3%) patients harboring a neoplasm. An encapsulated, non-invading, stage I thymoma was identified in 18 (67%) pathologic specimens whereas the remainder, nine (33%), were stage IIA exhibiting capsular invasion. All thymomas underwent an R0 resection with negative surgical margins. All patients with Stage IIA tumors were evaluated post-operatively by medical oncology with no adjuvant treatment recommended. The most common histologic thymoma, according the WHO classification, in our series was type AB (mixed) in 11 (41%) patients.

The mean size of all thymic glands removed was 17.1 cm × 7.5 cm × 2.4 cm, whereas the mean tumor size was 2.8 cm × 2.0 cm ×1.4 cm with a mean overall thymic gland weight of 69.9 (range, 30-330) mg. The thymus or tumor within it was not significantly different in size among those resected with either VATS or robotic approaches (P=0.9 and P=0.3, respectively).

Total thymectomy by VATS was performed in 45 (80.4%) patients, whereas robotic-assisted resections were performed in 11 (19.6%). Surgical technique was chosen based on surgeon preference and technical ability. Operative comparison is summarized in *Table 3*. VATS thymectomy had significantly lower blood loss (65±41 mL, range, 20-250 mL) and operative time (102±39 min, range, 48-231 min) than the blood loss (160±205 mL, range, 50-750 mL, P=0.042) and operative time (178±53 min, range, 114-258 min, P=0.011) of robotic-assisted thymectomy. In addition, intraoperative tube thoracostomy was performed less frequently in VATS procedures 25 (55%) than in robotic 11 (100%) (P=0.004). Laterality in surgical approach was not significantly different. Right-sided VATS and robotic procedures occurred in 21/45 (47%) and 5/11 (45%) respectively. Left-sided VATS and robotic procedures occurred in 23/45 (51%) and 6/11 (55%) respectively (P=0.9). Only one VATS case required bilateral cannulae to adequately visualize the contralateral phrenic nerve to prevent injury. There were no open conversions with either MIT approach.

No mortality occurred in either group. Intra-operative and post-operative morbidity is reported in *Table 4*. Intraoperative morbidity occurred in 6/56 (11%) patients, the most common being a small (2-3 mm) pericardiotomy in four VATS patients, which were all left alone. Trocar-induced liver injury during a robotic resection required urgent laparoscopic exploration and hemorrhage control (no transfusions were required). Overall post-operative morbidity occurred in 8/56 (14%) patients. VATS complications 7/45 (16%), included phrenic nerve palsy in three (7%), pericarditis in two (4%), atrial fibrillation in one (2%), and a pleural effusion requiring catheter drainage in one (2%). Phrenic nerve palsy was ipsilateral in 2/3 and contralateral in 1/3. Two patients did not have resolution of phrenic nerve palsy: one required sural to phrenic nerve grafting 9 months postoperatively (which was unsuccessful), and the other continued to have paradoxical hemidiaphragm motion on fluoroscopic sniff testing 7 months postoperatively. A single robotic patient 1/11 (9%) developed urinary retention requiring home going

Table 5 Post-operative clinical status in MG patients

DeFilippi classification	VATS	Robotic
(I) Remission, off medications	1	0
(II) Asymptomatic, reduced medications	4	0
(III) Improved, on medications	9	1
(IV) No change	2	0
(V) Worse	0	0
Lost to follow up	5	1

VATS, video-assisted thoracoscopic surgery; MG, myasthenia gravis .

catheterization. Mean length of stay was not significantly different: VATS (1.5 days, range, 1-4 days) *vs.* robotic (2.1 days, range, 1-5 days, P=0.05).

Clinical improvement, according to the DeFelippi classification, in the 23/24 (symptomatic) MG patients is reported in *Table 5*. Symptom improvement with reduced immunosuppressive medication was observed in 14/16 (88%) VATS patients and 1/2 (50%) robotic patients with a mean follow-up of 18.4 (range, 1-79) months. The cumulative complete symptom remission rate in VATS patients was 5% *vs.* 0% in the robotically resected patients. A total of six MG patients were lost to follow-up (five VATS, one robotic), thus accurate documentation of clinical improvement is lacking.

Discussion

The aim of this study was to review our experience with MIT and compare operative and clinical outcomes between VATS and robotic-assisted techniques. We found that total thymectomy can be safely performed with either surgical approach with minimal morbidity without mortality. Compared with robotic-assisted thymectomy, the VATS approach offered a surgical advantage in terms of significantly less operative time (102±39 min) and blood loss (65±41 mL). Although length of stay was not significantly different between the two MIT approaches in our series, VATS patients were discharged earlier. Interestingly, the one case of urinary retention in our series was in a patient who underwent robotic resection with prolonged operative time (232 min) and subsequent increased length of stay (3 days) due to the need for in and out catheterization and required teaching. Other investigators have identified a similar trend in swifter operative times with VATS thymectomy. Ye (14) reported median VATS time of 170 min in a series of 125 VATS thymectomies, whereas Li and Wang (15) reported 105 min among 43 thoracoscopic cases. However, a recent study by Rückert *et al*. (16) reported the opposite trend with robotic cases performed with greater surgical efficiency (187 *vs.* 200 min). In that series, the cumulative complete remission rate of MG for robotic thymectomy was also significantly better (39% *vs.* 20%) than VATS with 42 months follow-up. While the most surgically efficient approach to MIT remains controversial, it is agreed that thymectomy must be complete, especially when employed for MG or primary resection of malignant neoplasms (i.e., thymoma, thymic carcinoma, thymic carcinoid). A study by Hamaji *et al*. (17) emphasizes the importance of complete thymectomy at the time of initial operation for thymoma as recurrence, due to incomplete resection, had a significantly adverse effect on overall survival. In addition, on multivariate analysis, only surgical management was associated with prolonged survival and improved progression-free interval in recurrent thymoma when compared with chemoradiotherapy. Contrary to the better survival outcomes among surgically managed recurrent thymoma, recurrent thymic or carcinoid tumors do not have improved survival with surgical therapy.

Surgical technique, whether VATS or robotic, was not influenced by gland size. All patients in our series had preoperative CT imaging and there were no difference noted in gland size or weight among pathologic specimens with either VATS or robotic-assisted resection. The decision regarding which side of the chest to enter and the number of cannulae to insert for MIT depended upon preoperative imaging and surgeon experience. In our series, three-port VATS and robotic techniques were employed. In 2004, Rocco and associates (18,19) described a uniport thoracoscopic approach to limited pulmonary resections. Since then, uniport VATS has been employed for a variety of thoracic diseases including thymectomy (20).

Our findings of clinical improvement among MG patients following thymectomy support the findings of other researchers. At mean follow-up of 18 months, we report that 88% of VATS and 50% of robotically resected patients enjoyed symptom improvement with reduced immunosuppressive medication. Unfortunately, 74% of patients in our series reside out of state, limiting our long-term follow-up. A recent meta-analysis of 28 controlled studies showed that MG patients undergoing thymectomy were twice as likely to attain medication-free remission, 1.6 times more likely to become asymptomatic, and 1.7 times more likely to clinically improve (21). Similar

findings have been noted for patients undergoing VATS and robotic thymectomy (22-29).

Our results need to be interpreted in the context of several limitations. This was a single-institution experience, and thus the issue of external validity is relevant. Our data set might also not be readily applicable to other patients with thymic diseases. Although we analyzed all patients treated with MIT over a 20-year period, there may be some degree of selection bias among MIT patients, as evidenced by only early stage thymomas discovered on pathologic specimens with relatively bland histologic features by WHO classification. Furthermore, the high rate of complete (R0) surgical resection with no recurrences identified at the time of follow-up, raises the possibility that MIT patients had less extensive disease and would expect to have better outcomes as the incidence of recurrent thymic tumors typically ranges from 10% to 30% and is related to initial stage of disease as well as histologic features (WHO classification) (9,30-35). Finally, the duration of follow-up was relatively limited given the majority of patients in our series live out of state.

In conclusion, we believe that MIT can be performed for both non-neoplastic and neoplastic thymic diseases with minimal morbidity and mortality. While we are gaining experience with the da Vinci robotic system (Intuitive Surgical, Inc., USA), we still more commonly perform VATS thymectomy at our institution. Our data suggest that we currently perform VATS thymectomy with greater surgical efficiency, less blood loss, less need for tube thoracostomy, and are able to discharge patients slightly earlier than robotic-assisted procedures. It has been estimated that 50 identical robotic cases are required to perform any specific robotic surgery with consistent operative time and predictable outcome (36). With this learning curve in mind, we believe consideration of MIT should be pursued for all symptomatic MG patients with inadequate medical treatment and for all locoregional thymic neoplasms in patients who can tolerate single lung ventilation and in whom complete resection appears feasible.

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None.

Footnote

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

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Multi-institutional European experience of robotic thymectomy for thymoma

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Background: Robotic thymectomy for early-stage thymomas has been recently suggested as a technically sound and safe approach. However, due to a lack of data on long term results, controversy still exists regarding its oncological efficacy. In this multi-institutional series collected from four European Centres with high volumes of robotic procedures, we evaluate the results after robot-assisted thoracoscopic thymectomy for thymoma.

Methods: Between 2002 and 2014, 134 patients (61 males and 73 females, median age 59 years) with a clinical diagnosis of thymoma were operated on using a left-sided (38%), right-sided (59.8%) or bilateral (2.2%) robotic approach. Seventy (52%) patients had associated myasthenia gravis (MG).

Results: The average operative time was 146 minutes (range, 60-353 minutes). Twelve (8.9%) patients needed open conversion: in one case, a standard thoracoscopy was performed after robotic system breakdown, and in six cases, an additional access was required. Neither vascular and nerve injuries, nor perioperative mortality occurred. A total of 23 (17.1%) patients experienced postoperative complications. Median hospital stay was 4 days (range, 2–35 days). Mean diameter of resected tumors was 4.4 cm (range, 1–10 cm), Masaoka stage was I in 46 (34.4%) patients, II in 71 (52.9%), III in 11 (8.3%) and IVa/b in 6 (4.4%) cases. At last follow up, 131 patients were alive, three died (all from non-thymoma related causes) with a 5-year survival rate of 97%. One (0.7%) patient experienced a pleural recurrence.

Conclusions: Our data suggest that robotic thymectomy for thymoma is a technically feasible and safe procedure with low complication rates and short hospital stays. Oncological outcome appears to be good, particularly for early-stage tumors, but a longer follow-up period and more cases are necessary in order to consider this as a standard approach. Indications for robotic thymectomy for stage III or IVa thymomas are rare and should be carefully evaluated.

Keywords: Thymoma; robotic thymectomy; early stage thymoma; myasthenia gravis (MG); thoracoscopy

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Introduction

Radical thymectomy is the gold standard treatment for resectable thymomas, with completeness of resection representing the most important prognostic factor (1). Currently, median sternotomy is widely considered as the standard approach for thymoma resection at any stage, allowing a technically easy and oncologically safe operation (2). While the video-assisted thoracoscopic surgery (VATS) approach has been extensively used for mediastinal diseases in the last three decades, it was mainly confined to the treatment of several benign diseases or to thymectomy in cases of non-thymomatous

myasthenia gravis (MG) (3-5). The first VATS approach for thymoma was described in early 1990s (6); since then, only few authors have published small series of VATS thymoma resections with short-term follow-up, leading to a paucity of clear and sound data about the effectiveness of this approach (2,7-9). Consequently, a number of surgeons are still reluctant to use this surgical approach that remains controversial—the supposed increased risk of local recurrence (due to reduced safety margins after minimally invasive resection) and the possible rupture of the capsule with implantation of the tumor during endoscopic manipulations are the most common arguments against the VATS approach. Furthermore, the lack of long-term oncologic results, the learning curve required to perform this operation safely and the relative rarity of this tumor are additional reasons that slow the adoption of the VATS resection for early stage thymomas (10). The introduction of robotic-assisted technologies in the late 1990s provided a technical advancement able to overcome the limitations of conventional thoracoscopy. Specifically, the three-dimensional vision system and the articulated instruments of the da Vinci Surgical Robotic System (Intuitive Surgical, Inc., Sunnyvale, CA, USA) allow for an intuitive, 'open-like' intervention, but with minimally invasive access. The application of robotic technology has been tested in a variety of thoracic surgery procedures, particularly for mediastinal diseases, where the robotic system is thought to provide the maximum benefit (11,12). The aim of this study was to evaluate the safety and the feasibility of robotic thymectomy, analysing the oncologic outcome in a group of patients with clinically defined early-stage thymoma, in four European Centres with extensive experience in this type of operation.

Materials and methods

We reviewed the data of 134 patients undergoing robotic thymectomy for clinically defined early-stage thymoma (Masaoka stages I and II) collected between 2002 and 2014 by four European Thoracic Surgery Centres (University of Maastricht-Nederland; University of Padova-Italy; University of Pisa-Italy; University of Innsbruck-Austria). All patients signed a detailed consent form in which they were informed about possible complications of a thymoma resection with robotic approach and the lack of long-term data. The institutional review board of each centre approved the study. Information on patient demographics, presence of associated MG, tumor characteristics, stage, intra and postoperative data (e.g., complications, need for open conversion or additional ports or accesses, operative time, length of hospital stay) were collected. The Masaoka staging system was used to assess the pathological stage (2), while the new World Health Organization classification was used for histological definition (13). The Myasthenia Gravis Foundation of America (MGFA) classification (14) was applied to stratify the preoperative class of MG. Preoperative assessments included evaluation of pulmonary and cardiac functions, total body computed tomography (CT) or magnetic resonance imaging (MRI). Preferred radiological characteristics to be eligible for robotic thymectomy were the location of the tumor in the anterior mediastinum, a distinct fat plane between the tumor and surrounding structures, unilateral tumor predominance, tumor encapsulation, existence of residual normal appearing thymic tissue, and no mass compression effect (*Figure 1*) (7). In cases of unexpected intraoperative finding of involvement of surrounding structures (Masaoka stage III), pleuro-pericardial or pulmonary nodules (Masaoka stage IVa/b), the robotic approach was converted to an open approach if the resection was considered technically difficult, unfeasible or unsafe for the patient. Patients were followed up until death or May 2015, if alive, by periodic visits (with neurologists if affected by MG) and phone contact. A total body CT scan was performed every six months for the first two years postoperatively, then every year. There were 61 (45.5%) males and 73 (54.5%) females, with a median age of 59 years (range, 14–88 years). Seventy (52.2%) patients were affected by MG.

Surgical technique

The side of surgical access was based on a single surgeon's experience, or occasionally on the presence of unilateral tumor predominance. The surgical technique of robotic thymectomy from either the left or right side has been described in existing literature (15,16). This procedure was performed differently from thymectomy for non-thymomatous patients, with all surgeons adopting a "no-touch technique" for an "en bloc" resection of thymus and perithymic fat tissue. In this technique, the thymoma was never touched and the normal thymic tissue and peri-thymic fat were used for grasping and for traction. This technique avoids a direct manipulation of the tumor, in order to minimize the risk of tumor seeding in consequence of capsule damage. All thymus and perithymic fat were dissected with safe surgical margins, according to the International Thymic Malignancy Interest Group criteria (17), and the

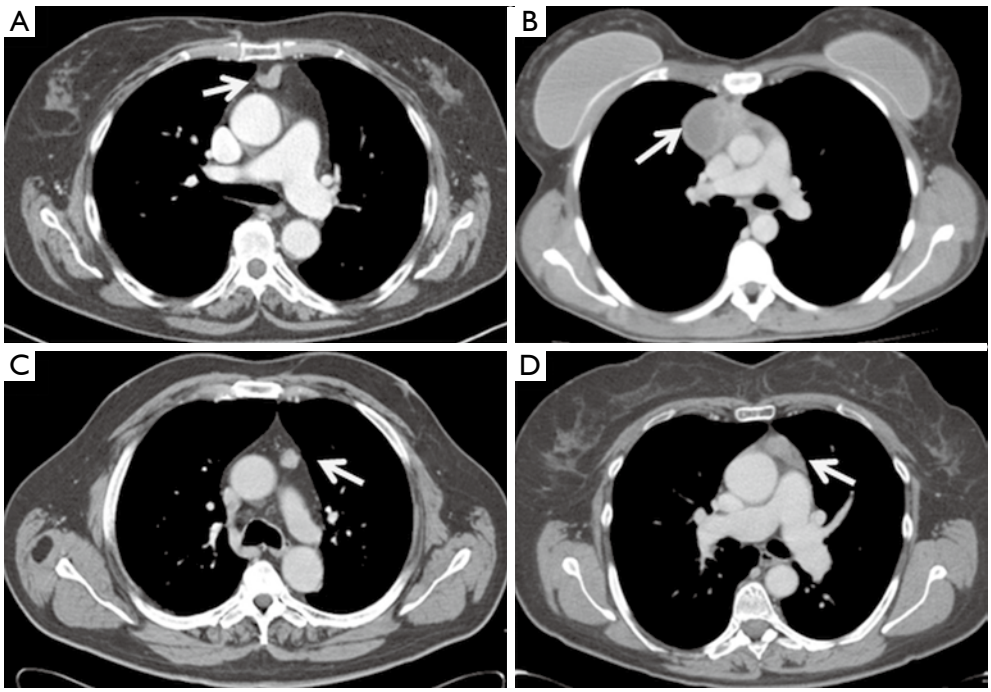

Figure 1 CT scans of: (A) small thymoma centrally located (white arrow) and surrounded by perithymic fatty tissue; (B) cystic thymoma (white arrow) with unilateral predominance on the right side; (C) small thymoma (white arrow) with unilateral left predominance and surrounded by perithymic fatty tissue; (D) thymoma (white arrow) with unilateral left predominance.

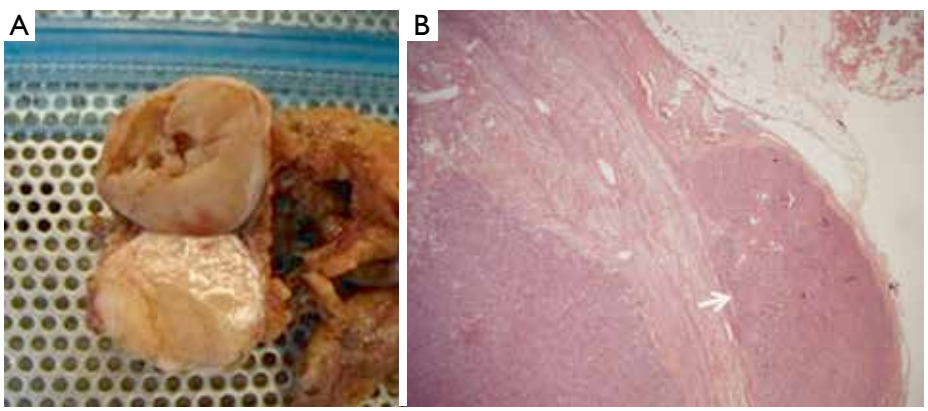

Figure 2 (A) Specimen of macroscopic encapsulated type AB thymoma in which (B) the pathological analysis revealed a microscopic capsular invasion (white arrow) (Haematoxylin-Eosin stain, original magnification ×25).

completeness of thymectomy was assessed by macroscopic inspection of the thymic bed, specimen and subsequent pathological analysis (*Figure 2*).

Statistical analysis

Data were expressed as absolute numbers, percentage, median or mean values ± standard deviation (SD). Survival curves were calculated by Kaplan-Meier method.

Results

The robotic approach was left-sided in 51 (38%), right-sided in 80 (59.8%) and bilateral in three (2.2%) patients. The

median operative time was 140 minutes, ranging between 60 and 353 minutes (mean 146.4±43 minutes). Twelve (8.9%) patients needed conversion to an open approach (in two cases due to large diameter of tumor interfering with a safe dissection, in 10 cases for unexpected invasion of surrounding structures as the great vessels, lung or pleura-pericardial implants). In one (0.7%) case, a standard thoracoscopy was used after robotic system breakdown. In six (4.4%) cases, an additional access (cervicotomy in one case, an additional homolateral thoracoscopic port for suction purpose in five cases) was required. No vascular and nerve injuries were recorded, and no perioperative mortality occurred. A total of 23 (17.1%) patients had postoperative complications: four cases of atrial fibrillation, three cases of myasthenic crisis, three pneumothoraces after chest tube removal, three pleural effusions, two cases of pneumonia, one haemothorax treated conservatively by blood transfusion, one chylothorax, one orthostatic hypotension, one wound infection, one urinary tract infection treated with medical therapy, one pulmonary embolism, one mediastinal infection, and one pulmonary herniation. Median hospital stay was 4 days (range, 2–35 days; mean 4.8±2.5 days). Mean diameter of the resected tumors was 4.4±1.3 cm (range, 1–10 cm), Masaoka stage was I in 46 (34.4%), II in 71 (52.9%), III in 11 (8.3%), IVa in 5 (3.7%) and IVb in 1 (0.7%) patient. Histologic evaluation revealed 22 (16.4%) type A, 23 (17.2%) type AB, 23 (17.2%) type B1, 40 (29.8%) type B2, and 26 (19.4%) type B3 thymomas. At the last follow up (May 2015: median 42 months, range, 5–159 months; mean 48±35.7 months), 131 (97.8%) patients were alive, 3 (2.2%) patients died all for non-thymoma related causes (leukemia, vulval carcinoma and colon carcinoma). A pleural recurrence was found in 1 (0.7%) patient with original Masaoka stage IVa. The five-year overall survival rates were 97%, and the five-year thymoma-related survival rates were 100%.

Discussion

Since its introduction into clinical practice in the early 1990s, VATS has gained broad acceptance for diagnostic and therapeutic interventions for both pulmonary and mediastinal benign diseases (3-6). The main recognized advantages of VATS compared with open approaches are minimal operative trauma, lower morbidity, early improved pulmonary function, shorter hospital stays and better cosmetic results (3,4,18). These obvious advantages have increased the acceptability of the VATS approach, especially among patients with MG, leading to an increased number of thoracoscopic thymectomies being performed for non-thymomatous MG with good surgical and neurological results (15,16,19). Contrary to the lung cancer experience however, in which VATS resection has become the standard approach for early-stage NSCLC, most surgeons are still reluctant to perform a thoracoscopic thymectomy in patients with thymoma, due to technical and oncological concerns. There are a number of technical reasons to not use thoracoscopy: the upper mediastinum is a delicate and difficult-to-reach anatomical area with vulnerable large vessels and nerves, particularly with thoracoscopy. In the two-dimensional view of the operative field, the surgeon's tremor is enhanced by the thoracoscopic instruments and they do not articulate, making it difficult to operate in a fixed three-dimensional space such as the mediastinum. Moreover, thoracoscopic thymectomy is considered a technically challenging operation with a steep learning curve (10). The oncological concerns relate to the possible breach of tumor capsule with risk of tumor seeding locally or in the pleural cavity, and the difficult evaluation of resection margins with reduced oncological accuracy and safety. The robotic surgical system has provided several advantages able to overcome some technical and methodological limits of conventional thoracoscopy: (I) the improved dexterity of instruments (7 degrees of freedom articulation, 360 degrees of rotation) allows complex three-dimensional movements, providing a safe and comfortable dissection around vessels, nerves, and tiny and remote areas such as the superior horns or the contralateral mediastinum; (II) the high-resolution, three-dimensional vision permits the best possible and magnified view of the surgical field; and (III) the filtering of hand tremors allows greater technical precision. In our opinion, these characteristics have significantly increased the safety and the oncological effectiveness of robotic thymectomy for thymoma. In fact, there is less manipulation of the thymic and perithymic tissue during the operation, and a better evaluation of healthy tissue as a result of the high quality image. This allows for a more precise and low-risk dissection with wide safety margins, and reduced possibility of an incautious tumor breaching, incomplete resection or iatrogenic injury. The lack of tactile feedback could theoretically increase the risk of damaging tumor capsule; however, this disadvantage seems widely compensated by the superior three-dimensional vision control of the system. In the last 15 years, several authors have published the results of thoracoscopic and robotic thymectomy for early-stage

Table 1 Review of the published studies on thoracoscopic and robotic thymectomy for thymoma

Author	Patients (N)	SA	Masaoka stage I/II	TS (cm)	5-year survival (%)	FU (months)	RR (%)	OC (%)	OT (min)	POS (days)
Roviaro *et al*. (2)	22	uVATS	22	–	–	–	4.5	4.5	75*	6*
Cheng *et al*. (7)	44	uVATS	27/17	7.7*	100	34.6*	0	0	194*	7.6*
Odaka *et al*. (8)	22	uVATS	–	–	–	21.6*	0	0	194*	4.6*
Agasthian *et al*. (9)	50	uVATS	25/25	5*	100	58*	2	0	150*	5*
Pennathur *et al*. (20)	18	bVATS	5/13	3.5*	100	27**	0	0	–	2.9*
Takeo *et al*. (21)	34	bVATS	15/19	5.2*	100	65*	2.8	0	219*	10.5*
Kimura *et al*. (22)	45	uVATS	41/4	4.8*	100	–	6.7	0	197*	14*
Liu *et al*. (23)	76	uVATS	57/19	9.2*	100	61.9*	2.6	1.3	141.7*	7.1*
Ye *et al*. (24)	125	uVATS	80/45	3.2*	–	41**	0.8	3.2	170**	8**
Sakamaki *et al*. (25)	71	uVATS	40/31	3.5**	97	48**	1.4	5.6	–	–
Mussi *et al*. (26)	13	robotic	7/6	3.3*	100	14.5**	0	7.7	139*	4*
Marulli *et al*. (27)	79	robotic	30/49	3.7*	90	51.7*	1.3	1.3	165*	4.4*
Ye *et al*. (28)	23	robotic	21/2	2.9*	100	16.9*	0	0	97*	3.7*
Keijzers *et al*. (29)	37	robotic	20/13	5.1*	100	36**	2.7	13.5	149*	3**
Present series	134	robotic	46/71	4.4*	97	48*	0.7	8.9	146*	4**

SA, surgical access; bVATS, bilateral video-assisted thoracic surgery; uVATS, unilateral video-assisted thoracic surgery; TS, tumor size; FU, median follow-up; RR, recurrence rate; OC, open conversion; OT, operative time; POS, post-operative length of stay. *, mean value; **, median value.

thymoma (*Table 1*). The available data confirm that this approach may be considered technically sound and safe in the hands of appropriately-trained surgeons. However, data are still inconclusive with regard to oncological outcome due to the lack of long-term follow-up. In fact, thymomas are indolent tumors, and a long lapse of time (at least 10 years) is necessary to evaluate the survival and relapse rate. Therefore, as pointed out by Davenport *et al*. in a systematic review (30), there is a lack of evidence in the current literature supporting a minimally invasive approach compared to a standard transsternal approach. At that time, the open transsternal surgical approach is widely considered the gold standard for resection of thymoma, ensuring the best chance for a complete resection (1,2). However, despite the lack of long oncological follow-up, the surgical results are outstanding: no major complications or mortality occurred in this large series. Other authors adopting either the conventional VATS or robotic approach also reported similar results (2,3,7-9,20,22-29). In contrast to other authors supporting a thoracoscopic subtotal thymectomy for non-invasive thymoma without MG as the preferred resection modality regardless of tumor size and tumor capsule characteristics (8-19,30,31), our policy was to undertake an extended thymectomy in all cases, such as in the open approach. In the absence of definitive long-term data, a standardization of the technique is necessary in order to avoid biases in the evaluation of the outcome. Moreover, we consider the intraoperative manipulation of the specimen to be safer when the perithymic fat tissue is contextually resected 'en bloc'. Most of our patients (87.3%) had an early-stage tumor due to the selection criteria we adopted, based on the radiological criteria proposed by Cheng *et al*. (7): the location in the anterior mediastinum, tumor encapsulation, a distinct fat plane between the thymoma and vital organs, the existence of residual normal appearing thymic tissue, no mass compression effect and unilateral tumor predominance, particularly for tumors of dimension greater than 3 cm. However, while most cases were clinically diagnosed as Masaoka stage I, 52.9% patients were found to be Masaoka stage II, 8.3% were in stage III and 4.4% in stage IVa/b after resection and final histological evaluation. A similar finding was reported by Takeo *et al*. (21), where it was revealed that 57% of patients had Masaoka stage II and III after an initial clinical diagnosis of stage I, while in a report by Quintanilla-Martinez *et al*. (32), 28.5% of the tumor reported by the surgeon to be encapsulated

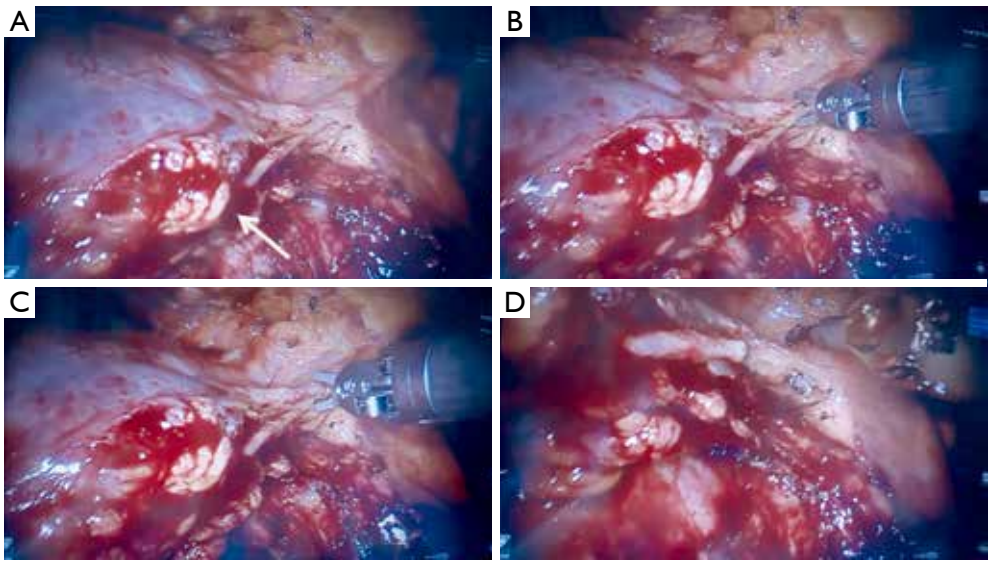

Figure 3 (A) Intraoperative left thoracoscopic view of thymoma invading the left phrenic nerve (white arrow) that is (B,C) doubly clipped and (D) sectioned by robotic instruments.

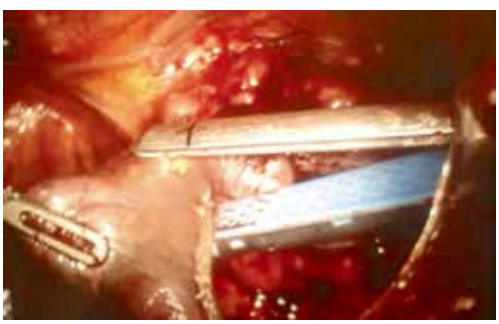

Figure 4 Intraoperative right thoracoscopic view of a thymoma invading the right lung, resected by wedge using an endoscopic stapler during a robotic procedure.

showed a microscopic evidence of capsular invasion. In regards to Masaoka stage III and IV discovered at surgical exploration, our policy was to convert to an open access (sternotomy or thoracotomy) based on individual surgeon's judgement. In particular, when the resection was considered unsafe or unfeasible by robotic approach, an open resection was performed; this occurred in 10 cases, while in the remaining seven cases, a resection extending to the pericardium, the phrenic nerve (*Figure 3*), lung (*Figure 4*) or parietal pleura were performed entirely by robotics. Despite being technically feasible, extended resections should be considered experimental and reserved to very select cases, as the oncological safety is still unknown. Another debated point is the appropriate size of thymoma for VATS or robotic resection; the majority of authors dealt with lesions smaller than 5 cm, but an average tumor diameter around 3 cm is generally considered as oncologically acceptable (10,27). In our experience, the mean diameter of resected lesions was 4.4 cm, with a range between 1 and 10 cm. A large tumor size was not considered an absolute contraindication; however it may interfere with the surgical procedure, making the manipulation more difficult with increased chance of an open conversion, prolonged operative time or capsule injury, as reported by Kimura *et al.* (22). In regards to the surgical results, no mortality, low morbidity and short hospital stay were observed. The operative times and open conversion rate were comparable with other series of thoracoscopic thymoma resection (*Table 1*). It is interesting to note that no conversions due to intraoperative vascular accidents were required, as the accurate vision allowed the surgeons to perform an optimal vascular dissection or identify early vascular invasion, avoiding any intraoperative damage. Looking at the oncologic outcome, a recurrence rate ranging between 0% and 6.7% has been reported in previous thoracoscopic and robotic series. In our experience, the single pleural relapse was observed in a Masaoka stage IVa despite a macroscopic radical intervention. Relapses also frequently occur in open surgery due to microscopic residual disease. Cheng *et al.* (33) and Pennathur *et al.* (20) compared the VATS and

transsternal approaches for thymoma in small series, reporting no significant difference in recurrence rate and overall survival between the two groups. Although very encouraging, the oncological results need definitive validation, since the indolent nature of thymoma requires more mature data from longer follow-up. The present study has some limitations, particularly the non-randomized, retrospective and multi-institutional methodology. In addition, the follow-up period is still inadequate to allow a definitive conclusion on the oncological outcome.

In summary, robotic thymectomy for early stage thymoma is a technically safe and effective operation. In addition to the advantages of a minimally invasive approach (short hospital length of stay, excellent cosmetic results, low morbidity), increased visualization and instrument dexterity enabled by robotic technology provides further benefit compared to conventional thoracoscopy. Our data on a large number of patients are encouraging, particularly for early stage thymoma, despite a relatively short oncologic follow-up period. Extended resections for Masaoka stage III/IV may be possible for selected patients, but they are considered experimental.

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Footnote

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

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Subxiphoid uniportal thoracoscopic extended thymectomy

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Abstract: The aim of this article is to present a thoracoscopic technique of extended thymectomy through a subxiphoid incision. Six consecutive patients were successively treated with this approach, which provided a good view of the bilateral pleural cavities. The procedure is safe and technically feasible and yields excellent cosmetic results. We believe that subxiphoid uniportal thoracoscopic approach is a satisfactory procedure for performing extended thymectomy in well selected patients.

Keywords: Thymectomy; uniport; subxiphoid; thoracoscopy/video-assisted thoracic surgery (VATS)

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Introduction

Uniportal video-assisted thoracic surgery (VATS) has become a sophisticated technique capable of handling some of the most intricate and difficult thoracic operations. The potential advantages of fewer surgical incisions, better cosmesis, less post-operative pain and fewer paraesthesias have made the technique increasingly popular around the world. We report here our first six consecutive experience in performing thoracoscopic extended thymectomy through a single subxiphoid incision.

Case series

Between October 2014 to February 2015, six patients (one male) with thymic diseases received subxiphoid uniportal thoracoscopic extended thymectomy. All the operations were conducted by the same surgical team. Mean age was 50.5±13.1 years (range, 26-62 years). Mean BMI was 26.0±4.5 (range, 23.9-32.4). Mean diameter of the thymic lesion was 3.3±0.8 cm (range, 2-4 cm).

Operative techniques

Under general anesthesia with selective one lung ventilation, the patient was placed in the supine position with a roll placed beneath the thoracic spine to elevate the thoracic cage. A 3 to 4 cm transverse incision was made just above the xiphoid process. After removal of the xiphoid process, a midline retrosternal tunnel was created by blunt finger dissection, and a wound protector was placed to provide optimal exposure (*Figure 1*). A 10-mm, 30 degree angled thoracoscope was used during the operation. Most dissection was performed by an endoscopic electrocautery and a long curved ring forceps. An angled suction tube was introduced for smoke evacuation and exposure of surgical field (*Figure 2*).

Firstly, the right pleural cavity was opened during left lung ventilation (*Figure 3A*), the right pericardial and epiphrenic fat pads were dissected from the pericardium and diaphragm with electrocautery (*Figure 3B*). The right lobe of thymus and mediastinal fat tissues anterior to the phrenic nerve was dissected from the pericardium and ascending aorta by moving cephalically (*Figure 3C*). With careful and meticulous dissection, the conjunction of the innominate vein and superior vena cava was clearly visualized (*Figure 3D*). The right superior thymic horn was dissected and pulled to the left side by ring forceps, facilitating separation of the gland from the underlying innominate vein. The course of the innominate vein was traced to identify all the thymic veins. Usually, two to four thymic veins draining into the left innominate vein were identified and ligated by LigaSure device (*Figure 3E*). Secondly, the left mediastinal pleura was divided during right lung ventilation (*Figure 3F*), the left

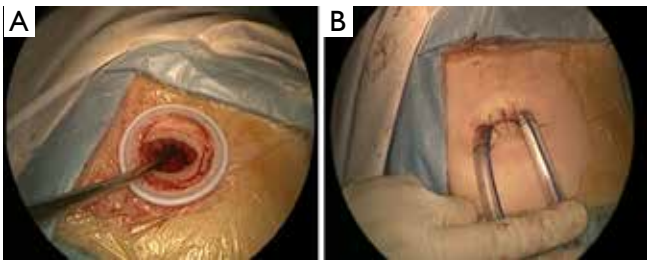

Figure 1 (A) A 4 cm-long incision was made above the xiphoid process, and the retrosternal space was created by finger dissection and a wound protector was placed to provide optimal exposure; (B) two thoracic tubes were introduced through the same working port after surgery.

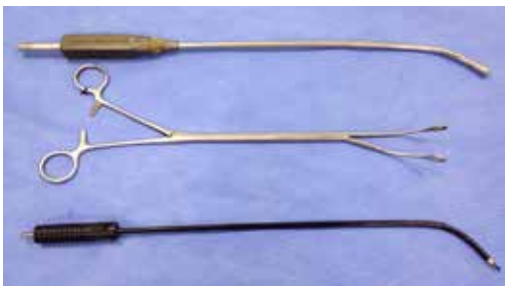

Figure 2 Common surgical instruments used during the operation, an endoscopic electrocautery, a long curved ring forceps and an angled suction tube.

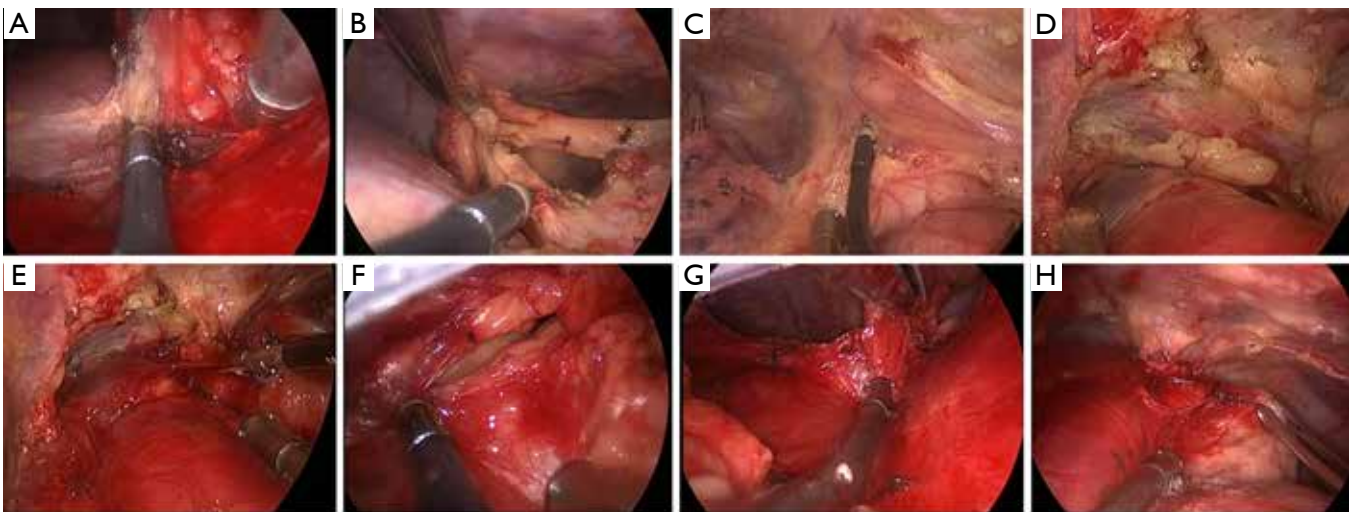

Figure 3 (A) Firstly, the right pleural cavity was opened; (B) the right pericardial and epiphrenic fat pads were dissected from the pericardium and diaphragm; (C) the right lobe of thymus and mediastinal fat tissues anterior to the phrenic nerve were dissected from the pericardium and ascending aorta by moving cephalically; (D) then the right superior thymic horn was dissected and pulled to the left side by ring forceps, the innominate vein and superior vena cava was clearly visualized with meticulous dissection; (E) the thymic veins draining into the left innominate vein were identified and ligated by LigaSure device; (F) secondly, the left mediastinal pleura was divided; (G) the left pericardial fat was dissected from the pericardium and diaphragm; (H) and the adipose tissue was dissected from the aorta-pulmonary window space.

pericardial fat was dissected from the pericardium (*Figure 3G*), and the adipose tissue was dissected from the aorta-pulmonary window space by moving cephalically (*Figure 3H*). Left superior thymic horn was also dissected completely. Finally, the totally freed thymus gland and mediastinal fat tissue could be brought out from the subxiphoid incision. A 28-Fr thoracic tube was inserted into each side of the pleural cavity through the incision and secured to the chest wall. Ventilation of both lungs was resumed. The incision was closed in a standard manner. Generally, the patient was extubated immediately after the operation. The thoracic tubes were usually removed on the 3rd to 4th postoperative day, and the patients were discharged the following day.

Results

The mean operative time was 155±55 minutes (range, 90-240 minutes). The mean intraoperative blood loss was 78.3±47.1 mL (range, 20-150 mL). There was no conversion to sternotomy. The mean postoperative hospital stay was 4.5±2.3 days (range, 3-9 days). Except for one patient who needed prolonged mechanical ventilatory support, there were

no other perioperative complications or mortalities. All of the subxiphoid wounds healed well. The postoperative diagnosis of the six cases was as follows: Masaoka stage I thymoma in three cases (Type B2 Thymoma in two patients, Type AB Thymoma in one patient), thymic cyst in two cases (one unilocular and one multilocular thymic cyst), and true thymic hyperplasia in one patient.

Comments

Median sternotomy, partial or full, remained the gold standard for thymectomy. With recent advances in thoracoscopic instrumentation and techniques, VATS has become a viable surgical technique for thymic abnormalities (1). These techniques include transcervical approach, subxiphoid approach, unilateral (2) or bilateral thoracoscopic surgery, hand-assisted thoracoscopic surgery, robotic-assisted thoracoscopic surgery (3) or a combination of these approaches (4,5).

Over the past decade, uniportal VATS has increasingly attracted professional and public interest and been widely applied in the treatment of thoracic diseases. Suda *et al.* reported a uniportal technique using a subxiphoid approach for extended thymectomy in 2012 (6). With some modification to that technique, we report here our first six consecutive experience in performing subxiphoid uniportal thoracoscopic extended thymectomy. The maximum diameter of the thymic lesions in our group is 4 cm. We regard patients with poor lung function unable to withstand the selective one-lung ventilation, extensive pleural symphysis and thymic malignancy, or any sign of invasion as contraindications to using this approach for resection.

Although the limitations of this technique include decreased maneuverability of instruments, two-dimensional view of the surgical field and risk of breaching the tumor capsule, our recent experience demonstrates that subxiphoid uniportal approach is a satisfactory procedure for performing extended thymectomy in well selected patients. It provides simultaneous access to both pleural cavities, which greatly improves the view by split-lung ventilation. The procedure is safe and feasible, with good cosmesis, and the short-term results are promising.

Our clinical outcomes are limited to a small number of patients with relatively short follow-up time. To further evaluate the feasibility, safety, and efficacy of this technique, more experiences woud be required in well selected patients.

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Footnote

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Subxiphoid and subcostal arch thoracoscopic extended thymectomy: a safe and feasible minimally invasive procedure for selective stage III thymomas

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Contributions: (I) Conception and design: Y Zhou, Q Lu, J Zhao, J Wang; (II) Administrative support: X Li, Y Zhou; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: J Zhao, J Wang, Q Lu; (V) Data analysis and interpretation: Y Zhou, Q Lu, J Zhao, J Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Video-assisted thoracoscopic surgery (VATS) has been applied to resection of small and well-encapsulated thymomas. However, few data are available regarding to the application of VATS in stage III thymomas.

Methods: A novel subxiphoid and subcostal arch approach for thoracoscopic extended thymectomy was developed by us. From January 2014 to August 2015, 14 patients with stage III thymoma were treated by using this new technique in the Department of Thoracic Surgery, Tangdu hospital, Xi'an, China. These patients were retrospectively reviewed and analyzed.

Results: Among the 14 patients, 1 patient was converted to transsternal approach owning to invasion of the superior vena cava. The other 13 patients with thymomas invading the pericardium, lung tissues and left innominate vein (LIV), were successfully operated on by using this new technique. The average operation time was 120.0±32.7 min (80–170 min), the average volume of estimated blood loss was 51.5±44.8 min (10–150 mL) and the average postoperative hospital stay was 4.8±1.5 days (3-9 days). There was no perioperative death. Two patients suffered postoperative complications including one patient with atrial fibrillation (AF) and the other one with myasthenic crisis (MC). The postoperative pain score decreased dramatically from 3.8±1.0 [3–6] at 24 hours to 1.5±0.9 [0–6] at 48 hours, and finally to 0 at 3 months after surgery (P=0.000). The patients reported a higher cosmetic score of 92.6±2.7 [90–96]. There was no tumor recurrence and the five patients with myasthenia gravis had improvement and did not need any medication until follow-up.

Conclusions: Based on our limited experience, the subxiphoid and subcostal arch thoracoscopic extended thymectomy is safe and feasible for selective stage III thymoma, and might reduce the postoperative pain and provide satisfied cosmetic effect.

Keywords: Invasive thymoma; video-assisted thoracic surgery (VATS); thymectomy; subxiphoid approach

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Introduction

Thymoma is the most common primary anterior mediastinal tumor in adults. Surgical resection plays critical role in the treatment of thymomas, and completeness of resection is the most important prognostic factor (1). Traditionally, transsternal total thymectomy has been considered as the standard treatment for thymomas. However, it has been fiercely challenged by video-assisted thoracoscopic surgery (VATS) thymectomy, a minimally invasive surgical procedure for thymectomy. Several reports have shown that thoracoscopic thymectomy performed by well trained surgeons might achieve equivalent clinical outcomes compared with that of open surgery in the treatment of early stage thymomas (Masaoka stage I and II) (2-9). However, the application of VATS thymectomy in locale invasive thymoma (Masaoka stage III) was controversial (10). There were few articles reported the experiences of VATS thymectomy in the treatment of stage III thymomas (11-13).

Recently, a novel subxiphoid and subcostal arch thoracoscopic extended thymectomy has been developed by us and has been successfully applied in the treatment of non-thymomas myasthenia gravis and early stage thymomas (The results has been reported in the 14th Annual Congress of Chinese Society for Thoracic and Cardiovascular Surgery, 2014; the manuscript has been submitted for publication). Here, the experiences of this novel procedure in stage III thymomas resection were summarized and analyzed.

Materials and methods

Patients

From January 2014 to August 2015, 65 patients with thymomas were treated by the subxphoid and subcostal arch thoracoscopic extended thymectomy in the Department of Thoracic Surgery, Tangdu hospital, Xi'an, China. All these patients were carefully evaluated before operation by using computed tomography (CT). The tumor location was carefully assessed to make sure there was no major invasion to the trachea, the heart, the aorta and the other big vessels. After operation, the patients were classified according to the Masaoka's staging system (14). The patients with postoperative pathological confirmed Masaoka stage III were retrospectively reviewed and analyzed.

The informed consents were obtained from all patients. The patients were informed about the risks and potential benefits of this new approach, as well as the possibility to convert to transsternal approach according to the judgments of the surgeon during operation. All the patients were also informed that the lack of long-term data on this new procedure for the treatment of thymomas. This retrospective study was approved by the ethics committee of Tangdu Hospital.

Figure 1 The position of the patient and the operation team during the subxiphoid and subcostal arch thoracoscopic extended thymectomy.

Position and anesthesia

The patient was placed in the supine position on the operating table with the legs open. The surgeon stood between the patient's legs and the assistant was on the left or right side (*Figure 1*). After intravenous induction, the patient was anesthetized and intubated with a single lumen endotracheal tube.

Surgical procedure

A 3-cm incision was made below the xiphoid. The rectus abdominis muscle was separated vertically, and the retrosternal space was dissected blindly by using a finger. The bilateral extra pleural space was enlarged and two 5-mm extra pleural thoracic ports under the bilateral costal arches were created. Under the guidance of the finger, a longer thoracoscopic grasping forceps (45 cm) and an ultrasonic scalpel (45 cm) were placed. Thereafter, a 30-degree oblique, 10 mm thoracoscope was introduced into the retrosternal space. The carbon dioxide (CO_2) with an 8-cm H_2O positive pressure was insufflated into the anterior mediastinum, which helped to enlarge the retrosternal space and blow the fume out of the anterior mediastinum during operation (*Figure 2*).

Then, according to the "no touch, tumor last" principle (11,12), the non-tumorous parts of the thymus was always

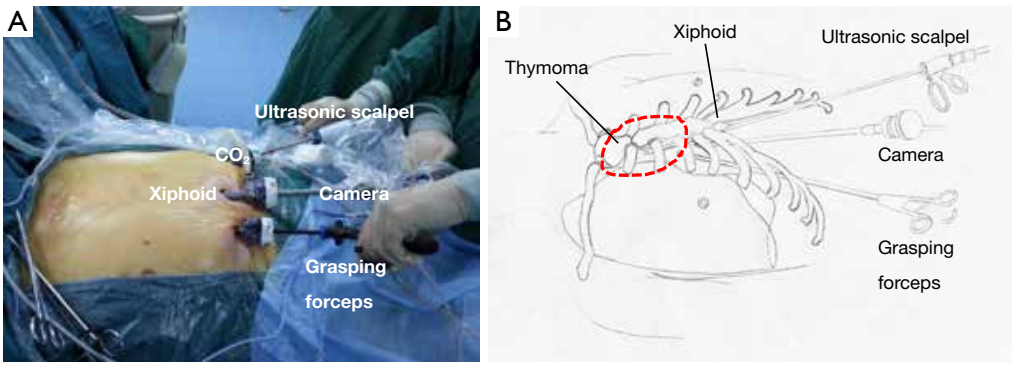

Figure 2 The incisions and the setup of the surgical instruments during the subxiphoid and subcostal arch thoracoscopic extended thymectomy. CO_2, carbon dioxide.

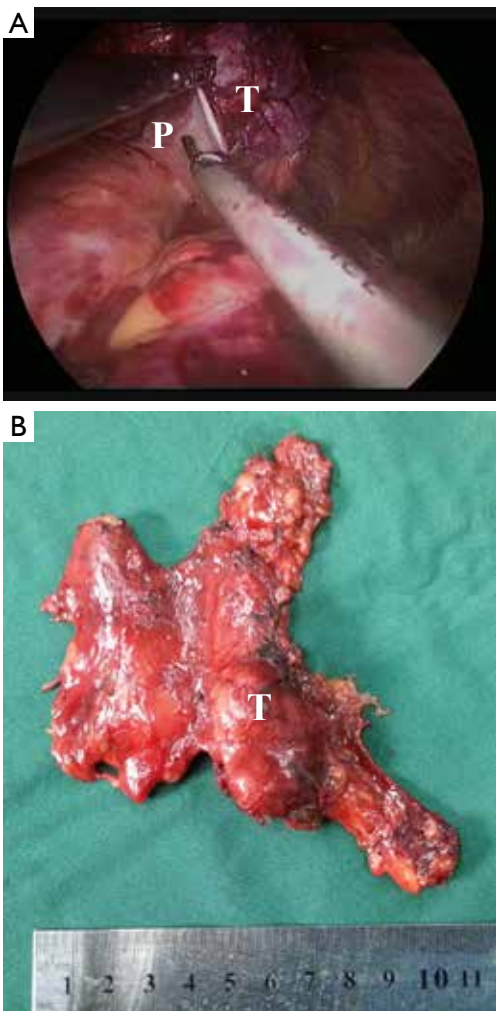

Figure 3 The thymoma invading the pericardium (Case No. 1): (A) the invaded pericardium could be resected by the ultrasonic scalpel; (B) the sample after operation. P, pericardium; T, tumor.

dissected firstly. In order to minimize the risk of tumor seeding, the surgeon should pay much attention to grasp the normal tissues but not touch the tumor capsule. During dissection, the thymic veins, usually branched from the innominate veins, were carefully identified and cut with the ultrasonic scalpel. After dissecting the normal parts of the thymus, the thymus with the tumor was carefully assessed. If the pericardium was invaded, the normal part of the pericardium was grasped and cut by using the ultrasonic scalpel (*Figure 3*). If the lung was invaded, one of the ports under the costal arches was enlarged to 1 cm, and a wedge resection of the lung was made by using a stapler (*Figure 4*). If the left innominate vein (LIV) was invaded, the LIV was carefully mobilized and two staplers were used to cut the involved vein (*Figure 5*). If the bilateral mediastinal pleura were invaded, or the patients suffered myasthenia gravis, the bilateral mediastinal pleura were resected completely. The whole thymus with the thymoma was en bloc resected, put into a plastic bag and removed through the subxiphoid port. If the patients suffered myasthenia gravis at the same time, the fat tissues near the cardiac-diaphragmatic angles, the aortopulmonary window, the phrenic nerves and the lower poles of the thyroid gland were dissected and removed.

The surgical field was checked and the thoracoscope was removed. The two subcostal arch ports were sutured first. Then, a drainage tube was inserted into the anterior mediastinum through the subxiphoid incision. The air was drained out by inflating the lungs. After that, the drainage tube was removed and the incisions were sutured.

The specimens were sectioned, examined and classified according to the World Health Organization (WHO) classification by the pathologists in the Department of Pathology, Tangdu Hospital.

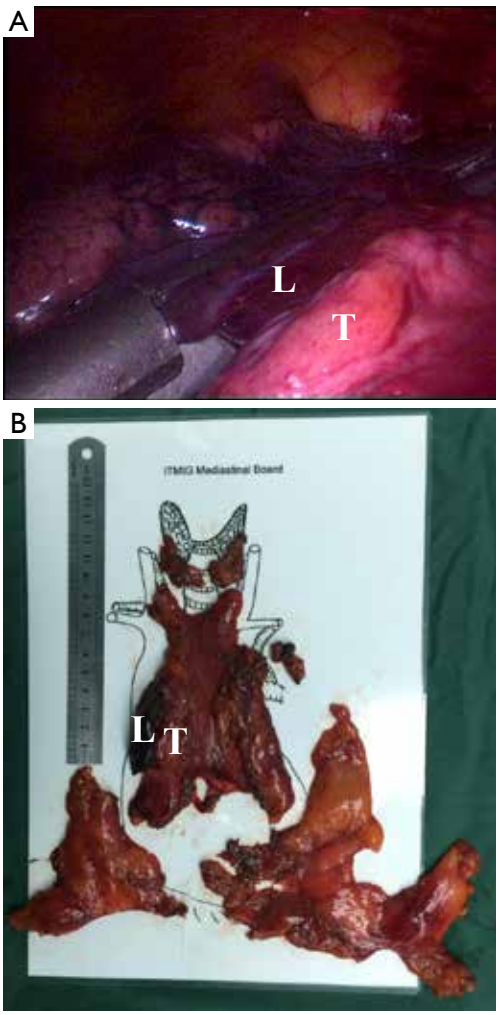

Figure 4 The thymoma invading the lung tissue (Case No. 10): (A) the invaded lung tissue could be resected by using an endoscopic stapler; (B) the sample after operation. L, lung tissue; T, tumor.

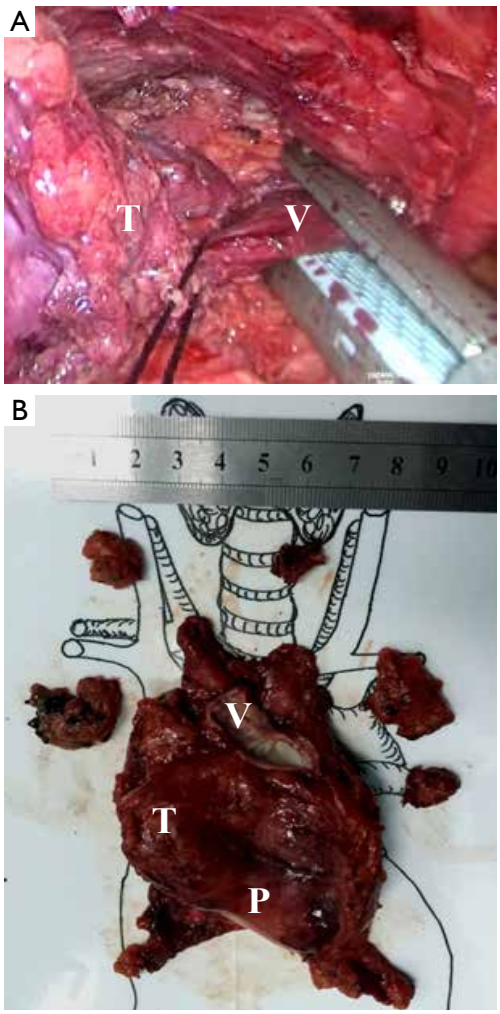

Figure 5 The thymoma invading the left innominate vein (LIV) and the pericardium (Case No. 13): (A) the invaded left innominated vein could be resected by using an endoscopic stapler; (B) the sample after operation. V, vessel; P, pericardium; T, tumor.

Postoperative care and evaluation

After operation, the oxygen saturation and electrocardiography monitoring was performed in the early period. A sitting chest X-ray was taken the day after operation.

The postoperative pain was evaluated by using the Visual Analog Pain Scale at 24, 48 hours after operation and 3 months after operation. A patient self-reported cosmetic evaluation score was used to evaluate the cosmetic effect when the patients were discharged. The cosmetic evaluation was reported by the patients themselves with a score from 0 to 100 to indicate very dissatisfied status to very satisfied status.

The patients were followed up at 3, 6, 12 months for the first year after operation and once yearly later. All the clinical data was collected. The GraphPad Prism software (Version 5.0, GraphPad Software, Inc., CA, USA) was used for the data analysis.

Results

From January 2014 to August 2015, 14 patients were finally classified as Masaoka's stage III according to the postoperative pathologic results, and were treated by the subxphoid and subcostal arch thoracoscopic extended

Table 1 Clinical characters

Case	Age (years)	Sex	Tumor size (centimeters)	WHO classification	Involved organs	Postoperative complications
1	61	M	3.0×2.5×2.0	B2	P	N
2*	56	M	4.0×3.5×3.0	B1	P	N
3	47	M	7.5×6.5×4.0	B2	P	N
4	54	M	7.0×3.0×3.0	B2–B3	P	N
5*	44	M	6.0×4.0×3.0	B2–B3	RUL	MC
6	45	F	7.0×6.5×4.0	B1	P	N
7	45	F	6.0×5.5×3.0	AB	P	N
8	69	M	6.0×6.0×5.0	B2–B3	P	AF
9*	70	M	6.0×5.0×5.0	B2–B3	P	N
10*	53	M	3.0×2.0×2.0	B1–B2	RUL	N
11	67	M	5.0×4.0×3.0	B2–B3	LIV	N
12*	52	F	4.0×4.0×4.0	B2–B3	P	N
13	46	M	5.0×4.0×3.0	B2–B3	P, LIV	N

*, Co-morbidity: ocular myasthenia gravis. F, female; M, male; WHO, World Health Organization; RUL, right upper lobe; LIV, left innominate vein; P, pericardium; N, none; MC, myasthenic crisis; AF, atrial fibrillation.

thymectomy at the Tangdu hospital, Xi'an, China. Among them, one patient was converted to transsternal approach owning to tumor invasion to the superior vena cava, and the angioplasty cannot be performed under the thoracoscope. The other 13 patients' clinical characteristics were reviewed and summarized in *Table 1*.

According to the postoperative pathological examination, there were one patient with AB, two patients with B1, two patients with B2, one patient with B1-B2 and seven patients with B2–B3. All the patients had clear surgical margins. The average longest diameter of thymoma was 5.4±1.6 cm (range, 3.0–7.5 cm). The invaded organs included the pericardiums in nine patients, the lung tissues in two patients, the LIVs in one patients, and both the pericardium and the LIV in one patient. Of the 13 cases accepted the subxphoid and subcostal arch thoracoscopic extended thymectomy, the average operation time was 120.0±32.7 min (80–170 min), the average volume of estimated blood loss was 51.5±44.8 mL (10–150 mL) and the average postoperative hospital stay was 4.8±1.5 days (3–9 days) .

Two patients suffered postoperative complications including one patient with atrial fibrillation (AF) and the other one with myasthenic crisis (MC). All these two patients recovered well when discharged. There was no perioperative death. The postoperative pain score decreased dramatically from 3.8±1.0 [3–6] at 24 hours to 1.5±0.9 [0–6] at 48 hours, and finally to 0 at 3 months after surgery (P=0.000). The patients reported a higher cosmetic score of 92.6±2.7 [90-96]. All the 13 patients were alive and no tumor recurrence happened. All the five patients with myasthenia gravis had improvement and did not need any medication.

Discussion

Surgery has been proved to be an effective method to treat the resectable thymomas (1). Even though subtotal resection may prolong the survival of patients with later stages thymomas (Masaoka's stage III and VI), complete resection has been shown as the most important prognostic factor (1). Recently, as a minimal invasive approach, VATS thymectomy has been prevalent in the treatment of thymomas. A number of studies have shown that the patients with thymomas treated by VATS had smaller size tumors, less blood loss, shorter hospital stay, shorter duration of chest tube drainage, but similar longer term survival, compared with those treated by sternotomy (2-9). Therefore, VATS thymectomy has been recommended as an option for the treatment of early stagy thymomas (9). Different approaches have been developed for the thoracoscopic resection of thymomas including unilateral, bilateral, uniportal and subxiphoid approaches (11,12,15-18).

However, the reports of VATS thymectomy in the treatment of stage III thymomas were limited (11-13). There were some possible reasons. Firstly, it was a technique

challenge to resect an invasive tumor under thoracoscope. Secondly, the retraction of tumors during VATS may induce the tumor seeding, recurrence and metastasis. Dr. Axel Aubert reported a woman with well encapsulated thymoma was biopsied by VATS, but suffered tumor recurrence at the port sites four years later (10). But Dr. Thirugnanam Agasthian reported that 13 patients with stage III thymomas were operated on through unilateral VATS approach (11). During operation, the surgeons followed the "no touch, tumor last" principle, which mean that the non-tumorous part of the thymus should be dissected firstly, and the tumor was dissected lastly and should be not touched during dissection. The mean duration of follow-up was 4.9 years and no port sites recurrence happened. But the mean size of tumor was small (3.4 cm). Thereafter, Dr. Guofei Zhang and his colleagues reported bilateral VATS thymectomy for stage III thymomas in 13 patients (12). They followed the same oncological principle. By using the bilateral approach, the mean size of tumor increased to 6.4 cm. All the patients recovered well with no recurrence after 17.4 months follow-up. The VATS thymectomy combined with lateral thoracotomy also been reported for the resection of stage III thymomas (13). By using the approaches mentioned above, some of the thymomas invading the lung and pericardium could be safely resected by VATS. But no thymomas invaded great vessels was operated on through VATS.

Regarding to the novel subxiphoid and subcostal arch approach, we thought there were several advantages for thoracoscopic extended thymectomy in the treatment of thymomas. Firstly, the anterior mediastinum could be well exposed through this approach and three ports facilitated the operation, which avoided the bilateral incisions. The great visualization allowed the resection of invaded tissues and the mediastinal fat tissues possible. Our results have shown that the invaded lung tissues, pericardium and even the LIV could be safely resected by using this approach. The fat tissues near the cardiac-diaphragmatic angles, the aortopulmonary window, the phrenic nerves, even near the lower poles of the thyroid gland, could be easily removed. Secondly, the intercostals nerves compression or injury could be avoided by this new approach, which might reduce the postoperative pain. Our results prove that all the patients reported no pain 3 months after operation. Thirdly, no separate ventilation was needed by using this approach, which may be benefit to the patients who cannot tolerate the single lung ventilation due to the severe lung diseases or poor lung function. However, If the thymoma was bigger (>8 cm, according to our limited experiences), this big mass might influence the exposure of important structures in the anterior mediastinum. At the same time, the reconstruction of invaded big vessels was difficult even by using this approach. Therefore, the surgeon should convert to sternotomy without any hesitation in these situations. In certain situations, the application of this novel technique might be limited. For example, the retrosternal space might be difficult to open for a patient with previous operations in the chest or the anterior mediastinum; a cervical incision might be added to facilitate the dissection for a patient with a mass extended to the cervical part.

Although there were several limitations in this study including small sample size, shorter follow-up and its restrospective nature, our study provided initial experiences regarding to the thoracoscopic resection of stage III thymomas through this novel subxiphoid and subcostal arch approach. To our knowledge, this is the first report of successful thorascopic resection of thymomas invading the vessels. In future, larger studies with longer follow-up data were required to further confirm the oncological results of this new procedure.

Conclusions

The subxiphoid and subcostal arch thoracoscopic extended thymectomy is safe and feasible for the resection of selective stage III thymomas.

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Footnote

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

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Thymectomy via a subxiphoid approach: single-port and robot-assisted

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Background: We have previously reported on single-port thymectomy (SPT), which involves performing thymectomy via a single subxiphoid incision, and trans-subxiphoid robotic thymectomy (TRT), which is performed using the da Vinci surgical system. The aim of this study was to investigate the early surgical outcomes of thymectomy using the SPT and TRT subxiphoid approaches and to discuss their appropriate uses.

Methods: The subjects included 80 patients who underwent thymectomy via a subxiphoid approach. These patients were selected from among 99 surgical cases of myasthenia gravis or anterior mediastinal tumors at Fujita Health University Hospital between March 2011 and November 2015. The patients were divided into a SPT group (n=72) and a TRT group (n=8).

Results: The operative time was shorter in the SPT group compared with that in the TRT group (135±48 and 20±40 min, respectively; P=0.0004). There were no significant differences between the groups in terms of blood loss volume (5.9±16.8 and 5.4±4.6 mL, respectively; P=0.48), postoperative hospital stay duration (4.0±2.0 and 4.3±3.6 days, respectively; P=0.21), or the period of postoperative oral analgesic use (10.7±5.4 and 10.1±3.4 days, respectively; P=0.89). There were no intraoperative complications, such as intraoperative bleeding, in either group. In the SPT group, there was one case (1.4%) of postoperative left phrenic nerve paralysis and one case (1.4%) of transient paroxysmal atrial fibrillation. No one died during or after the surgery.

Conclusions: TRT may be as equally minimally invasive as SPT. In cases where the thymoma has infiltrated the surrounding organs, the extent of the infiltration should be used to determine whether to select TRT, or median sternotomy.

Keywords: Thymectomy; minimally invasive surgery; thoracoscopy/VATS; robotics

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Introduction

To treat myasthenia gravis and anterior mediastinal tumors, thymectomy is conventionally performed via a median sternotomy; however, many less invasive surgical procedures are now possible. These include video-assisted thoracoscopic thymectomy (VATS) (1,2) via a lateral thoracic approach, transcervical thymectomy (3) via a cervical incision, and a subxiphoid approach (4). Currently, most hospitals that perform endoscopic thymectomy use a lateral thoracic approach to perform thoracoscopic thymectomy, even for robot-assisted surgery (5). However, the lateral thoracic approach makes it difficult to identify the contralateral phrenic nerve, and securing a visual field

in the neck is challenging. We have previously reported on single-port thymectomy (SPT), which involves performing thymectomy via a single subxiphoid incision, and dual-port thymectomy (DPT), which is similar to SPT but involves the addition of a port in the right parasternal intercostal space to improve the surgery. Furthermore, we have reported on trans-subxiphoid robotic thymectomy (TRT), which is performed using the da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA, USA) (6-9). The subxiphoid approach is an endoscopic surgical procedure to resect the thymus from below the xiphoid process. Moreover, because the camera can be inserted into the midline of the body, as opposed to the lateral thoracic approach, it is easier to identify the bilateral phrenic nerves and to secure a good visual field in the neck. The purpose of this paper was to explore the initial findings of our experiences in performing thymectomy with subxiphoid approaches and to discuss the indications for each approach.

Material and methods

Surgical technique

Single-port thymectomy (SPT)

The patient was placed in the supine position with the legs apart. In most cases, differential pulmonary ventilation was not required. The surgeon stood between the patient's legs, while the endoscopist stood on the right side of the patient and operated the camera. First, a 3-cm long horizontal incision was made that was 1 cm caudal to the xiphoid process. The attachment of the rectus abdominis muscle was dissected away from the xiphoid process, thereby exposing it. The posterior surface of the sternum was blindly dissected using a finger. A vertical incision that was approximately 1 cm in length was made in the rectus abdominis muscle fascia, and a space was created to enable port insertion in the posterior surface of the fascia. Ports that are employed for single-port access surgery, namely a SILS port (Covidien, Mansfield, MA, USA), an X-gate (Akita Sumitomo Bakelite Co., Akita, Japan), or a GelPOINT Mini (Applied Medical, Rancho Santa Margarita, CA, USA), were used. Three child ports were inserted into the main port that was used for single-port access surgery. In the cases using the SILS port and X-gate, three 5-mm port entrances were inserted into the single aperture surgical port, and in the case of the GelPOINT Mini, three 10-mm port entrances were inserted into the single aperture port. One of the entrances was used for the insertion of the camera. One of the child ports was used to insert the camera scope, which was a 30° oblique-view, 5-mm-rigid camera scope. CO_2 insufflation was performed at 8 mmHg. The positive pressure, which was caused by CO_2 insufflation, aided the dissection of the thymus from the posterior surface of the sternum and extended the space for the surgical field. In most of the subjects, the bilateral mediastinal pleural membranes and both the thoracic cavities were opened. In thymoma cases with suspected infiltration of a unilateral thoracic cavity, the contralateral thoracic cavity was not opened. Anatomically, the two upper poles of the thymus are connected to the thyroid gland; therefore, both upper poles positioned cephalad to the innominate vein need to be separated from the thyroid gland, trachea, and brachiocephalic artery. This requires opening a surgical field in the cervical region to obtain an optimal view. We passed a 2-mm Kirschner wire beneath the presternal skin, which enlarged the posterior surface of the sternum when elevated, to secure a visual field in the neck, particularly the space in the neck. However, even when the wire was not passed, it was found that using CO_2 insufflation alone dorsally displaced the mediastinum and heart, and resulted in a sufficiently favorable visual field in the neck. Therefore, this wire technique was not used from the tenth case onward. An Autonomy grasper (Cambridge Endo, Framingham, MA, USA) was operated with the surgeon's left hand, while a LigaSure™-V or Maryland LigaSure™ (Covidien) was operated with the right hand, and the thymus and thymoma were dissected away from the pericardium (*Figure 1A*). The resected thymus was inserted into a bag inside the mediastinum and extracted *en masse* via the subxiphoid incision.

Trans-subxiphoid robotic thymectomy (TRT)

Similar to the SPT technique, a 3-cm horizontal incision was created that was 1-cm inferior to the xiphoid process. A port for single-port access surgery was inserted and CO_2 insufflation was performed at 8 mmHg. The thymus was dissected away from the posterior surface of the sternum. Furthermore, the mediastinal pleura were cut bilaterally and both the thoracic cavities were opened. Two 1-cm skin incisions were made on either side in the parasternal sixth intercostal space along the anterior axillary line, and a port that was used for da Vinci robotic surgery was inserted. The da Vinci surgical system (Intuitive Surgical) was then docked from the cranial side. A port for the 12-mm camera was inserted into the subxiphoid single-port access surgery port and attached to the da Vinci camera scope. The da

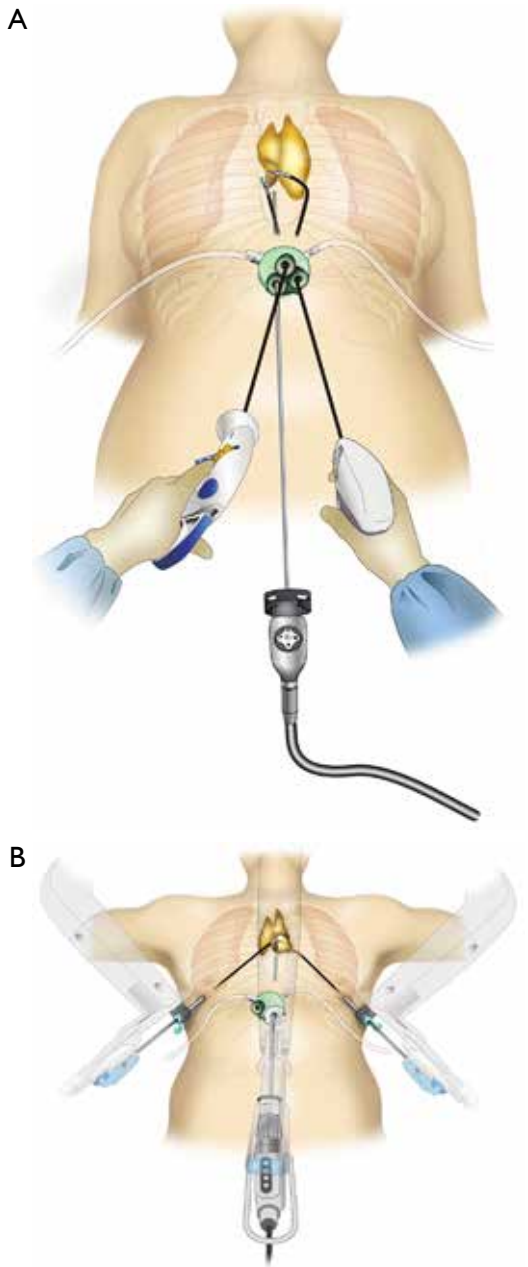

Figure 1 Subxiphoid approaches. (A) Single-port thymectomy (SPT); (B) trans-subxiphoid robotic thymectomy (TRT).

Vinci arms were then attached to the two ports, which were parasternal placed in the sixth intercostal space along the anterior axillary line (*Figure 1B*). A monopolar spatula or bipolar Maryland forceps, was attached to the right-arm of the da Vinci robot, and either bipolar fenestrated grasping forceps or Cadiere forceps was attached to the left arm. At times to expand the surgical field, the assistant used Autonomy Grasper 45-cm forceps (Cambridge Endo), which is used for single-port surgery. The thymic vein was cut using an EndoWrist Vessel Sealer (Intuitive Surgical).

When treating myasthenia gravis, an extended thymectomy is performed. This involves resecting all the adipose tissues anterior to the phrenic nerve. When treating anterior mediastinal tumors that are unrelated to the myasthenia gravis, a thymectomy is performed with the complete resection of the thymus together with the mass.

The subjects included 80 patients who underwent thymectomy via a subxiphoid approach, performed by two surgeons (T.S. and S.T.). The patients were selected from among 99 surgical cases of myasthenia gravis or anterior mediastinal tumors at Fujita Health University Hospital between March 2011 and November 2015.

The surgical indications for SPT were cases that were preoperatively diagnosed as not having phrenic nerve, pericardial, or vascular infiltration. If a partial lobectomy could be performed, tumor infiltration of the lungs was an indication for SPT. In cases with suspected vascular infiltration, a median sternotomy was indicated; however, TRT was performed in one case with suspected infiltration of the left brachiocephalic vein. In Japan, robot-assisted surgery for lung cancer or anterior mediastinal tumors is not covered under national health insurance; therefore, the patients must bear the surgery cost. Among the cases where there was a possible infiltration of the phrenic nerve, pericardium, or blood vessels by anterior mediastinal tumor, TRT was indicated in patients who requested it after they agreed to bear the treatment cost.

The patients were divided into SPT (n=72) and TRT groups (n=8). A comparative investigation of the following factors between the groups was performed: operative time, blood loss volume, postoperative hospital stay duration, and period of postoperative oral analgesic use. The background characteristics of the patients in each group are shown in *Table 1*. There was a significant difference in the percentage of thymomas between the two groups (P=0.0003). One case in the SPT group had a tumor that was adherent to right upper lobe; therefore, we performed a simultaneous partial lung resection. Four cases in SPT group were converted to DPT after encountering difficulties with the surgery because of excessive adipose tissue, pectus excavatum, risk of bleeding from a thymic hemangioma, and an iatrogenic pericardial incision. On the day after surgery, all cases were orally administered loxoprofen (60 mg three times daily), which was continued according to the patient's wishes. In both groups, intramuscular injections of pentazocine

Table 1 Patient characteristics

	SPT	TRT	P value
Sex (male/female)	31/41	5/3	0.29*
Age (mean, years)	53.4±14.8	55.5±9.9	0.78#
BMI	22.8±3.7	23.8±5.1	0.42#
Tumor size (cm)	3.2±1.7	4.1±2.1	0.21#
Myasthenia gravis	13 (18.1%)	2 (25.0%)	0.63*
Anterior mediastinal tumor	62 (86.1%)	8 (100%)	0.25*
Lung resection	1 (1.4%)	0 (0%)	
Pericardium resection	1 (1.4%)	1 (12.5%)	
Thymoma	18 (25.0%)	7 (87.5%)	0.0003*
WHO histological type (A/AB/B1-3/C/other)	1/10/6/0/1	0/0/6/1/0	
p-Masaoka stage (10) (I/II)	14/4	4/3	0.30*

*, chi-squared test; #, Mann–Whitney U-test. SPT, single-port thymectomy; TRT, trans-subxiphoid robotic thymectomy; BMI, body mass index; WHO, World Health Organization.

at a dose of 15 mg or sodium diclofenac suppositories at a dose of 50 mg were administered on the day of surgery and the day after surgery, according to the patient's wishes. However, from postoperative day 2, none of the patients received intramuscular pentazocine or sodium diclofenac suppositories. There were no cases with a positive tumor margin. One case in the TRT group was postoperatively diagnosed with thymic carcinoma and underwent postoperative radiotherapy.

This study was approved by the ethics committee at the Fujita Health University.

Statistical analysis

The data are expressed as mean ± standard deviation. Comparative analyses were performed using the Chi-squared test for the 0-1 data, and the Mann–Whitney U-test for the ordinal and continuous data. In all of the analyses, statistical significance was set at a P value of <0.05. The Statview version 5.0 software package (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

Results

The operative time was shorter in the SPT group compared with that in the TRT group (135±48 and 204±40 min, respectively; P=0.0004; *Figure 2*). There were no significant differences between the groups in terms of blood loss volume (5.9±16.8 and 5.4±4.6 mL, respectively; P=0.48; *Figure 3*), postoperative hospital stay duration (4.0±2.0 and 4.3±3.6 days, respectively; P=0.21; *Figure 4*), or period of postoperative oral analgesic use (10.7±5.4 and 10.1±3.4 days, respectively; P=0.89; *Figure 5*). There were no intraoperative complications, such as intraoperative bleeding in either group. In the SPT group, there was one case (1.4%) of postoperative left phrenic nerve paralysis and one case (1.4%) of transient paroxysmal atrial fibrillation. No deaths occurred.

Discussion

In recent years, VATS and robot-assisted thymectomy have been generally performed using a lateral thoracic approach to avoid a median sternotomy (5). However, when using a lateral thoracic approach, it is difficult to identify the contralateral phrenic nerve and to secure the surgical field in the neck. We have previously reported on SPT, DPT, and TRT as the three approaches for performing thymectomy via the subxiphoid approach (5-7). The advantages of using a subxiphoid approach include the fact that sternotomy is unnecessary, there is less pain, and the cosmetic outcome is superior. Another advantage is that the camera scope can be inserted via the subxiphoid approach, meaning that the same visual field can be obtained as the median sternotomy approach. Furthermore, it is easier to identify the neck and bilateral phrenic nerves than performing a VATS thymectomy via a lateral thoracic approach (9). In addition, when using a lateral thoracic approach, if there is an injury

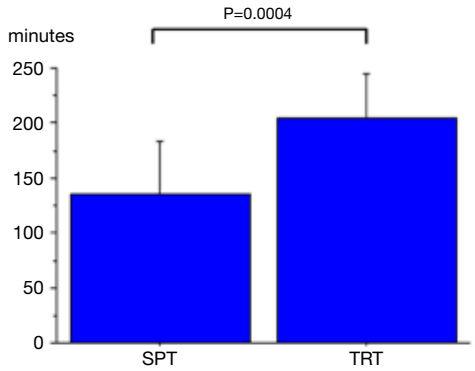

Figure 2 The operating time (min) in the TRT group was longer than that in the SPT group. SPT, single-port thymectomy; trans-subxiphoid robotic thymectomy (TRT).

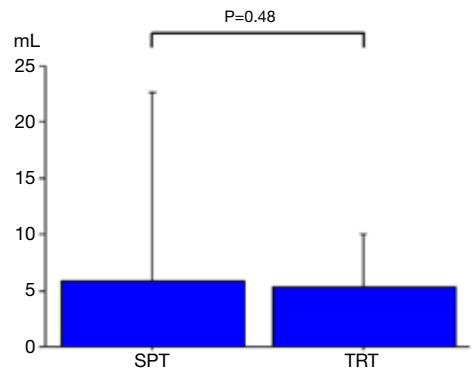

Figure 3 The amount of blood loss (mL) did not differ between the two groups. SPT, single-port thymectomy; trans-subxiphoid robotic thymectomy (TRT).

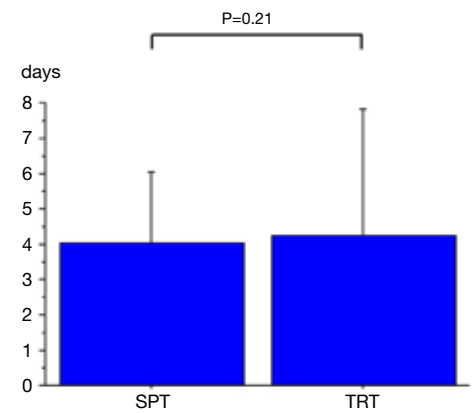

Figure 4 The duration of hospital stay (days) did not differ between the two groups. SPT, single-port thymectomy; trans-subxiphoid robotic thymectomy (TRT).

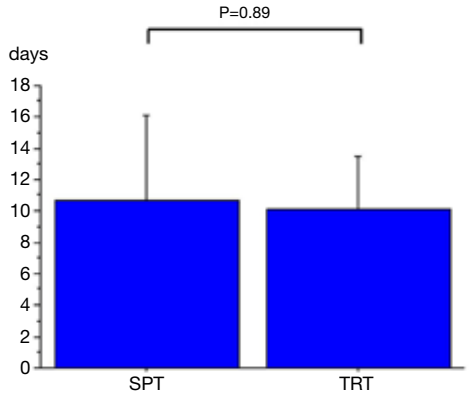

Figure 5 The duration of postoperative oral analgesics did not differ between the two groups. SPT, single-port thymectomy; trans-subxiphoid robotic thymectomy (TRT).

to the left brachiocephalic vein, it is difficult to clamp the vessel peripherally at the site of the injury. However, because surgery is performed in the supine position when operating via a subxiphoid approach, one advantage is that the procedure can be rapidly converted to a median sternotomy and the injury can be repaired.

In this study, we investigated the early outcomes of the two subxiphoid approaches. In terms of the operative time, TRT was longer; however, we believe this was because of the time it takes to set up the robotic system and the higher proportion of thymomas in the TRT group. Previously, we reported that the blood loss volume and the period of postoperative analgesic use were lower during SPT, and that the surgery was more minimally invasive compared with VATS thymectomy via a lateral thoracic approach (9). The results demonstrated that there were no significant differences in TRT compared to SPT in terms of the blood loss volume, postoperative hospital stay duration, and period of postoperative analgesic use. This indicates that TRT may be as equally minimally invasive as SPT. Moreover, there were few complications, and irrespective of the approach, the surgery was safely performed.

SPT is the least invasive approach because the intercostal space is not crossed, resulting in a lack of intercostal nerve injuries. However, one disadvantage of SPT is the difficulty of the surgery. Training is required to learn the highly specific technique of single-port surgery. For the dissection of the left lobe of the thymus, the grasper forceps are bent to the right to pull the thymus to the right side of the patient. The surgeon is required to cross the hands. For the dissection of the right lobe of the thymus,

the grasper forceps are bent to the left to pull the thymus to the left side of the patient. Training with a dry box is effective for learning these techniques. However, because the instruments and camera are inserted via a single port during SPT, there is interference between the instruments and suturing is difficult.

During DPT, which is performed using the same approach as SPT but with an additional port, there is no interference caused by the surgeon using the forceps in both hands, and, compared with SPT, the surgical procedure and suturing are significantly easier. When this approach is used, a single intercostal space is crossed; therefore, intercostal nerve injury can only occur in one intercostal space. However, when performing VATS thymectomy, three or more intercostal spaces are crossed, meaning that the extent of pain and intercostal nerve injury are less frequent when performing DPT. We recommend performing DPT first for the surgeon to become accustomed to the subxiphoid approach before initiating SPT. DPT is a useful approach when treating cases in which technical challenges arise or in cases that require suturing, such as pericardial reconstruction. These challenges may be noted before initiating SPT or during SPT.

The major advantage of the da Vinci surgical system is the articulated arm. Articulated forceps make it possible to perform dissection in a natural direction within a narrow space. This is a major advantage compared with the linear tools that are used during normal VATS surgery. On the basis of our experience, combined resection of the pericardium or reconstruction of the pericardium using prosthesis is possible during DPT; however, it is not easy to perform. We have found that the use of the robotic system makes surgery easy to perform. We do not have any experience of vessel closure other than the use of a stapler; however, a robotic system support may be required when more precise vascular closure is required. The robotic system makes it possible to perform endoscopic surgery, which to date surgeons have not been able to perform manually.

Owing to its minimal invasiveness, we consider SPT to be indicated in cases without infiltration that require thymectomy or extended thymectomy. SPT can be performed until partial lobectomy, even in cases where the tumor has infiltrated the lungs (11). In cases where infiltration of the pericardium is suspected, DPT and TRT are more appropriate than SPT because of the requirement for suturing the resulting deficit in the pericardium. In cases where there is infiltration of the heart, great vessels, or left brachiocephalic vein, it is standard to perform a median sternotomy; however, if there is only partial infiltration of the left brachiocephalic vein, then DPT or TRT could be used. In cases where the thymoma has infiltrated the surrounding organs, the extent of infiltration should be used to determine whether to select DPT, TRT, or median sternotomy.

There were a number of limitations to this study. This was a non-randomized, retrospective study, the sample size was small, and the surgical indications were biased. For example, TRT was performed on patients who consented to bear the treatment cost, which is not covered under health insurance. This, therefore, led to an appreciable selection bias.

In conclusion, it is possible to perform surgery safely via a subxiphoid approach. Selecting the appropriate subxiphoid approach on the basis of the degree of progression of the thymoma is imperative.

Going forward, we will need to investigate the long-term treatment outcomes of treating myasthenia gravis and thymoma via a subxiphoid approach.

Acknowledgements

None.

Footnote

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

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Left- and right-sided video-assisted thoracoscopic thymectomy exhibit similar effects on myasthenia gravis

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Background: Unilateral video-assisted thoracoscopic (VATS) thymectomy features less operative trauma, improved cosmesis, and similar efficiency compared with transsternal (TS) thymectomy for treatment of patients with myasthenia gravis (MG). Unilateral VATS thymectomy can be easily performed from either side of the thorax, because thymus is located in the middle of mediastinum. Nevertheless, the side that provides better outcomes remains controversial. This study presents our experience on treatments for MG and reveals the differences between the unilateral VATS thymectomy performed on each side.

Methods: Eighty-one consecutive patients with MG who underwent TS or VATS thymectomy on either side between January 2003 and December 2012 were enrolled in the study. Clinicopathologic data and surgical outcomes were retrospectively analyzed and compared among different surgical approaches.

Results: TS thymectomy was administered in 50 patients, whereas unilateral VATS approaches were performed on the remaining 31 patients, 15 on the left side and 16 on the right side. The VATS group exhibited a significantly shorter surgery duration (P<0.001), less intraoperative blood loss (P=0.009), shorter postoperative hospital stay (P=0.025), smaller thoracic drainage volume (P=0.033), shorter thoracic drainage duration (P=0.006), and less postoperative complications (P<0.001) compared with the TS group. However, disease remission rates did not significantly differ among the groups (P=0.988). The left-sided group exhibited considerably longer thoracic drainage duration than the right-sided group (P=0.041). Moreover, surgical time (P=0.736), intraoperative blood loss (P=0.281), postoperative hospital stay (P=0.599), thoracic drainage volume (P=0.571), postoperative complications (P=0.742) and therapeutic effect (P=1.000) did not significantly differ among the groups. Multivariate analysis revealed that the ocular type of MG is the only independent factor for clinical remission (P=0.002).

Conclusions: Unilateral VATS thymectomy can reduce surgical risks and shorten hospitalization duration without threatening the therapeutic effect. This technique can be safely and effectively performed by experienced surgeons in either side of the thorax.

Keywords: Myasthenia gravis (MG); thoracoscopy; thymectomy; outcomes

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Introduction

Despite the lack of evidence-based medicine, thymectomy has been widely used for treatment of patients with myasthenia gravis (MG) for nearly a century. The effectiveness of thymectomy and medication alone is difficult to compare in a randomized controlled study because of the low prevalence of MG, medication requirement after surgery, and long time required to achieve remission. Nevertheless, several retrospective studies suggest a positive correlation between thymectomy and prognosis of MG (1,2). A meta-analysis conducted by the American Academy of Neurology illustrated the superiority of surgical treatments over non-surgical treatments regardless of the differences in selection criteria and outcome assessment (2). Therefore, thymectomy is the generally recommended option to achieve MG remission or improvement.

The surgical approach of thymectomy can be classified into transsternal (TS), transcervical, and video-assisted thoracoscopic (VATS) surgery. TS extended thymectomy has been considered the standard surgical approach, despite that this technique causes long-lasting postoperative pain and cutaneous scar, which may lead to the delay of surgical treatment. Transcervical thymectomy minimizes surgical trauma and improves outcome acceptance, particularly for young women who occupy a large proportion of patients with MG. Nevertheless, the remission rate of transcervical thymectomy may be less satisfied because it exhibits higher probability of leaving ectopic thymic tissue (3). VATS thymectomy was first reported by Sugarbaker in 1993 (4), and has been rapidly developed since then. This technique presents evident advantages, particularly shorter operative time, less operative trauma, improved cosmesis, and shorter hospital stay but similar efficiency to TS thymectomy (5,6). VATS thymectomy can be categorized as unilateral (right or left), bilateral, subxiphoid, and bilateral VATS with cervical incision. Resection potential and treatment outcomes have been investigated. Bilateral VATS thymectomy with and without cervical incision were speculated to be more thorough than unilateral VATS thymectomy because of better visualization of both sides of the mediastinum and cervical thymic lobes; nevertheless, these techniques exhibit similar therapeutic effects (7). Unilateral VATS, particularly the procedure performed on the right side, is clinically preferred; in this technique, the landmark of the superior vena cava, where the left innominate vein converges, can be conveniently identified (8). However, other researchers recommended left-sided VATS thymectomy (9). Hence, advantages, securities, and difficulties must be compared between unilateral VATS thymectomy performed on each side of patients with MG.

This study presents our experience regarding VATS thymectomy, compares short-term outcomes with that of TS procedures, and identifies differences of unilateral VATS thymectomy conducted on both sides.

Patients and methods

Study design and patients

This study was permitted by the Ethics Committee of Sun Yat-sen Memorial Hospital. Informed consents were provided by all of the participants. From January 2003 to December 2012, data of 81 consecutive patients with MG who underwent extended thymectomy at the Department of Thoracic Surgery Sun Yat-sen Memorial Hospital were retrospectively reviewed. All the patients were diagnosed with MG based on the weakness and fatigability of affected muscles, decremental responses to repetitive nerve stimulation tests, and striking responses to intramuscular injection of one bolus of neostigmine methyl sulfate. A team consisting of experienced neurologists and thoracic surgeons worked to treat the patients. The neurologists were responsible for the diagnosis, classification, pharmaceutical treatment, efficacy assessment, and follow-up of the patients, whereas the thoracic surgeons took charge of the surgery and perioperative care.

All the patients are taking anticholinesterase agent till the day before surgery. A single stress dose of a corticosteroid was given before induction of anesthesia. Inhaled anesthetic agents provide sufficient muscle relaxation. Neuromuscular blocking agents are avoided. Postoperatively, patients are extubated in the operating room. The same dose of anticholnesterase as preoperatively was prescribed to them to control the MG symptom.

Clinicopathologic data, including gender, age at disease onset, date of surgery, clinical classification, medication, surgery information, morbidity, thymoma histology, maximum diameter, and position were obtained from clinical and pathologic records. Each patient with thymoma was staged according to Masaoka staging system (10). After the surgery, all the patients were followed up and drug doses were adjusted according to variations in MG symptoms. The patients were required to visit the neurologists at 2-month intervals if their symptoms persisted or at 6-month intervals if they were symptom free. Preoperative disease status was classified based on the Myasthenia Gravis Foundation of America (MGFA) classification (11).

Postoperative responses after thymectomy were classified according to the modified post-intervention status scoring system of the MGFA (12); these responses were assessed using the following grading scale: Grade 1 indicates a complete stable remission without medications for at least 2 years, Grade 2 implies an asymptomatic status with pharmacological remission, Grade 3 signifies minimal manifestation of decreased pretreatment clinical symptoms or MG medications, Grade 4 reflects no change, and Grade 5 signifies worsening symptoms.

Operative procedures

Extended thymectomy was performed on all of the patients through unilateral VATS or TS resection. All the surgical procedures were performed by qualified thoracic surgeons during the study period. TS resection was initially the main procedure in the treatment of patients with MG. VATS has been conducted since 2006 through right- or left-sided thoracoscopic approach and is primarily determined by thymoma location, as well as surgeon's preference and experience. Thymomas larger than 8 cm or with suspected vascular invasion were resected through the TS approach. The surgical techniques employed are described in previous studies (13,14).

Similar right- and left-sided VATS were performed. The pleura overlying the thymus is incised along the phrenic nerve. The thymus is then dissected form the anterior pericardium and followed upward to the neck. Dissection is continued deep inside, incising the contralateral pleura to visualize the phrenic nerve in the other hemithorax. Visualization of the innominate vein and its branches may be the only difference between the two procedures. In the right-sided VATS, the innominate vein can be easily separated when dissecting along the superior vena cava. However, the typical organ is absent in dividing innominate vein in the left-sided VATS.

Statistical analysis

All statistical analyses were performed with the SPSS 16.0 program package (SPSS, Inc. Chicago, IL USA). Continuous data were compared using Student's *t*-test, and categorical variables were assessed using the Pearson Chi-square test or Fisher's exact test as appropriate. Complete stable remissions (CSR) during the follow-up period were calculated by the Kaplan-Meier method, and compared by the log-rank tests. Multivariate analysis was performed using the logistic regression model with potential factors whose P values were less than 0.10 in the univariate analysis. Result was considered statistically significant when the two-tailed P value was less than or equal to 0.05.

Results

Patient characteristics

Eighty-one consecutive patients with MG (33 males and 48 females) were enrolled in the study. The average age of the patients at thymectomy was 35.5 years (range, 8–73 years). TS thymectomy was conducted on 50 (61.7%) patients, whereas unilateral VATS approaches were performed on the remaining 31 (38.3%) patients, 15 on the left side and 16 on the right side. No conversion from VATS to TS thymectomy was implemented. The MGFA clinical classification ranged from class I to class V. Ocular MG (class I) was the most common class and observed in 48 patients (59.3%). Before thymectomy, 77 patients (95.1%) required pyridostigmine bromide to relieve symptoms, 58 patients (71.6%) were given with prednisone, and 12 patients (14.8%) received intravenous immunoglobulin (IVIG) therapy. After the surgery, patient development was followed up for at least 2 years. The median length of follow-up for the overall population was 76.0 months (range, 25–166 months). After the surgery, pyridostigmine bromide and prednisone were successfully discontinued in 33 (40.7%) and 31 (38.3%) patients, respectively. IVIG treatment was no longer needed in any of these patients.

VATS versus transsternal (TS) thymectomy

Gender, age at onset, symptom duration, MGFA classification, and histology were not statistically significantly different between the VATS and TS groups. The follow-up period was significantly shorter in the VATS group because the VATS approach has not been adopted in our practice until 2006 (*Table 1*).

The perioperative outcomes of the 81 patients in the VATS and TS groups are listed in *Table 2*. The VATS group exhibited a significantly shorter surgery duration (P<0.001), less intraoperative blood loss (P=0.009), shorter postoperative hospital stay (P=0.025), smaller thoracic drainage volume (P=0.033), shorter thoracic drainage duration (P=0.006), and less postoperative complications (P<0.001) than the TS group. The most common postoperative complications included MG crisis (P=0.025) and arrhythmia (P=0.002), whose incidences were significantly reduced in the VATS group. Nevertheless,

Table 1 Demographic and clinical features of 81 patients with myasthenia gravis

Variables[a]	VATS group	TS group	P[b]
Sample size	31 (38.3)	50 (61.7)	
Gender			
Male	11 (35.5)	22 (44.0)	0.301
Female	20 (64.5)	28 (56.0)	
Age at onset (years, mean ± SD)	33.9±11.5	36.4±16.0	0.414
Early onset (≤40 years)	23 (74.2)	31 (62.0)	0.258
Late onset (>40 years)	8 (25.8)	19 (38.0)	
Symptom duration			
<12 months	17 (54.8)	31 (62.0)	0.643
≥12 months	14 (45.2)	19 (38.0)	
MGFA classification[c]			0.448
I	20 (64.5)	28 (56.0)	
II	6 (19.4)	10 (20.0)	
III	1 (3.2)	5 (10.0)	
IV	4 (12.9)	6 (12.0)	
V	0	1 (2.0)	
Histology			
Thymoma	17 (54.8)	24 (48.0)	0.550
Nonthymoma	14 (45.2)	26 (52.0)	
Thymoma size [cm, median (range)]	3.3 (1.7–7.0)	4 (1.5–12.5)	0.280
≤5 cm	15 (88.2)	20 (83.3)	1.000
>5 cm	2 (11.8)	4 (16.7)	
Thymoma staging			
Masaoka I	10 (58.8)	15 (62.5)	0.661
Masaoka II	6 (35.3)	6 (25.0)	
Masaoka III	1 (5.9)	3 (12.5)	
Thymoma position			
Left-of-center	8 (47.1)	9 (37.5)	0.540
Right-of-center	9 (52.9)	15 (62.5)	
Follow-up [months, median (range)]	42 [25–97]	88 [28–166]	0.002

[a], categorical variables were described as n (%); [b], Chi-squared test for categorical variables, Student's *t*-test or Mann-Whitney test for continuous variables; [c], class I versus class II–V. VATS, video-assisted thoracoscopic; TS, transsternal; SD, standard deviation; MGFA, myasthenia gravis foundation of America.

disease remission rate was not statistically different between the TS and VATS groups (P=0.988). The 5-year CSR in VATS and TS groups were 52.1% and 42%, respectively. The difference between them was not statistically significant (P=0.512, *Figure 1A*).

Left-sided versus right-sided VATS thymectomy

Baseline characteristics, including gender, age at onset, and MGFA classification, were not significantly different between the left- and right-sided groups. Furthermore, surgery duration, intraoperative blood loss, postoperative hospital stay, thoracic drainage volume, and postoperative complications were not significantly different. The time for thoracic drainage was significantly shorter in the right-sided group (P=0.041). Disease remission rate was not significantly different between the left- and right-sided groups (P=1.000). The 5-year CSR in left- and right-sided groups were 42.7% and 64.3%, respectively. The difference between them was not statistically significant (P=0.588, *Figure 1B*). Seventeen

Table 2 Comparison between video-assisted thoracic surgery group and transsternal surgery group

Variables[a]	VATS group	TS group	P[b]
Surgery duration (minutes)	80 [65–120]	110 [90–140]	<0.001
Estimated blood loss (mL)	120 [20–400]	175 [30–800]	0.009
Postoperative hospital stay (days)	9 [5–16]	11 [4–43]	0.025
Thoracic drainage volume (mL)	250 [5–1,890]	477 [25–3,980]	0.033
Thoracic drainage duration (days)	2 [1–7]	3 [1–6]	0.006
Overall morbidity (n)	2 (6.5)	20 (40.0)	0.001
MG crisis	1 (3.2)	11 (22.0)	0.025
Pneumonia	1 (3.2)	7 (14.0)	0.145
Arrhythmia	1 (3.2)	16 (32.0)	0.002
Wound infection	2 (6.5)	5 (10.0)	0.702
Pyridostigmine withdraw (n)	13 (41.9)	20 (40.0)	0.863
Prednisone withdraw (n)	13 (41.9)	18 (36.0)	0.593
MGFA post-intervention status[c] (n)			0.988
Grade 1	11 (35.5)	16 (32.0)	
Grade 2	10 (32.3)	19 (38.0)	
Grade 3	5 (16.1)	7 (14.0)	
Grade 4	2 (6.5)	4 (8.0)	
Grade 5	3 (9.7)	4 (8.0)	

[a], variables were described as median [range] or n (%); [b], Chi-squared test or Fisher's exact test for categorical variables, Mann-Whitney test for continuous variables; [c], Grades 1–3 versus Grades 4–5. VATS, video-assisted thoracic surgery; TS, transsternal; MG, myasthenia gravis; MGFA, myasthenia gravis foundation of America.

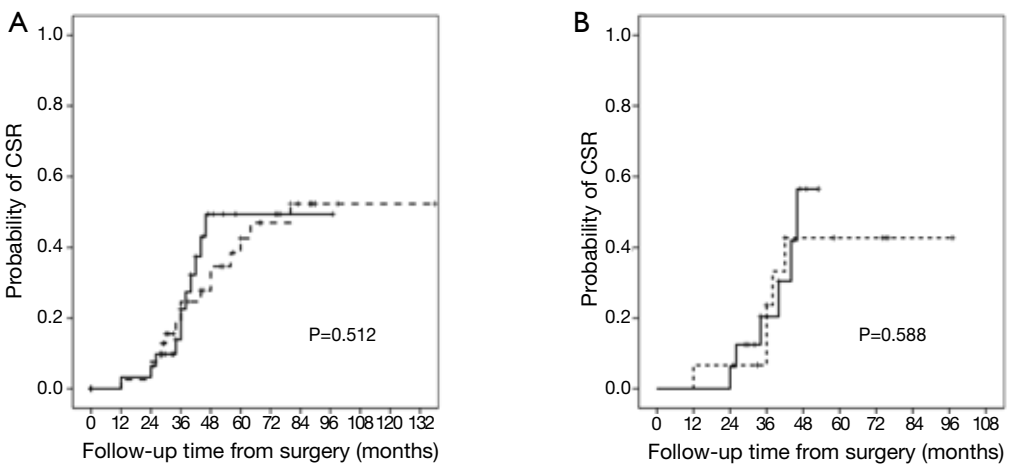

Figure 1 Kaplan-Meier cumulative estimate of the complete stable remission (CSR) rate following extended thymectomy. (A) The difference between video-assisted thoracoscopy group (solid line) and transsternal group (dash line); (B) the difference between right (solid line) and left (dash line) video-assisted thoracoscopy group.

Table 3 Comparison between left and right video-assisted thoracic surgery in minimally invasive thymectomy

Variables[a]	Left VATS	Right VATS	P[b]
Sample size	15	16	
Gender			
Male	7 (46.7)	4 (25.0)	0.189
Female	8 (53.3)	12 (75.0)	
Age at onset (years)	33.2±3.5	34.6±2.3	0.748
MGFA classification[c]			0.685
I	11 (73.3)	9 (56.3)	
II	2 (13.3)	4 (25.0)	
III	1 (6.7)	0	
IV	1 (6.7)	3 (18.8)	
V	0	0	
Surgery duration (minutes)	75 [65–100]	85 [65–120]	0.736
Estimated blood loss (mL)	80 [5–350]	150 [10–400]	0.281
Postoperative hospital stay (days)	9 [7–16]	9 [5–12]	0.599
Thoracic drainage volume (mL)	260 [5–1,890]	200 [90–1,240]	0.571
Thoracic drainage duration (days)	3 [1–7]	2 [1–6]	0.041
Overall morbidity	1 (50.0)	1 (50.0)	0.742
Histology			
Thymoma	11 (73.3)	6 (37.5)	0.073
Nonthymoma	4 (26.7)	10 (62.5)	
Thymoma position			0.153
Left-of-center	6 (66.7)	2 (25.0)	
Right-of-center	3 (33.3)	6 (75.0)	
MGFA post-intervention status[d]			1.000
Grade 1	5 (33.3)	6 (37.5)	
Grade 2	5 (33.3)	5 (31.3)	
Grade 3	3 (20.0)	2 (12.5)	
Grade 4	1 (6.7)	1 (6.3)	
Grade 5	1 (6.7)	2 (12.5)	

[a], variables were described as median [range] or n (%); [b], Chi-squared or Fisher's exact test for categorical variables; Mann-Whitney test for continuous variables; [c], Class I versus Class II–V; [d], Grades 1–3 versus Grades 4–5. VATS, video-assisted thoracic surgery; MGFA, myasthenia gravis foundation of America.

patients were preoperatively suspected with thymoma, which was confirmed after pathological diagnoses. Although more left-of-center thymomas were found in the left-sided group, the difference between the groups was not significant (*Table 3*).

Favorable factors of disease remission

According to the MGFA post-intervention status, 68 patients in Grades 1–3 were considered in clinical remission. The 2-year clinical remission and complete remission rates were 84.0% (68/81) and 33.3% (27/81), respectively. In the univariate analysis, only the ocular type of MG was significantly found to be a favorable predicator for clinical remission (P=0.005). Surgical approach was not associated with remission rates (*Table 4*). In the analysis of the multivariate model after adjusting for gender, age at onset, symptom duration, histology, and surgical approach, the

Table 4 Univariate analysis of prognostic factors for clinical remission in patients with myasthenia gravis

Variables[a]	MGFA post-intervention status		P[b]
	Grade 1–3	Grade 4–5	
Gender			0.855
Male	28 (41.2)	5 (38.5)	
Female	40 (58.8)	8 (61.5)	
Age at onset			0.134
Early onset (<40 years)	43 (63.2)	11 (84.6)	
Late onset (≥40 years)	25 (36.8)	2 (15.4)	
Symptom duration			0.855
<12 months	40 (58.8)	8 (61.5)	
≥12 months	28 (41.2)	5 (38.5)	
MGFA classification			0.005
Class I	45 (66.2)	3 (23.1)	
Class II–V	23 (33.8)	10 (76.9)	
Histology			0.140
Thymoma	37 (54.4)	4 (30.8)	
Nonthymoma	31 (45.6)	9 (69.2)	
Surgical approach			0.988
Video-assisted thoracic surgery	26 (38.2)	5 (38.5)	
Transsternal	42 (61.8)	8 (61.5)	

[a], variables were described as n (%); [b], Chi-squared or Fisher's exact test. MGFA, myasthenia gravis foundation of America.

ocular type of MG remained as significant independent factor (odd ratio: 6.522, 95% confidence interval: 1.633–26.042, P=0.002).

Discussion

As a minimally invasive option for the treatment of MG, VATS plays an increasingly role in therapy for MG, and has been one of the most common surgical approaches, because of its minimal invasiveness. Some researchers reported the possibility of incomplete resection because of visual limitation in VATS, which might be the key to MG healing (15). However, studies reported that successful symptom improvement did not differ between TS and VATS thymectomy (5,14). Data in our study also indicated that the VATS group exhibited a shorter surgical time, less intraoperative blood loss, less postoperative hospital stay, less thoracic drainage, and less postoperative complications but the similar remission rates to the TS group. Rückert *et al.* (16) demonstrated improved preserved pulmonary function in the immediate postoperative period after VATS thymectomy; this condition leads to less pulmonary infection and fast recovery. Chicaiza-Becerra *et al.* (17) reported that VATS thymectomy is a cost-effective strategy in treatment of patients in developing countries. These findings consolidated the position of VATS thymectomy in treatment of patients with MG, although a randomized, prospective clinical investigation must be further performed.

The side that is the better route of VATS remains controversial because thymus is often located in the middle of the mediastinum. In 1995, Yim *et al.* (18) proposed that a right-sided approach could be appropriate for VATS. The main advantages of the right-sided approach include larger operating space for the scope and equipment in the right pleura cavity and easily recognizable innominate vein. However, Mineo *et al.* (9) preferred the left-sided pathway because the left side of the thymus appears usually larger extending down to the pericardiophrenic area; this approach enables an extensive removal of fat allocated in the aortocaval groove, aortopulmonary window, and both pericardiophrenic sides. An anatomic study also demonstrated that the left approach left less tissue than the right approach (19). Tomulescu *et al.* (1) demonstrated similar operative time, hospitalized length, and remission rates between the right- and left-sided VATS thymectomy. However, only patients with MG without thymoma were included in their study. Given that the position of thymoma could be on the right, left, or in the middle of the mediastinum, we speculate that selecting a better way for treatment of patients with MG, especially thymomatous ones, is important. In this study, left-sided VATS was selected for 75.0% patients with left-of-center thymoma, whereas right-sided VATS was selected for 66.7% patients with right-of-center thymoma. Surgical time, intraoperative blood loss, postoperative hospital stay, thoracic drainage volume, and postoperative complication were not significantly different among different approaches. Therapeutic effects were also not different. Thus, we recommend that VATS thymectomy could be safely and effectively performed from the either side of the thorax when the area containing all the thymus and fat tissue are dissected, as also described by Jurado *et al.* (14). Surgeons could select either route depending on their own experience, predominant location of thymus or thymoma, possible pleural adhesion, and concomitant operation such as pulmonary resection.

The indications for thymectomy in patients with MG

remain unclear. The first and the only randomized control trial on thymectomy combined with prednisone treatment and prednisone alone is ongoing (20). However, even if thymectomy is beneficial compared with the optimized medical management, the debate persists on which kinds of patients would benefit from the operation. A recent study on the 8-year follow-up of 306 patients with MG revealed the presence of ocular MG before operation and the absence of thymoma and concomitant diseases, which are favorable factors to obtain satisfactory efficacy (21). Consistent with other studies (21,22), the present study showed that ocular MG is also found to be the only favorable predictor of clinical remission. Thymectomy remains controversial for patients with ocular MG because it is not a life threatening disease and has good response to medication. However, other scholars argued that ocular MG may severely impair the quality of life and emotion of affected patients because it presents constantly fluctuating diplopia and ptosis. Moreover, two-thirds of the cases may progress to advanced MG stages (23); as such, we are more inclined toward thymectomy for treatment of patients with ocular MG in our institute. The remission rates of patients with thymomatous MG were not significantly different from those without thymoma in the present study. We suspected that the short follow-up period of merely 2 years and mild disease component of the current study population could be the influencing factors. Other researchers also claimed that the complete remission rate of MG thymoma was not inferior to that of MG without thymoma (24). Yu *et al.* (25) achieved equivalent results within 40 postoperative months in their study, but the effective rates of thymomatous MG were significantly lower than nonthymomatous MG after 40 months of follow-up. They speculated that the adverse effect on thymomatous patients with MG could be due to its more severe symptoms and less responsiveness to medical treatment (25). Identification of eligible patients with MG for thymectomy should be studied in the future, as personalized therapy has received increased popularity.

One limitation of this study is that data were obtained from a retrospective database in a single institute; hence, selected and observational biases are inevitable. The limited number of patients may lead to a false-negative result. The long period spent on recruiting patients is another limitation. The learning curves of VATS thymectomy in such a long time may affect remission rates. Finally, most cases involved in this study were patients with ocular MG, which may restrict the broad application of our findings to the whole population with MG, especially for those with generalized MG. Additional prospective studies involving multiple centers are needed to confirm our results in a broader population.

In conclusion, VATS thymectomy can produce satisfactory outcomes, reduce surgical risks perioperatively, and shorten the hospitalization time compared with the conventional TS procedure. Unilateral VATS thymectomy is a clinically acceptable procedure, and can be safely and effectively performed on either side of the thorax.

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Footnote

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Video assisted thoracic surgery (VATS) for recurrent thymoma

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Between 10%-30% of patients that undergo a radical operation for thymoma develop a recurrence in a variable range of time. The surgical treatment of thymoma relapses is an established and effective therapeutic approach, particularly for a single intrathoracic recurrence; however, no agreement has been reached on the best surgical approach and the extent of surgical resection, particularly in the most common event of pleural relapses. In the era of minimally invasive approach for most thoracic pathologies, the role of the video assisted thoracic surgery (VATS) approach for thymoma recurrence resection is still unclear and controversial: to date, only few authors have reported in their series a thoracoscopic resection of pleuro-pulmonary relapses, mostly when a single lesion was present. Furthermore, a thoracoscopic approach for mediastinal recurrence has been rarely reported after a previous sternotomy to resect the primary tumor. It is likely that in the future, the role of VATS for thymic recurrence resection will be better defined and extensively studied.

Keywords: Thymoma; recurrence; surgical treatment; video assisted thoracic surgery (VATS); thoracoscopy

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Introduction

Thymomas are the most common tumors of the anterior mediastinum. Radical surgical resection is the mainstay of treatment for this type of tumor and the most important prognostic factor (1-3). Unfortunately, in 8%-30% of patients that undergo radical surgical resection, a recurrence of the tumor may occur over a wide range of time, from few months to several years after the first operation (4-7). The probability of recurrence seems to be related to the initial Masaoka stage of the disease (8,9), as well as the WHO histology (10) with an increased relapse rate for Masaoka stage III and types B2-3 primary tumors. The most common site of tumour relapse from thymoma is the thoracic cavity, mainly in the form of single or multiple pleuro-pericardial implants (46%-80% of all recurrences, probably due to the seeding of the pleural cavity during dissection of the tumor or spillage from the surface of the invaded capsule) (3,4,11,12). In a minority of patients, the relapse may localize in the anterior mediastinum due to incomplete resection or contamination of the field from extracapsular invasion. The management of thymoma recurrence still remains unclear and the role of surgery is not yet well defined in terms of indication, surgical access and extent of resection.

Evidence supporting surgery for recurrent thymoma

Treatment for recurrence may not be easy and the optimal strategy for managing these patients is still a matter of debate. Thymoma is a rare disease and recurrences are even rarer; therefore, to date, no randomized clinical trials have been performed to explore the best management of this disease. The majority of available data comes from retrospective single or multiinstitutional series (the largest of which includes 103 patients) (2,4-10,13-20), that have analyzed the results of surgical approach to thymoma recurrence and compared these with non-surgical treatments (i.e., chemotherapy, radiotherapy or a combination of both). Various authors (4-9,13-19) have emphasized the efficacy of surgical re-resection to prolong

the survival of these patients; other authors (10,20) found no differences in the results obtained through surgery and chemo- or radiotherapy. However, the results of these studies are often burdened by significant biases, related to the heterogeneous degrees of severity, variable patterns of recurrence, different types of therapeutic approach and various selection criteria (regarding the presence of primary Masaoka stage IVa, type C thymic carcinoma, recurrence on patients with incomplete resection, and technical resectability). In fact, the comparison of patients treated by surgery with those receiving chemo-radiotherapy is often inappropriate due to differences in extension (single or multiple relapses), location of the disease (local *vs*. distant metastases) and performance status of the patients. Currently, the general consensus indicates surgical resection of cases of a single, potentially resectable, loco-regional thymoma recurrence, irrespective of location (i.e., pleural, pulmonary or mediastinal) if the relapse is judged resectable. This approach is associated with a good long-term prognosis (13,14,17). In 2008, Davenport *et al*. (21) published a systematic review targeted to provide some evidence-based recommendations about the role of surgery in the management of primary and recurrent thymomas. The authors concluded that surgical treatment of relapses seems acceptable, although the data supporting such a recommendation is methodologically weak and based only on reports coming from retrospective series. In a meta-analysis recently published by Hamaji *et al*. (8) considering 11 studies, the authors reached similar conclusions, underlining that the best results may be obtained when a complete resection is anticipated by the preoperative radiological assessment. It is undoubted, however, that given most of the studies evaluating the role of surgery for recurrent thymoma are retrospective, they suffer from an inherent selection bias. Surgery is usually reserved for patients with limited disease (the best prognostic factor) and better performance status, with a theoretical predicted survival advantage. A survey among the European Society of Thoracic Surgeons (ESTS) members (22) published in 2011, reported a general agreement regarding the preference (91%) for surgical approach to recurrence when resection is feasible. In this survey, some centres reported that they performed multiple subsequent resections in patients with repeated recurrence. Furthermore, many centres added in their comments that correct patient selection is crucial and that they proceed to resection only when complete resection may be anticipated. The average rates of 5- and 10-year overall survival after recurrence are 70.9%±16.2% (range, 40%-85.7%) and 49.6%±27.4%, respectively for surgical series.

Type of surgery

Even for recurrence, the radicality of re-resection is a major prognostic factor. Therefore, a complete macroscopic resection represents the goal and the surgical approach (both in term of way of approach and extension of resection) should be planned and tailored to accomplish this aim. The number and location of recurrence are determinant in the surgical planning: a single pulmonary recurrence may be easily treated by a wedge (if peripheral) or anatomic (if central) pulmonary resection (*Figure 1A*). Similarly, a mediastinal non-invasive recurrence, particularly if characterized by unilateral predominance may be approached from the right or left chest cavity by thoracoscopic or robotic approach or thoracotomy, avoiding a sometimes difficult redo-sternotomy (*Figure 1B*).

A more complex discussion is required when there is evidence of single (*Figure 2A,B*) or multiple (*Figure 2C*) pleuro-pericardial implants. In these cases, the majority of the authors (4-6,14,15,17,18) advocate a limited pleural resection or a partial pleurectomy, comprising only the lesions macroscopically evident, in case of single or limited pleural relapses.

Some authors, however, have described extended resections, from pleurectomy/decortications to extrapleural pneumonectomy. In some cases, these procedures are accompanied by induction chemotherapy or intraoperative hyperthermic pleural cavity irrigation or chemoperfusion, both for Masaoka stage IVa or diffuse pleural relapses. The results of these studies are controversial and often poor (23-25).

Role of minimally invasive approach

Looking at the available literature (*Table 1*), the most common surgical approach for thymoma recurrences is represented by thoracotomy. The video assisted thoracic surgery (VATS) approach is rarely reported, and mainly reserved for wedge resection of pulmonary nodules or single pleural relapse (17,19,27). There are multiple reasons for this low rate of minimally invasive approach, including: (I) the majority of the series covers a long period of time and a large number of cases have been treated in the "pre-VATS era" or in a period of low adoption of VATS; (II) in a certain percentage of cases, a VATS approach may be contraindicated for technical reasons (e.g., diffuse

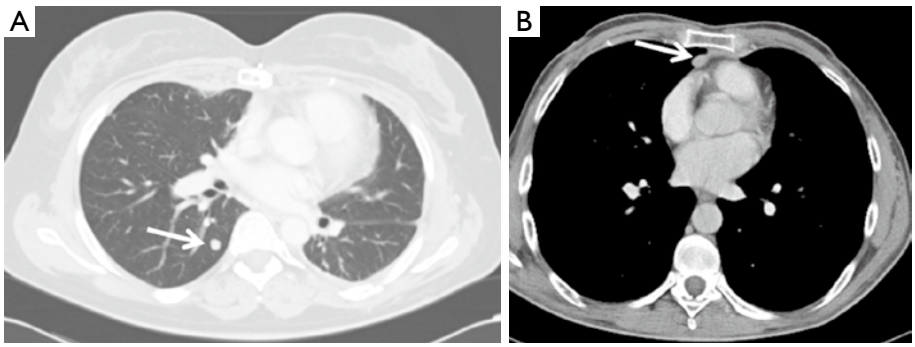

Figure 1 (A) Single pulmonary recurrence (arrow) on the right lower lobe and; (B) single mediastinal recurrence (arrow) with unilateral right predominance in a patient with a previous thymoma resection by left thoracotomy.

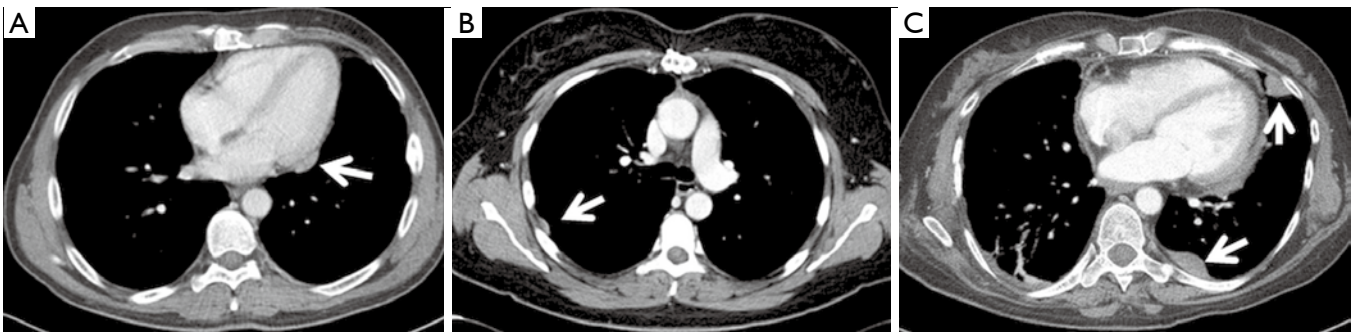

Figure 2 (A) Single pericardial implant (arrow) on the left side; (B) single pleural recurrence (arrow) on the right chest cavity; (C) multiple left pleural relapses (arrows).

recurrence, previous thoracotomy, adhesions, previous irradiation); (III) a total pleurectomy or pleurectomy/decortication by VATS in case of diffuse pleural recurrence (the most common type of relapse) is considered difficult and often inadequate to obtain a macroscopic radical resection.

VATS for recurrent thymoma: pros & cons

Given the widespread adoption of the VATS approach in the last decade for a variety of thoracic malignant diseases (primary and metastatic tumors of the chest cavity), this approach merits some consideration regarding its potential application for recurrent thymoma.

Firstly, recent technical advancements (i.e., dedicated instruments, high definition optics, new devices) have increased the quality and the range of operations that may be safely performed by VATS. Second, the well-known advantages of minimally invasive surgery (limited surgical trauma, low complications, short hospitalization, better cosmetic results, and early recovery of pulmonary function) may have a particular positive clinical impact in this subset of patients, often affected by myasthenia gravis. Third, the high definition of modern preoperative diagnostic radiological techniques allows for a precise assessment of the extent of the recurrent disease and a reliable prediction of the surgical resectability. In this way, it is possible to plan the best approach and the extension of surgical resection.

It is well established that the minimally invasive approach cannot threaten the quality of operation in term of radicality of resection. This represents the most important prognostic factor. To date, single pleuro-pulmonary or mediastinal unilateral non-invasive recurrences represent the best indication for VATS resection, but the role of minimally invasive approach for more extended operations (i.e., partial or extended pleurectomy) needs to be clarified.

Conclusions

In conclusion, surgery for recurrent thymoma is effective

Table 1 Literature review on surgical treatment of recurrent thymoma

Author/year (Reference)	No. patients	Site of recurrence			Treatment			Surgical access		
		Locoregional	Distant	Locoregional and distant	No treatment	CT and/or RT	Surgery alone or plus CT/RT	VATS	Thoracotomy	Sternotomy
Regnard 1997 (5)	28	22	–	6	–	–	28	ND	ND	ND
Ruffini 1997 (4)	30	13	17	–	–	–	30	0	ND	ND
Haniuda 2001 (20)	24	19	–	5	–	9	15	0	14	1
Rea 2004 (2)	16	3	3	10	–	5	11	ND	ND	ND
Lucchi 2009 (15)	20	20	–	–	–	–	20	0	19	1
Margaritora 2011 (6)	43	37	6	–	1	12	30	ND	ND	ND
Bott 2011 (9)	25	19	6	–	–	14	11	0	9	2
Hamaji 2012 (14)	48	38	10	–	11	12	25	ND	ND	ND
Bae 2012 (26)	41	34	5	2	9	17	15	1	13	1
Sandri 2014 (18)	81	62	6	13	6	14	61	ND	ND	ND
Murakawa 2015 (19)	6	6	–	–	–	–	6	3	3	0
Marulli 2015 (17)	103	80	14	9	–	30	73	3	56	14

ND, no data; CT, chemotherapy; RT, radiotherapy; VATS, video assisted thoracic surgery.

and safe, leading to good long-term survival rates. Complete macroscopic resection is the goal also for recurrent disease and should be accomplished, if possible. In our opinion, the role of VATS for recurrent thymoma is still unclear and not well explored. It is very likely that over the following years, an increasing amount of research will be available aiming at a more precise and established definition of the indications for minimally invasive approaches in thymic relapses.

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Footnote

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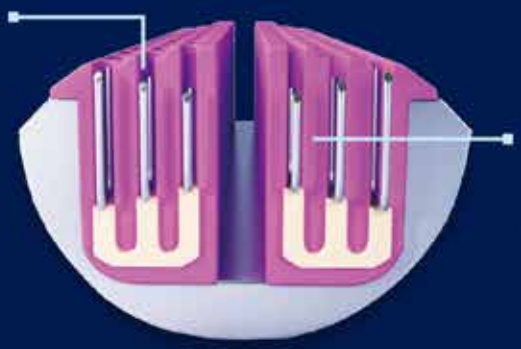

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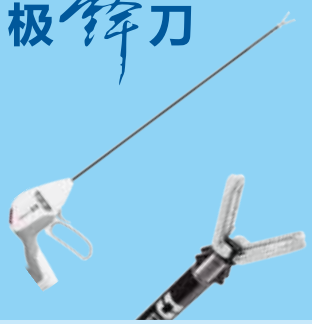

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