Journal of Thoracic Disease

Volume 8 Nomber 4 April 2016 Pages 640-743

Vol 8, No 4 April 2016

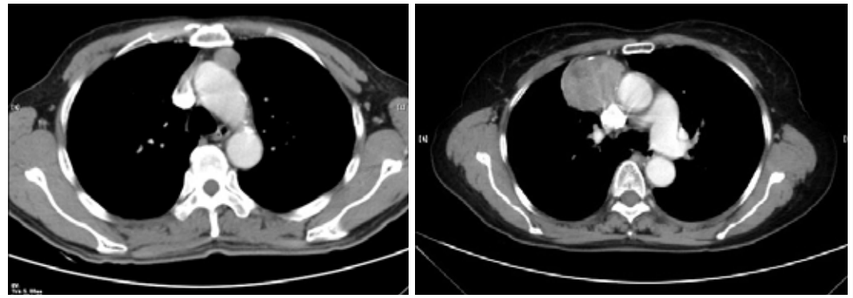
ISSN 2072-1439

JOURNAL of THORACIC DISEASE

jtd.amegroups.com

FOCUSED ISSUE: Thymic Malignancy—Perspectives from the Chinese Alliance for Research in Thymomas (ChART)

Guest Editor: Wentao Fang



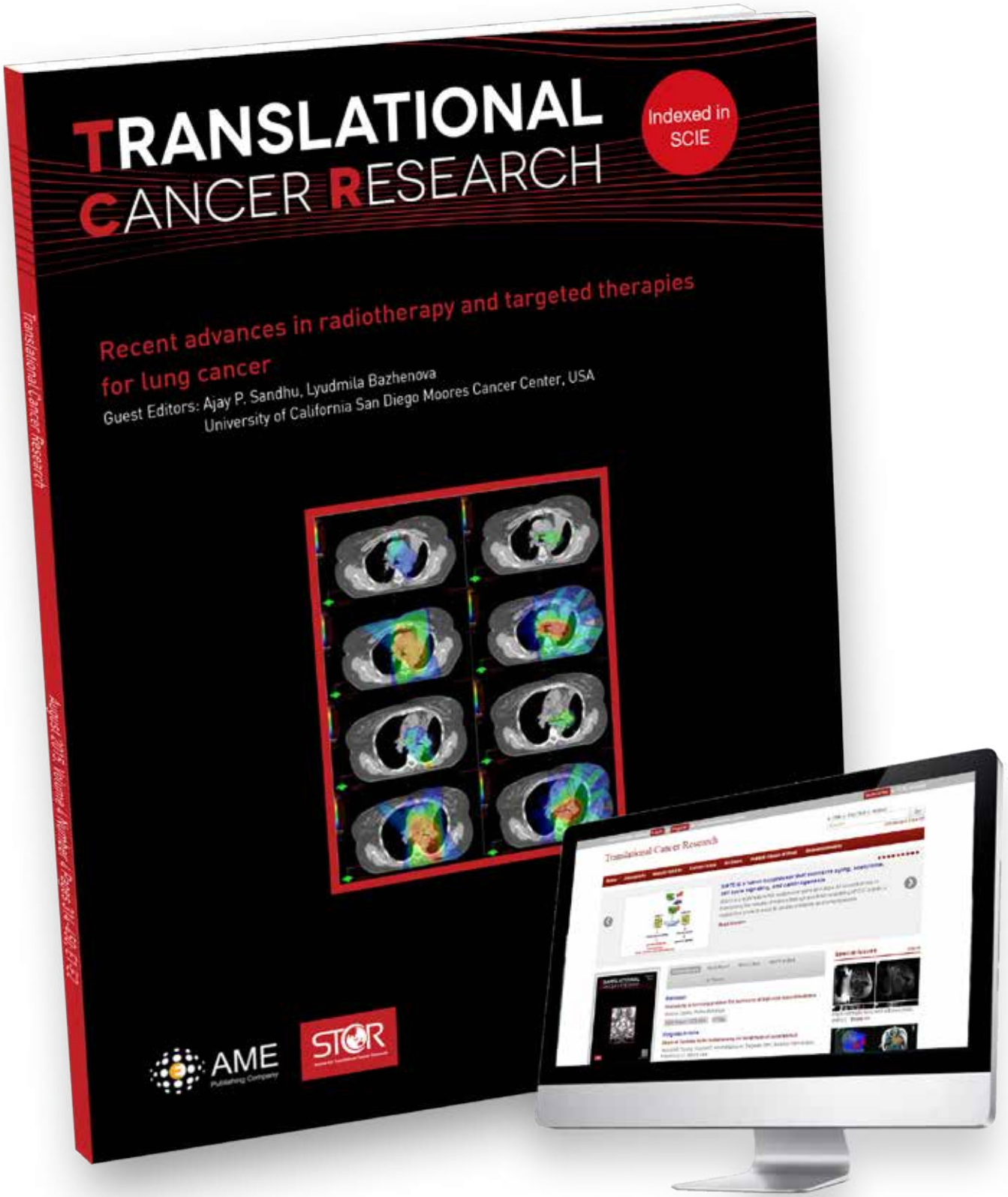
The Official Publication of

AME Publishing Company

2014 IMPACT FACTOR 1.783

Indexed in PubMed, SCI


Vol 7, No 10 October 2015
ISSN 2072-1439
2014
IMPACT FACTOR
1.783
JOURNAL of THORACIC DISEASE
www.jthoracdis.com
The Official Publication of
AME
Journal of Thoracic Disease


TRANSLATIONAL CANCER RESEARCH
Indexed in SCIE
Recent advances in radiotherapy and targeted therapies for lung cancer
Guest Editors: Ajay P. Sandhu, Lyudmila Bazhenova
University of California San Diego Moores Cancer Center, USA
AME Publishing Company
STCR
Translational Cancer Research

Introduction to
Annals of Cardiothoracic Surgery

Editor-in-Chief: Tristan D. Yan

JOVS
Journal of Visualized Surgery

Editor-in-Chief: Alan D. L. Sihoe

The Journal of Visualized Surgery (ISSN 2221-2965; J Vis Surg; JOVS) is an international, Open Access, multi-media periodical focusing on instructional and educational video clips, photos, schematics of Visualized Surgical procedures, rather than lengthy text.

Features of JOVS

· Highlights the roles of each member of the multi-disciplinary surgical team

· Represents a source of the latest developments in video-enabled operations

· Serves as an archive of video instructions from the masters of such surgery from around the globe

JOVS is embarking on an exciting expedition into the hugely important world of Visualized Surgery. We warmly welcome you to join this voyage as an author, a reader, a reviewer … and as a friend !

jovs.amegroups.com

AME Publishing Company


Print ISSN 2305-5839
Online ISSN 2305-5847
Vol 3, No 20 Nov 2015
ANNALS OF TRANSLATIONAL MEDICINE
Annals of Translational Medicine
Official Publication
Tailored by
inspire 2 live


Print ISSN 2218-6751
Online ISSN 2226-4477
TRANSLATIONAL LUNG CANCER RESEARCH
Official publication of Society for Translational Cancer Research (STCR)
Endorsed by the Spanish Lung Cancer Group (SLCG)
and the Bonnie J. Addario Lung Cancer Foundation (ALCF).
Vol 4, No 2. April 2015
SPECIAL ISSUE: Molecular Genetics of Lung Cancer
Guest Editor: Wendy A. Cooper
tlcr.amegroups.com
TLCR
AME
STCR
GE
CP

Aims and Scope

The *Journal of Thoracic Disease* (JTD, J Thorac Dis, pISSN: 2072-1439; eISSN: 2077-6624) was founded in Dec 2009, indexed in PubMed/PubMed Central in Dec 2011, and Science Citation Index (SCI) on Feb 4, 2013. It is published quarterly (Dec 2009- Dec 2011), bimonthly (Jan 2012- Dec 2013), and monthly (Jan 2014-), and openly distributed worldwide. JTD publishes manuscripts that describe new findings in the field to provide current, practical information on the diagnosis and treatment of conditions related to thoracic disease (lung disease, cardiac disease, breast disease and esophagus disease). Original articles are considered most important and will be processed for rapid review by the members of Editorial Board. Clinical trial notes, Cancer genetics reports, Epidemiology notes and Technical notes are also published. Case reports implying new findings that have significant clinical impact are carefully processed for possible publication. Review articles are published in principle at the Editor's request. There is no fee involved throughout the publication process. The acceptance of the article is based on the merit of quality of the manuscripts. All the submission and reviewing are conducted electronically so that rapid review is assured.

The Official Publication of:

- Guangzhou Institute of Respiratory Disease (GIRD)
- China State Key Laboratory of Respiratory Disease
- First Affiliated Hospital of Guangzhou Medical University
- Society for Thoracic Disease (STD)

Endorsed by:

- International COPD Coalition (ICC)

Editorial Correspondence

HK office:
Daoyuan Wang.
AME Publishing Company
Room 604, 6/F Hollywood Center, 77-91 Road, Sheung Wan, Hong Kong.

Guangzhou office:
Guangqiao Zeng, MD
Guangzhou Institute of Respiratory Disease & The First Affiliated Hospital of Guangzhou Medical University.
No. 151, Yanjiang Rd, Guangzhou 510120, China.

Email: jtd@amepc.org
jtd.amegroups.com

Note to NIH Grantees

Pursuant to NIH mandate, AME Publishing Company will post the accepted version of contributions authored by NIH grant-holders to PubMed Central upon acceptance. This accepted version will be made publicly available 2 months after publication. For further information, see www.amepc.org

Conflict of Interest Policy for Editors

The full policy and the Editors' disclosure statements are available online at: jtd.amegroups.com

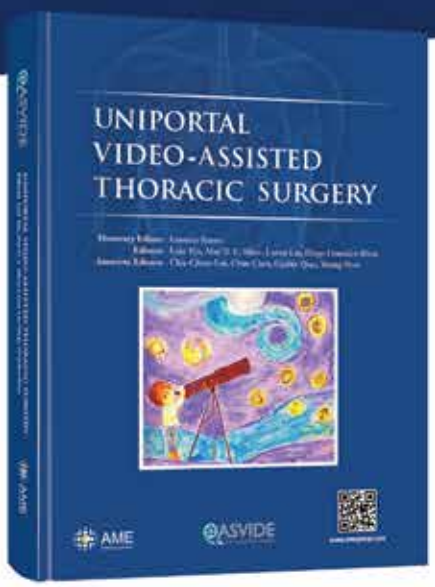
Cover Image:

A tumor attenuation is considered homogeneous or heterogeneous (See P648 in this issue).

For submission instructions, subscription and all other information, please visit jtd.amegroups.com

UNIPORTAL VIDEO-ASSISTED THORACIC SURGERY

Stay Calm, Think Uniportal



Honorary Editor:
Gaetano Rocco

Editors:
Lijie Tan
Alan D. L. Sihoe
Lunxu Liu
Diego Gonzalez-Rivas

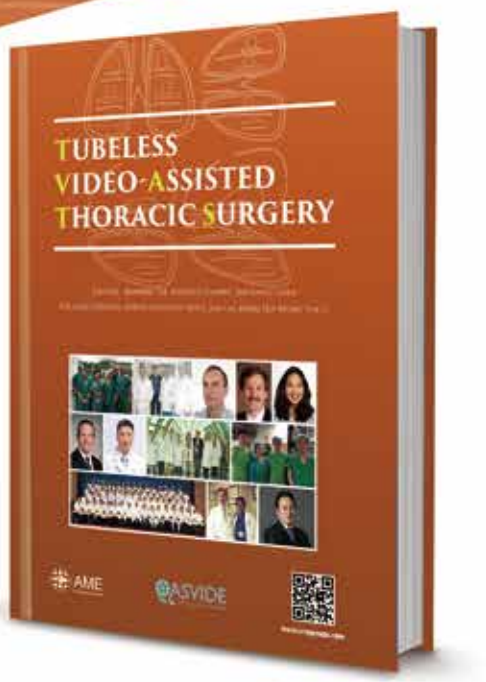
Associate Editors:
Chia-Chuan Liu
Chun Chen
Guibin Qiao
Yaxing Shen

amazon

AME Publishing Company

ASVIDE AME Surgical Video Database

TUBELESS VIDEO-ASSISTED THORACIC SURGERY



NO INTUBATION

NO CHEST DRAINAGE TUBE

NO URINARY CATHETER

amazon

EDITORS:

JIANXING HE, MD, EUGENIO POMPEO, MD

JIN-SHING CHEN, MD

ASSOCIATE EDITORS:

DIEGO GONZALEZ-RIVAS, MD, JUN LIU, MD

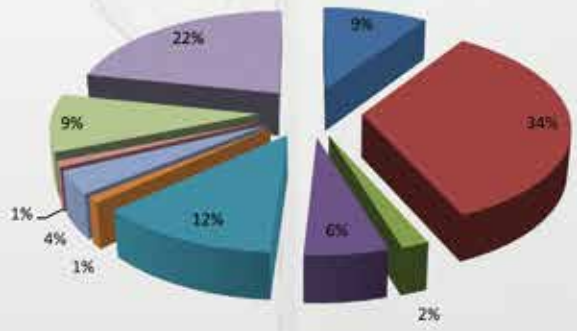
MING-HUI HUNG, MD, YIN LI, MD

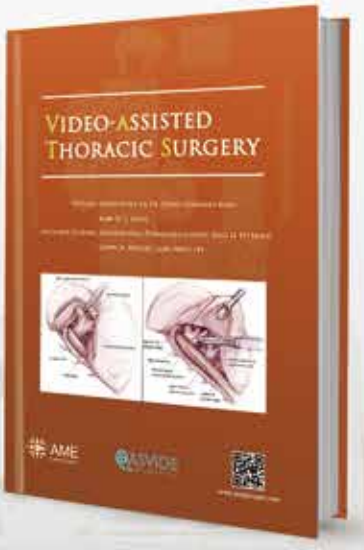
AME Publishing Company

ASVIDE AME Surgical Video Database

Video-assisted Thoracic Surgery

Editors: Jianxing He, Jie He,
Diego Gonzalez-Rivas,
Alan D. L. Sihoe
Associate Editors: Shugeng Gao, Dominique Gossot,
Rene H. Petersen, Gavin M. Wright,
Jang Ming Lee





AME Publishing Company

ASVIDE AME Surgical Video Database

amazon

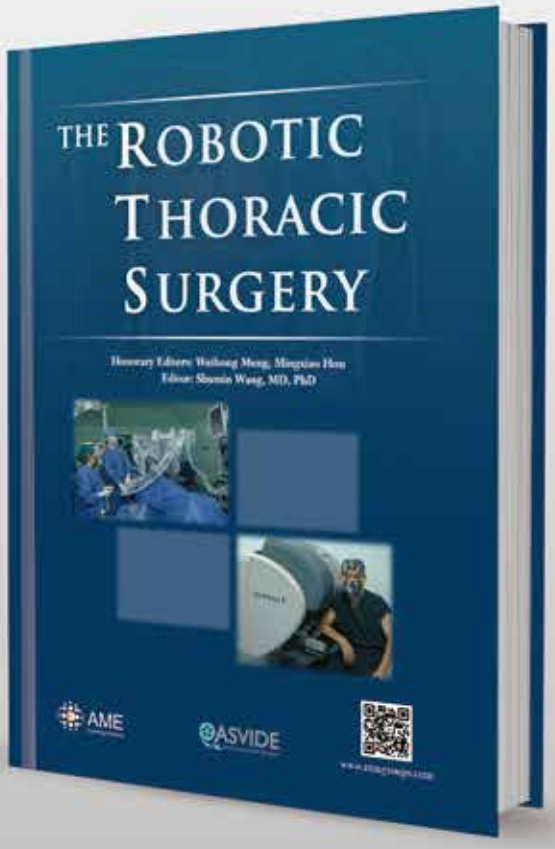
THE ROBOTIC THORACIC SURGERY

- *Pioneer in the academic arena dedicated to robotic thoracic surgery*
- *Featuring the state of the art and the international experience on robotic thoracic surgery*

Honorary Editors: Weihong Meng, Mingxiao Hou

Editor: Shumin Wang, MD, PhD

Please scan the above code for purchase information



AME Publishing Company

ASVIDE AME Surgical Video Database

Table of Contents

Preface

640 ***Journal of Thoracic Disease*** **Focused Issue: Management of Thymoma**
Robert J. Korst, MD

Consensus

641 **Management of thymic tumors—consensus based on the Chinese Alliance for Research in Thymomas Multi-institutional retrospective studies**
Wentao Fang, Jianhua Fu, Yi Shen, Yucheng Wei, Lijie Tan, Peng Zhang, Yongtao Han, Chun Chen, Renquan Zhang, Yin Li, Keneng Chen, Hezhong Chen, Yongyu Liu, Youbing Cui, Yun Wang, Liewen Pang, Zhentao Yu, Xinming Zhou, Yangchun Liu, Gang Chen; Members of the Chinese Alliance for Research in Thymomas

Original Article

646 **CT staging and preoperative assessment of resectability for thymic epithelial tumors**
Yan Shen, Zhitao Gu, Jianding Ye, Teng Mao, Wentao Fang, Wenhu Chen

656 **Pretreatment biopsy for histological diagnosis and induction therapy in thymic tumors**
Jie Yue, Zhitao Gu, Zhentao Yu, Hongdian Zhang, Zhao Ma, Yuan Liu, Wentao Fang; Members of the Chinese Alliance for Research in Thymomas

665 **Preoperative induction therapy for locally advanced thymic tumors: a retrospective analysis using the ChART database**
Yucheng Wei, Zhitao Gu, Yi Shen, Jianhua Fu, Liejie Tan, Peng Zhang, Yongtao Han, Chun Chen, Renquan Zhang, Yin Li, Keneng Chen, Hezhong Chen, Yongyu Liu, Youbing Cui, Yun Wang, Liewen Pang, Zhentao Yu, Xinming Zhou, Yangchun Liu, Yuan Liu, Wentao Fang; Members of the Chinese Alliance for Research in Thymomas

673 **Perioperative outcomes and long-term survival in clinically early-stage thymic malignancies: video-assisted thoracoscopic thymectomy versus open approaches**
Hao Wang, Zhitao Gu, Jianyong Ding, Lijie Tan, Jianhua Fu, Yi Shen, Yucheng Wei, Peng Zhang, Yongtao Han, Chun Chen, Renquan Zhang, Yin Li, Keneng Chen, Hezhong Chen, Yongyu Liu, Youbing Cui, Yun Wang, Liewen Pang, Zhentao Yu, Xinming Zhou, Yangchun Liu, Yuan Liu, Wentao Fang; Members of the Chinese Alliance for Research in Thymomas

680 **Thymectomy versus tumor resection for early-stage thymic malignancies: a Chinese Alliance for Research in Thymomas retrospective database analysis**
Zhitao Gu, Jianhua Fu, Yi Shen, Yucheng Wei, Lijie Tan, Peng Zhang, Yongtao Han, Chun Chen, Renquan Zhang, Yin Li, Keneng Chen, Hezhong Chen, Yongyu Liu, Youbing Cui, Yun Wang, Liewen Pang, Zhentao Yu, Xinming Zhou, Yangchun Liu, Yuan Liu, Wentao Fang; Members of the Chinese Alliance for Research in Thymomas

687 **The role of postoperative radiotherapy for stage I/II/III thymic tumor—results of the ChART retrospective database**
Qianwen Liu, Zhitao Gu, Fu Yang, Jianhua Fu, Yi Shen, Yucheng Wei, Lijie Tan, Peng Zhang, Yongtao Han, Chun Chen, Renquan Zhang, Yin Li, Keneng Chen, Hezhong Chen, Yongyu Liu, Youbing Cui, Yun Wang, Liewen Pang, Zhentao Yu, Xinming Zhou, Yangchun Liu, Jin Xiang, Yuan Liu, Wentao Fang; Members of the Chinese Alliance for Research in Thymomas

696 **The application of postoperative chemotherapy in thymic tumors and its prognostic effect**
Ke Ma, Zhitao Gu, Yongtao Han, Jianhua Fu, Yi Shen, Yucheng Wei, Lijie Tan, Peng Zhang, Chun Chen, Renquan Zhang, Yin Li, Keneng Chen, Hezhong Chen, Yongyu Liu, Youbing Cui, Yun Wang, Liewen Pang, Zhentao Yu, Xinming Zhou, Yangchun Liu, Yuan Liu, Wentao Fang; Members of the Chinese Alliance for Research in Thymomas

705 **Outcome of nonsurgical treatment for locally advanced thymic tumors**
Chang-Lu Wang, Lan-Ting Gao, Chang-Xing Lv, Lei Zhu, Wen-Tao Fang

711 **Postoperative survival for patients with thymoma complicating myasthenia gravis—preliminary retrospective results of the ChART database**
Fangrui Wang, Liewen Pang, Jianhua Fu, Yi Shen, Yucheng Wei, Lijie Tan, Peng Zhang, Yongtao Han, Chun Chen, Renquan Zhang, Yin Li, Keneng Chen, Hezhong Chen, Yongyu Liu, Youbing Cui, Yun Wang, Zhentao Yu, Xinming Zhou, Yangchun Liu, Yuan Liu, Zhitao Gu, Wentao Fang; Members of the Chinese Alliance for Research in Thymomas

718 **Clinicopathological analysis of 241 thymic epithelial tumors—experience in the Shanghai Chest Hospital from 1997–2004**
Lei Zhu, Jie Zhang, Alexander Marx, Christel Weiss, Wen-Tao Fang

727 **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**
Guanghui Liang, Zhitao Gu, Yin Li, Jianhua Fu, Yi Shen, Yucheng Wei, Lijie Tan, Peng Zhang, Yongtao Han, Chun Chen, Renquan Zhang, Keneng Chen, Hezhong Chen, Yongyu Liu, Youbing Cui, Yun Wang, Liewen Pang, Zhentao Yu, Xinming Zhou, Yangchun Liu, Yuan Liu, Wentao Fang; Members of the Chinese Alliance for Research in Thymomas

Review Article

738 **The enlightenments from ITMIG Consensus on WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting**
Jie Wu, Wentao Fang, Gang Chen

Preface

Journal of Thoracic Disease Focused Issue: Management of Thymoma

Thymic epithelial tumors (TET) are uncommon tumors of the anterior mediastinum. Despite their rarity, they are actually the most common tumor type located in this mediastinal compartment. TET are comprised of three main types: thymoma (85–90%), thymic carcinoma (8–12%), and neuroendocrine tumors of the thymus (1–4%). Given the rare incidence of TET, it is not surprising that evidence-based practice patterns have not evolved to the extent that has been seen with other, more common malignancies. The published literature consists mainly of case reports and series, a few prospective, observational clinical trials, and no randomized controlled trials. Perhaps the most significant reason for the paucity of high quality published research is any given institution sees only a handful of cases per year, and the lack of the ability to perform coordinated research amongst centers.

The only way to conduct high quality research regarding TET is to develop the infrastructure and commitment to coordinate studies between multiple institutions. To this end, a notable organization that has taken on this challenge in China is the Chinese Alliance for Research in Thymomas (ChART). Established in 2012, ChART organized retrospective data from over 2,300 patients from multiple institutions into a single database for research purposes. This dataset provides the basis for many of the studies presented in this Focused Issue of the *Journal of Thoracic Disease*.

In addition to performing its own coordinated research, ChART has also contributed its data to the much larger, worldwide retrospective database of the International Thymic Malignancy Interest Group (ITMIG). ITMIG, founded in 2010, is an organization dedicated to research, education and support for patients with thymic malignancies with over 600 members worldwide. Building upon its success in developing its retrospective database comprising data from over 7,000 cases, ITMIG has also developed a prospective data collection mechanism that is utilized by member institutions on six continents, and is linked to a virtual tissue bank. These extremely large datasets allow ITMIG and its members to perform research studies that were never conceivable in the past due to the rarity of TET. On the educational front, ITMIG has established standard practice guidelines for clinicians who treat patients with TET, and has produced other educational tools and documents aimed at educating not only physicians, but also patients about these rare tumors.

It is only through such collaborative mechanisms and organizations that knowledge regarding thymic tumors will be advanced in the future, which should also serve as model for performing research for other rare diseases. This Focused Issue of the *Journal of Thoracic Disease* is evidence of the progress allowed only through such collaboration.

Robert J. Korst, MD

Robert J. Korst, MD

Medical Director, The Daniel and Gloria Blumenthal Cancer Center, Director, Thoracic Surgery, The Valley Health System, Chair, Oncology Services, Valley Medical Group, Paramus, NJ 07652, USA.

(*Email: korsro@valleyhealth.com*)

doi: 10.21037/jtd.2016.02.01

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

View this article at: http://dx.doi.org/10.21037/jtd.2016.02.01

Cite this article as: Korst RJ. *Journal of Thoracic Disease* Focused Issue: Management of Thymoma. J Thorac Dis 2016;8(4):640. doi: 10.21037/jtd.2016.02.01

Consensus

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

Wentao Fang[1], Jianhua Fu[2], Yi Shen[3], Yucheng Wei[3], Lijie Tan[4], Peng Zhang[5], Yongtao Han[6], Chun Chen[7], Renquan Zhang[8], Yin Li[9], Keneng Chen[10], Hezhong Chen[11], Yongyu Liu[12], Youbing Cui[13], Yun Wang[14], Liewen Pang[15], Zhentao Yu[16], Xinming Zhou[17], Yangchun Liu[18], Gang Chen[19]; Members of the Chinese Alliance for Research in Thymomas[a]

[1]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [2]Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China; [3]Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266001, China; [4]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [5]Department of Endocrinology, Tianjin Medical University General Hospital, Tianjin 300052, China; [6]Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu 610041, China; [7]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou 350001, China; [8]Department of Thoracic Surgery, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [9]Department of Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, China; [10]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing 100142, China; [11]Department of Cardiothoracic Surgery, Changhai Hospital, Shanghai 200433, China; [12]Department of Thoracic Surgery, Liaoning Cancer Hospital, Shenyang 110042, China; [13]Department of Thoracic Surgery, First Affiliated Hospital of Jilin University, Changchun 130021, China; [14]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China; [15]Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200032, China; [16]Department of Esophageal Cancer, Tianjin Cancer Hospital, Tianjin 300060, China; [17]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China; [18]Department of Thoracic Surgery, Jiangxi People's Hospital, Nanchang 330006, China; [19]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China

Correspondence to: Wentao Fang. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 Huaihai Road West, Shanghai 200030, China. Email: vwtfang12@shchest.org.

Submitted Mar 17, 2015. Accepted for publication Mar 18, 2015.
doi: 10.21037/jtd.2016.03.23
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.23

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.

Acknowledgements

None.

Footnote

[a]*Members of the Chinese Alliance for Research in Thymomas* (*ChART*): Yi Shen, Yucheng Wei, Affiliated Hospital of Qingdao University, Qingdao, China; Yin Li, and Guanghui Liang, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Keneng Chen and Hao Fu, Beijing Cancer Hospital, Beijing, China; Hezhong Chen and Shihua Yao, Changhai Hospital, Shanghai, China; Youbin Cui and Yanzhong Xin, First Affiliated Hospital of Jilin University, Changchun, China; Renquan Zhang and Ningning Kang, First Hospital of Anhui Medical University, Hefei, China; Lijie Tan, Jianyong Ding, Hao Wang, Gang Chen, and Jie Wu, Zhongshan Hospital, Fudan University, Shanghai, China; Chun Chen and Wei Zheng, Fujian Medical University Union Hospital, Fuzhou, China; Liewen Pang and Fangrui Wang, Huashan Hospital, Fudan University, Shanghai, China; Yangchun Liu and Qing Lin, Jiangxi People's Hospital, Nanchang, China; Yongyu Liu and Yongkai Wu, Liaoning Cancer Hospital, Shenyang, China; Wentao Fang, Jie Zhang, Yan Shen, Changlu Wang, Lei Zhu and Zhitao Gu, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Yongtao

Han, Lin Peng, Sichuan Cancer Hospital, Chengdu, China; Jianhua Fu and Qianwen Liu, Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Zhentao Yu and Jie Yue, Tianjin Cancer Hospital, Tianjin, China; Peng Zhang and Yuan Chen, Tianjin Medical University General Hospital, Tianjin, China; Yun Wang and Yingcai Geng, West China Hospital, Sichuan University, Chengdu, China; Xinming Zhou and Hongguang Zhao, Zhejiang Cancer Hospital, Hangzhou, China.

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

References

1. Detterbeck F, Parsons AM. Thymic tumors: a review of current diagnosis, classification, and treatment. In: Patterson GA, Cooper JD, Deslauriers J, et al.(Eds.) Thoracic and Esophageal Surgery. 3rd Ed. Philadelphia: Elsevier; 2008:1589-614.
2. Detterbeck FC, Zeeshan A. Thymoma: current diagnosis and treatment. Chin Med J (Engl) 2013;126:2186-91.
3. Huang J, Detterbeck FC, Wang Z, et al. Standard outcome measures for thymic malignancies. J Thorac Oncol 2010;5:2017-23.
4. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485-92.
5. Travis WD, Brambilla E, Müller-Hermelink HK, et al. Pathology & Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press. 2004.
6. Wang F, Pang L, Fu J, et al. Postoperative survival for patients with thymoma complicating myasthenia gravis—preliminary retrospective results of the ChART database. J Thorac Dis 2016;8:S422-8.
7. Fang W, Chen W, Chen G, et al. Surgical management of thymic epithelial tumors: a retrospective review of 204 cases. Ann Thorac Surg 2005;80:2002-7.
8. Wang H, Gu Z, Ding J, et al. Perioperative outcomes and long-term survival in clinically early-stage thymic malignancies: video-assisted thoracoscopic thymectomy versus open approaches. J Thorac Dis 2016;8:S384-90.
9. Gu Z, Fu J, Shen Y, et al. Thymectomy versus tumor resection for early-stage thymic malignancies: a Chinese Alliance for Research in Thymomas retrospective database analysis. J Thorac Dis 2016;8:S391-7.
10. Shen Y, Gu Z, Ye J, et al. CT staging and preoperative assessment of resectability for thymic epithelial tumors. J Thorac Dis 2016;8:S357-66.
11. Nicholson AG, Detterbeck FC, Marino M, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposals for the T Component for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol 2014;9:S73-80.
12. Wei Y, Gu Z, Shen Y, et al. Preoperative induction therapy for locally advanced thymic tumors: a retrospective analysis using the ChART database. J Thorac Dis 2016;8:S376-83.
13. Wang CL, Gao LT, Lv CX, et al. Outcome of nonsurgical treatment for locally advanced thymic tumors. J Thorac Dis 2016;8:S416-21.
14. Yue J, Gu Z, Yu Z, et al. Pretreatment biopsy for histological diagnosis and induction therapy in thymic tumors. J Thorac Dis 2016;8:S367-75.
15. Zhu L, Zhang J, Marx A, et al. Clinicopathological analysis of 241 thymic epithelial tumors—experience in the Shanghai Chest Hospital from 1997–2004. J Thorac Dis 2016;8:S429-37.
16. Liu Q, Gu Z, Yang F, et al. The role of postoperative radiotherapy for stage I/II/III thymic tumor—results of the ChART retrospective database. J Thorac Dis 2016;8:S398-406.
17. Ma K, Gu Z, Han Y, et al. The application of postoperative chemotherapy in thymic tumors and its prognostic effect. J Thorac Dis 2016;8:S407-15.

Cite this article as: Fang W, Fu J, Shen Y, Wei Y, Tan L, Zhang P, Han Y, Chen C, Zhang R, Li Y, Chen K, Chen H, Liu Y, Cui Y, Wang Y, Pang L, Yu Z, Zhou X, Liu Y, Chen G; Members of the Chinese Alliance for Research in Thymomas. Management of thymic tumors—consensus based on the Chinese Alliance for Research in Thymomas Multi-institutional Retrospective Studies. J Thorac Dis 2016;8(4):641-645. doi: 10.21037/jtd.2016.03.23

Original Article

CT staging and preoperative assessment of resectability for thymic epithelial tumors

Yan Shen[1*], Zhitao Gu[2*], Jianding Ye[1], Teng Mao[2], Wentao Fang[2], Wenhu Chen[2]

[1]Department of Radiology, [2]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China

Contributions: (I) Conception and design: W Fang; (II) Administrative support: None; (III) Provision of study materials or patients: Y Shen, J Ye, T Mao, W Chen; (IV) Collection ad assembly of data: Z Gu, Y Shen; (V) Data analysis and interpretation: Z Gu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Wentao Fang, MD. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 Huaihai Road West, Shanghai 200030, China. Email: vwtfang@hotmail.com.

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

Submitted Jan 10, 2016. Accepted for publication Feb 12, 2016.
doi: 10.21037/jtd.2016.03.01
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.01

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

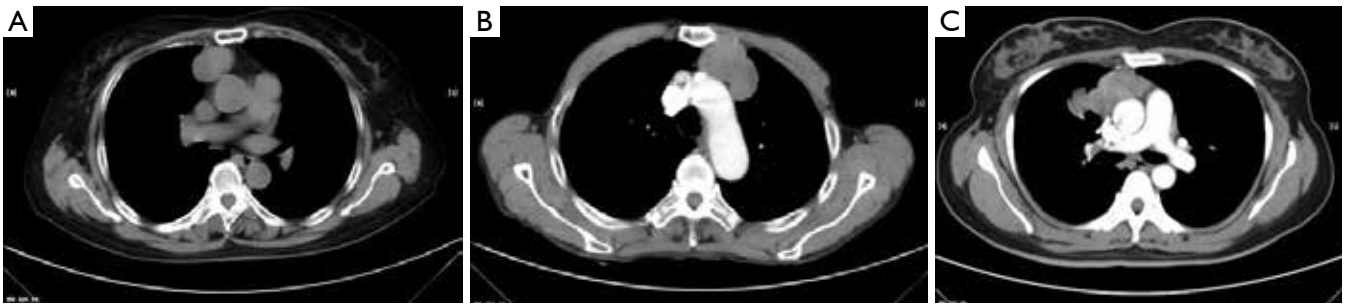


Figure 1 A tumor contour is considered smooth in the absence of spiculation, partial smooth or unsmooth; as well as, tumor shape is considered round, lobulated and irregular. (A) Round shape with smooth counter; (B) lobulated shape with partial smooth counter; (C) irregular shape with unsmooth counter.

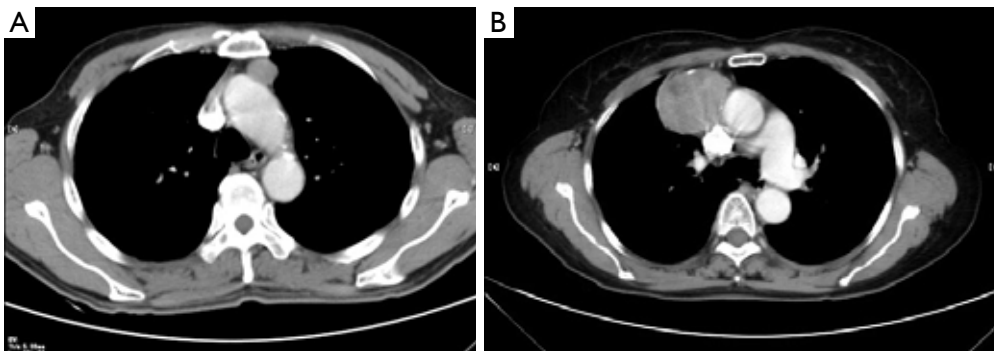


Figure 2 A tumor attenuation is considered homogeneous or heterogeneous. (A) Enhanced CT of a homogeneous tumor; (B) enhanced CT of a heterogeneous tumor.

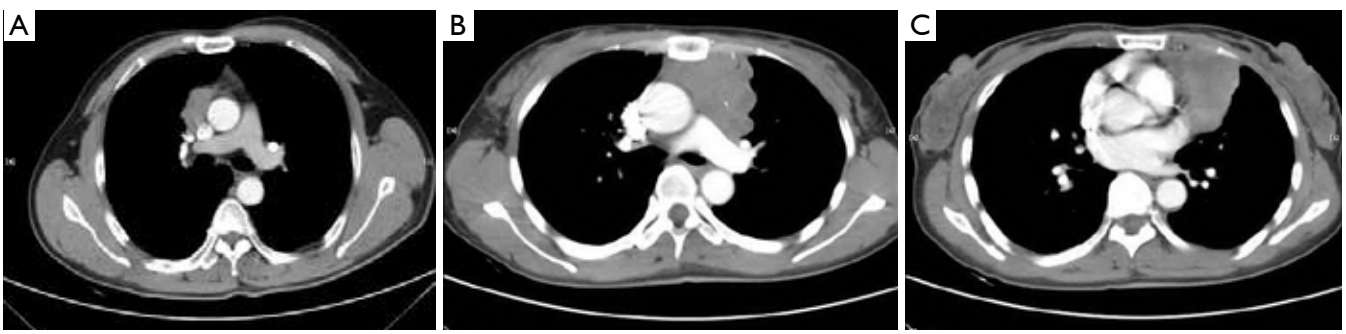


Figure 3 Tumor invasion of surrounding structures, as mediastinal pleura, lung or pericardium is showed on CT. (A) If the tumor exhibited a lobulated interface of the tumor with the adjacent mediastinum pleura, it was characterized as pleura invasion; (B) when the tumor abutted ≥50% of the lung and there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

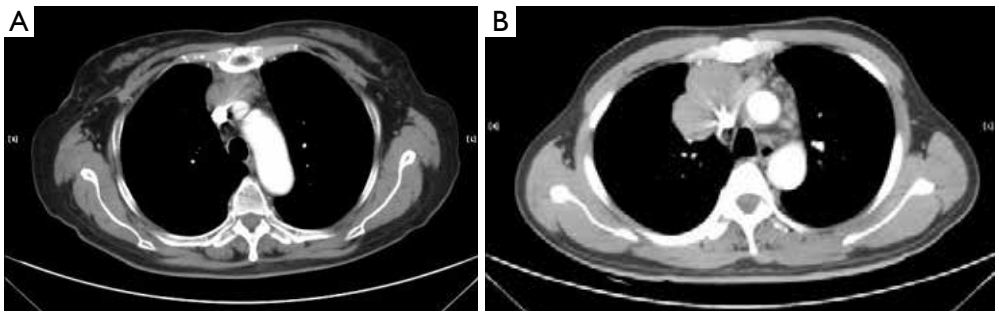


Figure 4 Tumor invasion of vessels is showed on CT. (A) When the tumor abutted ≥50% of the vascular circumference with loss of the fat plane and the vascular wall is rough, involvement of the vessel was considered present; (B) when the vascular lumen was directly penetrated by the tumor, involvement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

Acknowledgements

Funding: This work was partially sponsored by the Shanghai Municipal Commission of Health and Family Planning Scientific Research Task (201440442).

Footnote

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

References

1. Duwe BV, Sterman DH, Musani AI. Tumors of the mediastinum. Chest 2005;128:2893-909.
2. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878-84; discussion 884-5.
3. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485-92.
4. Lardinois D, Rechsteiner R, Läng RH, et al. Prognostic relevance of Masaoka and Müller-Hermelink classification in patients with thymic tumors. Ann Thorac Surg 2000;69:1550-5.
5. Marom EM. Imaging thymoma. J Thorac Oncol 2010;5:S296-303.
6. Marom EM, Milito MA, Moran CA, et al. Computed tomography findings predicting invasiveness of thymoma. J Thorac Oncol 2011;6:1274-81.
7. Tomiyama N, Müller NL, Ellis SJ, et al. Invasive and noninvasive thymoma: distinctive CT features. J Comput Assist Tomogr 2001;25:388-93.
8. Priola AM, Priola SM, Di Franco M, et al. Computed tomography and thymoma: distinctive findings in invasive and noninvasive thymoma and predictive features of recurrence. Radiol Med 2010;115:1-21.
9. Qu YJ, Liu GB, Shi HS, et al. Preoperative CT findings of thymoma are correlated with postoperative Masaoka clinical stage. Acad Radiol 2013;20:66-72.
10. Hayes SA, Huang J, Plodkowski AJ, et al. Preoperative computed tomography findings predict surgical resectability of thymoma. J Thorac Oncol 2014;9:1023-30.
11. Toker A, Sonett J, Zielinski M, et al. Standard terms, definitions, and policies for minimally invasive resection of thymoma. J Thorac Oncol 2011;6:S1739-42.
12. Marom EM, Rosado-de-Christenson ML, Bruzzi JF, et al. Standard report terms for chest computed tomography reports of anterior mediastinal masses suspicious for thymoma. J Thorac Oncol 2011;6:S1717-23.
13. Harris K, Elsayegh D, Azab B, et al. Thymoma

calcification: is it clinically meaningful? World J Surg Oncol 2011;9:95.
14. Fang W, Chen W, Chen G, et al. Surgical management of thymic epithelial tumors: a retrospective review of 204 cases. Ann Thorac Surg 2005;80:2002-7.
15. Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung Cancer 2004;44:369-79.
16. Wright CD, Choi NC, Wain JC, et al. Induction chemoradiotherapy followed by resection for locally advanced Masaoka stage III and IVA thymic tumors. Ann Thorac Surg 2008;85:385-9.

Cite this article as: Shen Y, Gu Z, Ye J, Mao T, Fang W, Chen W. CT staging and preoperative assessment of resectability for thymic epithelial tumors. J Thorac Dis 2016;8(4):646-655. doi: 10.21037/jtd.2016.03.01

Original Article

Pretreatment biopsy for histological diagnosis and induction therapy in thymic tumors

Jie Yue[1*], Zhitao Gu[2*], Zhentao Yu[1], Hongdian Zhang[1], Zhao Ma[1], Yuan Liu[2], Wentao Fang[2]; Members of the Chinese Alliance for Research in Thymomas[a]

[1]Department of Esophageal Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy of Tianjin City, Tianjin 300060, China; [2]Department of Thoracic Surgery, Shanghai Chest Hospital, Jiao Tong University, Shanghai 200030, China

Contributions: (I) Conception and design: Z Yu, W Fang; (II) Administrative support: None; (III) Provision of study materials or patients: Members of ChART; (IV) Collection ad assembly of data: J Yue, H Zhang, Z Ma, Z Gu; (V) Data analysis and interpretation: J Yue, Z Gu, Y Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Zhentao Yu, MD. Department of Esophageal Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy of Tianjin City, Tianjin 300060, China. Email: yuzhtao@hotmail.com; Wentao Fang. Department of Thoracic Surgery, Shanghai Chest Hospital, Jiao Tong University, Shanghai 200030, China. Email: vwtfang12@shchest.org.

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

Submitted Jan 23, 2016. Accepted for publication Feb 25, 2016.
doi: 10.21037/jtd.2016.03.04
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.04

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.

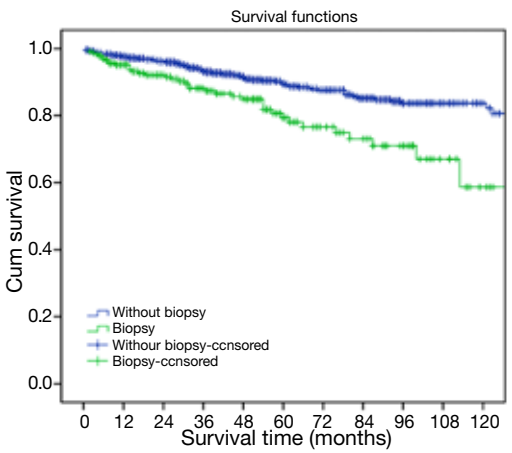


Figure 1 Survivals in patients with or without pretreatment biopsy for histological diagnosis.

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).

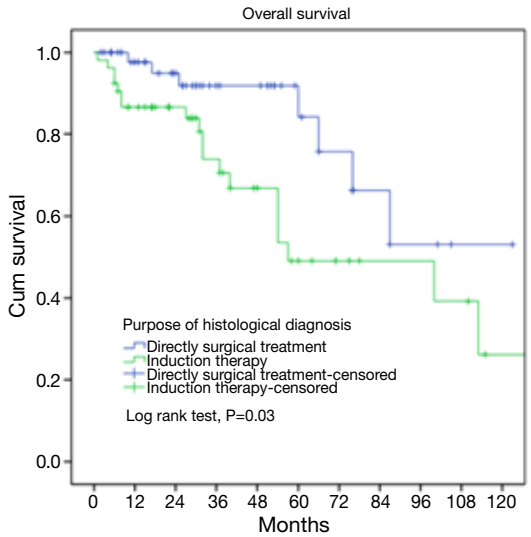


Figure 2 Survivals in patients who had induction therapy or upfront surgery after biopsy.

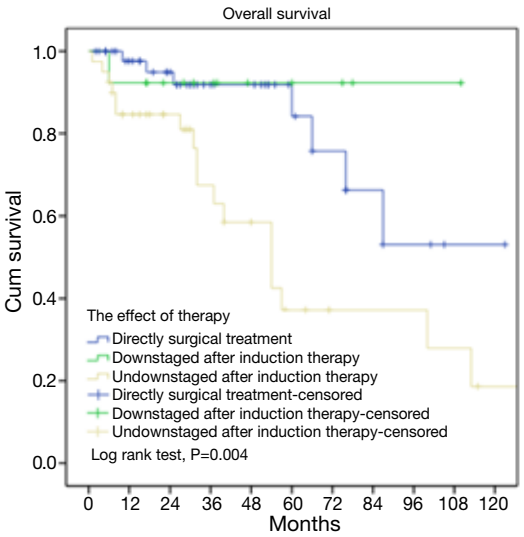


Figure 3 Survivals in tumors downstaged or not downstaged after induction therapy (subgroup) and those having upfront surgery after biopsy.

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	

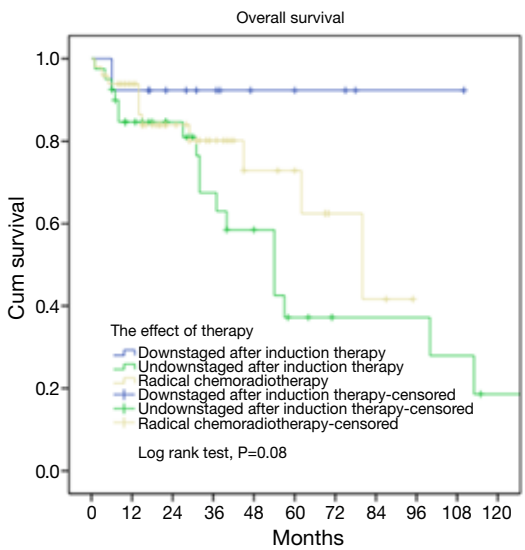


Figure 4 Survivals in tumors downstaged or not downstaged after induction therapy (subgroup) and those having definitive chemoradiotherapy.

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.

Acknowledgements

None.

Footnote

[a]*Members of Chinese Alliance for Research in Thymomas* (*ChART*): Yi Shen, Yucheng Wei, Affiliated Hospital of Qingdao University, Shandong, China; Keneng Chen, Hao Fu, Beijing Cancer Hospital, Beijing, China; Hezhong Chen, Shihua Yao, Changhai Hospital, Shanghai, China; Youbin Cui, Yanzhong Xin, First Affiliated Hospital of Jilin University, Jilin, China; Renquan Zhang, Ningning

Kang, First Hospital of Anhui Medical University, Anhui, China; Lijie Tan, Jianyong Ding, Hao Wang, Zhongshan Hospital, Fudan University, Shanghai, China; Chun Chen, Wei Zheng, Fujian Medical University Union Hospital, Fujian, China; Yin Li, Guanghui Liang, Affiliated Cancer Hospital of Zhengzhou University, Henan, China; Liewen Pang, Fangrui Wang, Huashan Hospital, Fudan University, Shanghai, China; Yangchun Liu, Qing Lin, Jiangxi People's Hospital, Jiangxi, China; Yongyu Liu, Yongkai Wu, Liaoning Cancer Hospital, Liaoning, China; Wentao Fang, Zhitao Gu, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Yongtao Han, Lin Peng, Sichuan Cancer Hospital, Sichuan, China; Jianhua Fu, Qianwen Liu, Sun Yat-sen University Cancer Center, Guangdong, China; Zhentao Yu, Jie Yue, Tianjin Cancer Hospital, Tianjin, China; Peng Zhang, Yuan Chen, Tianjin Medical University General Hospital, Tianjin, China; Yun Wang, Yingcai Geng, West China Hospital, Sichuan University, Sichuan, China; Xinming Zhou, Hongguang Zhao, Zhejiang Cancer Hospital, Zhejiang, China.

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

References

1. Maggi G, Giaccone G, Donadio M, et al. Thymomas. A review of 169 cases, with particular reference to results of surgical treatment. Cancer 1986;58:765-76.
2. Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and associations with subsequent malignancies. Int J Cancer 2003;105:546-51.
3. Casey EM, Kiel PJ, Loehrer PJ Sr. Clinical management of thymoma patients. Hematol Oncol Clin North Am 2008;22:457-73.
4. Ryu HS, Koh JS, Park S, et al. Classification of thymoma by fine needle aspiration biopsy according to WHO classification: a cytological algorithm for stepwise analysis in the classification of thymoma. Acta Cytol 2012;56:487-94.
5. Koppitz H, Rockstroh JK, Schüller H, et al. State-of-the-art classification and multimodality treatment of malignant thymoma. Cancer Treat Rev 2012;38:540-8.
6. Detterbeck FC. Clinical value of the WHO classification system of thymoma. Ann Thorac Surg 2006;81:2328-34.
7. Riely GJ, Huang J. Induction therapy for locally advanced thymoma. J Thorac Oncol 2010;5:S323-6.
8. Detterbeck FC, Zeeshan A. Thymoma: current diagnosis and treatment. Chin Med J (Engl) 2013;126:2186-91.
9. Cardillo G, Carleo F, Giunti R, et al. Predictors of survival in patients with locally advanced thymoma and thymic carcinoma (Masaoka stages III and IVa). Eur J Cardiothorac Surg 2010;37:819-23.
10. Modh A, Rimner A, Allen PK, et al. Treatment Modalities and Outcomes in Patients With Advanced Invasive Thymoma or Thymic Carcinoma: A Retrospective Multicenter Study. Am J Clin Oncol 2016. [Epub ahead of print].
11. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: a single-institution experience with a long follow-up. J Thorac Oncol 2006;1:308-13.
12. Rea F, Marulli G, Di Chiara F, et al. Multidisciplinary approach for advanced stage thymic tumors: long-term outcome. Lung Cancer 2011;72:68-72.
13. Falkson CB, Bezjak A, Darling G, et al. The management of thymoma: a systematic review and practice guideline. J Thorac Oncol 2009;4:911-9.
14. Girard N, Lal R, Wakelee H, et al. Chemotherapy definitions and policies for thymic malignancies. Zhongguo Fei Ai Za Zhi 2014;17:116-21.
15. Shin DM, Walsh GL, Komaki R, et al. A multidisciplinary approach to therapy for unresectable malignant thymoma. Ann Intern Med 1998;129:100-4.
16. Venuta F, Rendina EA, Pescarmona EO, et al. Multimodality treatment of thymoma: a prospective study. Ann Thorac Surg 1997;64:1585-91; discussion 1591-2.
17. Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung Cancer 2004;44:369-79.
18. Kunitoh H, Tamura T, Shibata T, et al. A phase II trial of dose-dense chemotherapy, followed by surgical resection and/or thoracic radiotherapy, in locally advanced thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9606). Br J Cancer 2010;103:6-11.
19. Wei ML, Kang D, Gu L, et al. Chemotherapy for thymic carcinoma and advanced thymoma in adults. Cochrane Database Syst Rev 2013;8:CD008588.
20. Huang J, Rizk NP, Travis WD, et al. Feasibility of multimodality therapy including extended resections in stage IVA thymoma. J Thorac Cardiovasc Surg 2007;134:1477-83; discussion 1483-4.
21. Maruyama R, Suemitsu R, Okamoto T, et al. Persistent

and aggressive treatment for thymic carcinoma. Results of a single-institute experience with 25 patients. Oncology 2006;70:325-9.
22. Fang W, Chen W, Chen G, et al. Surgical management of thymic epithelial tumors: a retrospective review of 204 cases. Ann Thorac Surg 2005;80:2002-7.
23. Okumura M, Shiono H, Inoue M, et al. Outcome of surgical treatment for recurrent thymic epithelial tumors with reference to world health organization histologic classification system. J Surg Oncol 2007;95:40-4.

Cite this article as: Yue J, Gu Z, Yu Z, Zhang H, Ma Z, Liu Y, Fang W; Members of the Chinese Alliance for Research in Thymomas. Pretreatment biopsy for histological diagnosis and induction therapy in thymic tumors. J Thorac Dis 2016;8(4): 656-664. doi: 10.21037/jtd.2016.03.04

Original Article

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

Yucheng Wei[1*], Zhitao Gu[2*], Yi Shen[1], Jianhua Fu[3], Liejie Tan[4], Peng Zhang[5], Yongtao Han[6], Chun Chen[7], Renquan Zhang[8], Yin Li[9], Keneng Chen[10], Hezhong Chen[11], Yongyu Liu[12], Youbing Cui[13], Yun Wang[14], Liewen Pang[15], Zhentao Yu[16], Xinming Zhou[17], Yangchun Liu[18], Yuan Liu[2], Wentao Fang[2]; Members of the Chinese Alliance for Research in Thymomas[a]

[1]Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266001, China; [2]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [3]Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China; [4]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [5]Department of Endocrinology, Tianjin Medical University General Hospital, Tianjin 300052, China; [6]Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu 610041, China; [7]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou 350001, China; [8]Department of Thoracic Surgery, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [9]Department of Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, China; [10]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing 100142, China; [11]Department of Cardiothoracic Surgery, Changhai Hospital, Shanghai 200433, China; [12]Department of Thoracic Surgery, Liaoning Cancer Hospital, Shenyang 110042, China; [13]Department of Thoracic Surgery, First Affiliated Hospital of Jilin University, Changchun 130021, China; [14]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China; [15]Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200032, China; [16]Department of Esophageal Cancer, Tianjin Cancer Hospital, Tianjin 300060, China; [17]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China; [18]Department of Thoracic Surgery, Jiangxi People's Hospital, Nanchang 330006, China

Contributions: (I) Conception and design: Y Shen, W Fang; (II) Administrative support: W Fang, Z Gu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Z Gu, Y Wei; (V) Data analysis and interpretation: Y Liu, Z Gu, W Fang, Y Shen, Y Wei; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Yi Shen. Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266003, China. Email: qdshenyi@163.com; Wentao Fang. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China. Email: vwtfang12@shchest.org.

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

Submitted Jan 24, 2016. Accepted for publication Feb 25, 2016.
doi: 10.21037/jtd.2016.03.02
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.02

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)

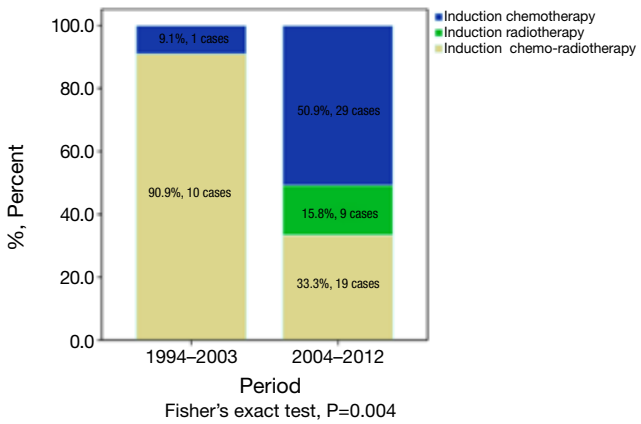


Figure 1 Mode of induction therapies in two time periods (1994–2003 and 2004–2012).

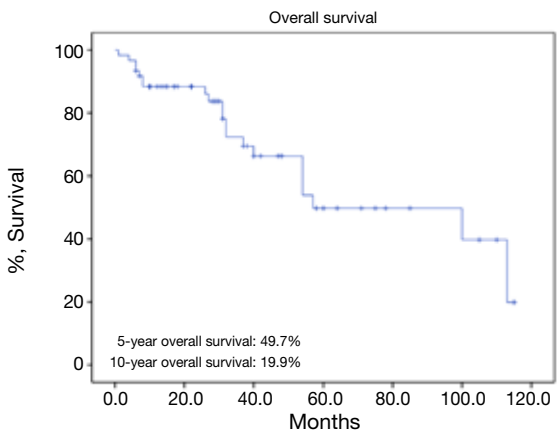


Figure 2 Five-year overall survival rate of patients in the induction therapy group.

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

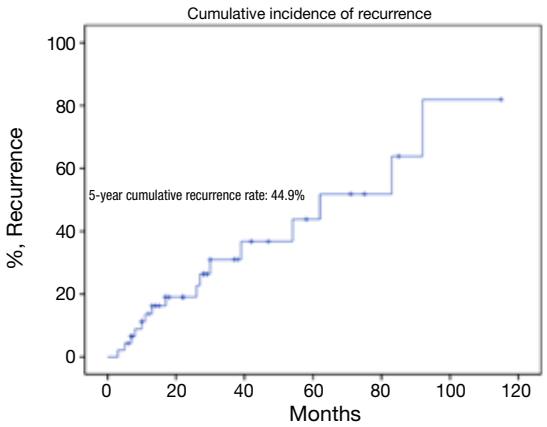


Figure 3 Five-year cumulative incidence of recurrence in the induction therapy group.

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*).

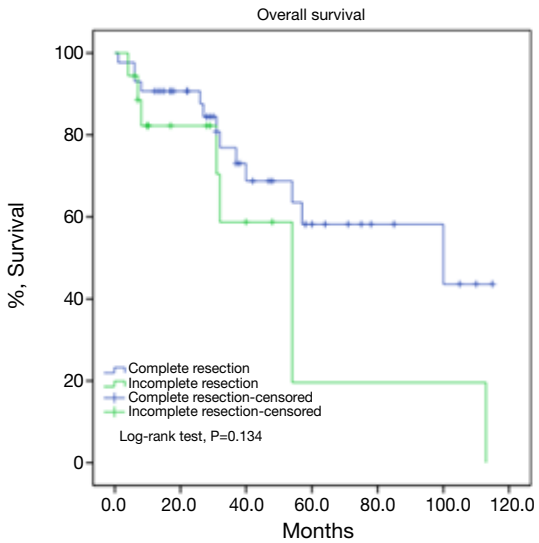


Figure 4 Five-year overall survivals after complete resection (R0, 58.2%) and incomplete resection (R1 and R2, 19.6%, P=0.134) in the induction therapy group.

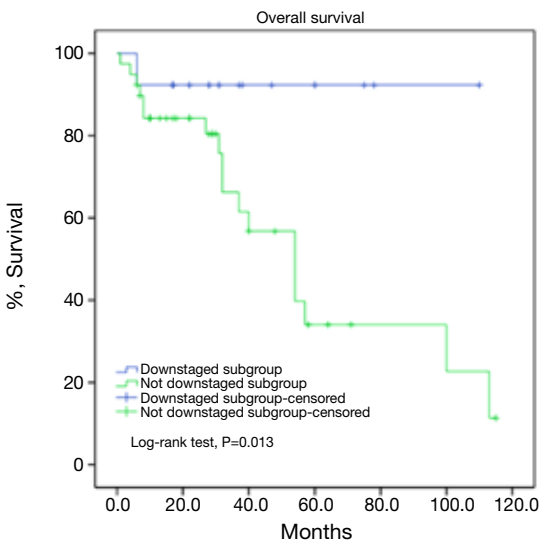


Figure 5 Five-year overall survivals in tumors downstaged or not downstaged after induction therapy (93.8% *vs.* 35.6%, P=0.013).

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.

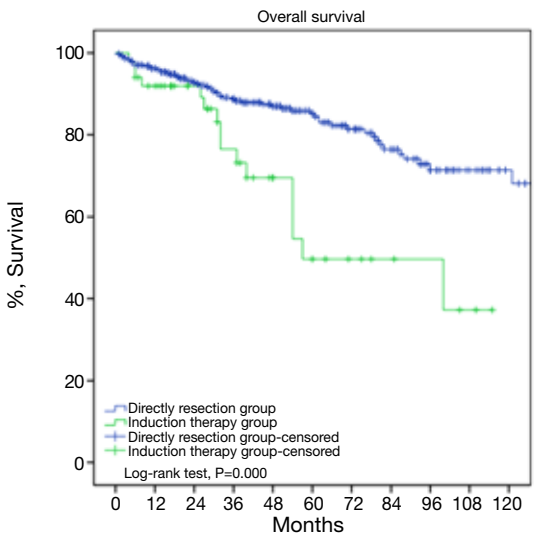


Figure 6 Five-year overall survival of Masaoka-Koga pStaging III patients in the direct surgery group was significantly higher than Masaoka-Koga pStage I–III patients in the induction therapy group (85.2% *vs.* 68.1%, P=0.000).

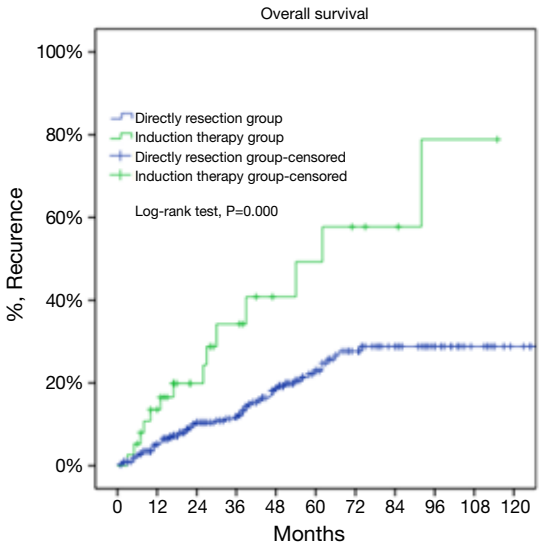


Figure 7 Cumulative incidence of recurrence in Masaoka-Koga pStage III patients in the direct surgery group was significantly lower than in Masaoka-Koga pStage I–III in the induction therapy group (23% *vs.* 58%, P=0.000).

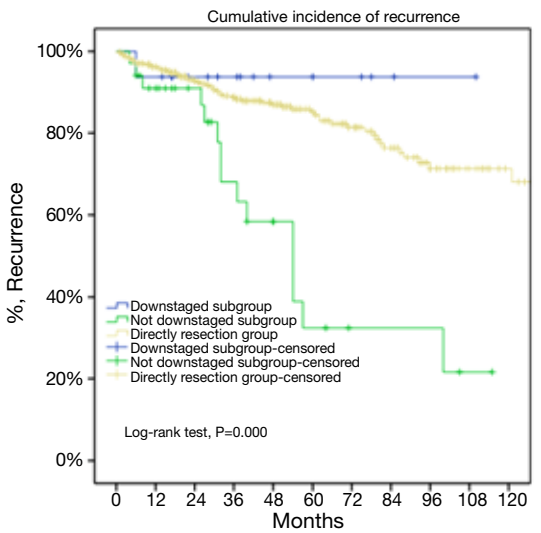


Figure 8 For locally advanced thymic malignancies, 5-year overall survival of tumors downstaged after induction was similar to those in the direct surgery group (93.8% *vs.* 85.2%, P=0.438), both significantly higher than those not downstaged by induction (P=0.000).

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.

Acknowledgements

None.

Footnote

[a]*Members of the Chinese Alliance for Research in Thymomas* (*ChART*)*:* Yi Shen, Yucheng Wei, Affiliated Hospital of Qingdao University, Qingdao, China; Yin Li, Guanghui Liang, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Keneng Chen, Hao Fu, Beijing Cancer Hospital, Beijing, China; Hezhong Chen, Shihua Yao, Changhai Hospital, Shanghai, China; Youbin Cui, Yanzhong Xin, First Affiliated Hospital of Jilin University, Changchun, China; Renquan Zhang, Ningning Kang, First Hospital of Anhui Medical University, Hefei, China; Lijie Tan, Jianyong Ding, Hao Wang, Gang Chen, Jie Wu, Zhongshan Hospital, Fudan University, Shanghai, China; Chun Chen, Wei Zheng, Fujian Medical University Union Hospital, Fuzhou, China; Liewen Pang, Fangrui Wang, Huashan Hospital, Fudan University, Shanghai, China; Yangchun Liu, Qing Lin, Jiangxi People's Hospital, Nanchang, China; Yongyu Liu, Yongkai Wu, Liaoning Cancer Hospital, Shenyang, China; Wentao Fang, Jie Zhang, Yan Shen, Changlu Wang, Lei Zhu, Zhitao Gu, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Yongtao Han, Lin Peng, Sichuan Cancer Hospital, Chengdu, China; Jianhua Fu, Qianwen Liu, Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Zhentao Yu, Jie Yue, Tianjin Cancer Hospital, Tianjin, China; Peng Zhang, Yuan Chen, Tianjin Medical University General Hospital, Tianjin, China; Yun Wang and Yingcai Geng, West China Hospital, Sichuan University, Chengdu, China; Xinming Zhou, Hongguang Zhao, Zhejiang Cancer Hospital, Hangzhou, China.

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

References

1. Blumberg D, Port JL, Weksler B, et al. Thymoma: a multivariate analysis of factors predicting survival. Ann Thorac Surg 1995;60:908-13; discussion 914.
2. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878-84; discussion 884-5.
3. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485-92.
4. Macchiarini P, Chella A, Ducci F, et al. Neoadjuvant chemotherapy, surgery, and postoperative radiation therapy for invasive thymoma. Cancer 1991;68:706-13.
5. Riely GJ, Huang J. Induction therapy for locally advanced thymoma. J Thorac Oncol 2010;5:S323-6.
6. Bretti S, Berruti A, Loddo C, et al. Multimodal management of stages III-IVa malignant thymoma. Lung Cancer 2004;44:69-77.
7. Cardillo G, Carleo F, Giunti R, et al. Predictors of survival in patients with locally advanced thymoma and thymic carcinoma (Masaoka stages III and IVa). Eur J Cardiothorac Surg 2010;37:819-23.
8. Giaccone G, Ardizzoni A, Kirkpatrick A, et al. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. J Clin Oncol 1996;14:814-20.
9. Loehrer PJ Sr, Chen M, Kim K, et al. Cisplatin, doxorubicin, and cyclophosphamide plus thoracic radiation therapy for limited-stage unresectable thymoma: an intergroup trial. J Clin Oncol 1997;15:3093-9.
10. Kunitoh H, Tamura T, Shibata T, et al. A phase II trial of dose-dense chemotherapy, followed by surgical resection and/or thoracic radiotherapy, in locally advanced

thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9606). Br J Cancer 2010;103:6-11.
11. Lemma GL, Lee JW, Aisner SC, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. J Clin Oncol 2011;29:2060-5.
12. Kirkove C, Berghmans J, Noel H, et al. Dramatic response of recurrent invasive thymoma to high doses of corticosteroids. Clin Oncol (R Coll Radiol) 1992;4:64-6.
13. Kobayashi Y, Fujii Y, Yano M, et al. Preoperative steroid pulse therapy for invasive thymoma: clinical experience and mechanism of action. Cancer 2006;106:1901-7.
14. Wright CD, Choi NC, Wain JC, et al. Induction chemoradiotherapy followed by resection for locally advanced Masaoka stage III and IVA thymic tumors. Ann Thorac Surg 2008;85:385-9.
15. Girard N, Shen R, Guo T, et al. Comprehensive genomic analysis reveals clinically relevant molecular distinctions between thymic carcinomas and thymomas. Clin Cancer Res 2009;15:6790-9.
16. Girard N, Teruya-Feldstein J, Payabyab EC, et al. Insulin-like growth factor-1 receptor expression in thymic malignancies. J Thorac Oncol 2010;5:1439-46.
17. Breinig M, Mayer P, Harjung A, et al. Heat shock protein 90-sheltered overexpression of insulin-like growth factor 1 receptor contributes to malignancy of thymic epithelial tumors. Clin Cancer Res 2011;17:2237-49.
18. Girard N. Chemotherapy and targeted agents for thymic malignancies. Expert Rev Anticancer Ther 2012;12:685-95.

Cite this article as: Wei Y, Gu Z, Shen Y, Fu J, Tan L, Zhang P, Han Y, Chen C, Zhang R, Li Y, Chen K, Chen H, Liu Y, Cui Y, Wang Y, Pang L, Yu Z, Zhou X, Liu Y, Liu Y, Fang W; Members of the Chinese Alliance for Research in Thymomas. Preoperative induction therapy for locally advanced thymic tumors: a retrospective analysis using the ChART database. J Thorac Dis 2016;8(4):665-672. doi: 10.21037/jtd.2016.03.02

Original Article

Perioperative outcomes and long-term survival in clinically early-stage thymic malignancies: video-assisted thoracoscopic thymectomy versus open approaches

Hao Wang[1*], Zhitao Gu[2*], Jianyong Ding[1], Lijie Tan[1], Jianhua Fu[3], Yi Shen[4], Yucheng Wei[4], Peng Zhang[5], Yongtao Han[6], Chun Chen[7], Renquan Zhang[8], Yin Li[9], Keneng Chen[10], Hezhong Chen[11], Yongyu Liu[12], Youbing Cui[13], Yun Wang[14], Liewen Pang[15], Zhentao Yu[16], Xinming Zhou[17], Yangchun Liu[18], Yuan Liu[2], Wentao Fang[2]; Members of the Chinese Alliance for Research in Thymomas[a]

[1]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [2]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [3]Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China; [4]Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266001, China; [5]Department of Endocrinology, Tianjin Medical University General Hospital, Tianjin 300052, China; [6]Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu 610041, China; [7]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou 350001, China; [8]Department of Thoracic Surgery, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [9]Department of Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, China; [10]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing 100142, China; [11]Department of Cardiothoracic Surgery, Changhai Hospital, Shanghai 200433, China; [12]Department of Thoracic Surgery, Liaoning Cancer Hospital, Shenyang 110042, China; [13]Department of Thoracic Surgery, First Affiliated Hospital of Jilin University, Changchun 130021, China; [14]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China; [15]Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200032, China; [16]Department of Esophageal Cancer, Tianjin Cancer Hospital, Tianjin 300060, China; [17]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China; [18]Department of Thoracic Surgery, Jiangxi People's Hospital, Nanchang 330006, China

Contributions: (I) Conception and design: L Tan, W Fang; (II) Administrative support: W Fang, Z Gu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Z Gu, H Wang, J Ding; (V) Data analysis and interpretation: Y Liu, Z Gu, W Fang, H Wang, L Tan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Jianyong Ding. Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China. Email: ding.jianyong@zs-hospital.sh.cn; Wentao Fang. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China. Email: vwtfang@hotmail.com.

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

Submitted Jan 26, 2016. Accepted for publication Feb 26, 2016.
doi: 10.21037/jtd.2016.03.05
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.05

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

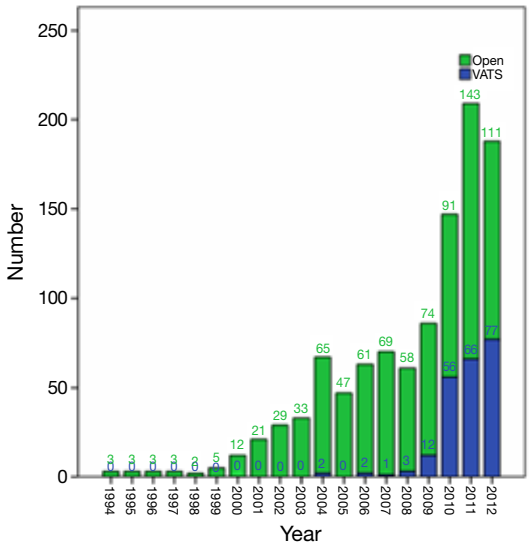


Figure 1 Annual numbers of patients undergoing thymectomy via open or VATS approach from 1994 to 2012. VATS, video-assisted thoracoscopic surgery.

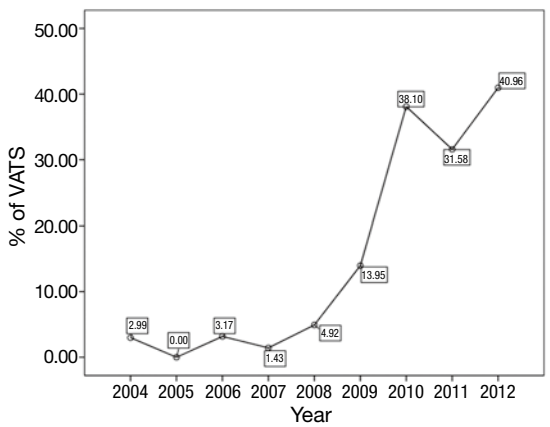


Figure 2 Annual percentages of VATS thymectomy from 2004 to 2012. VATS, video-assisted thoracoscopic surgery.

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.

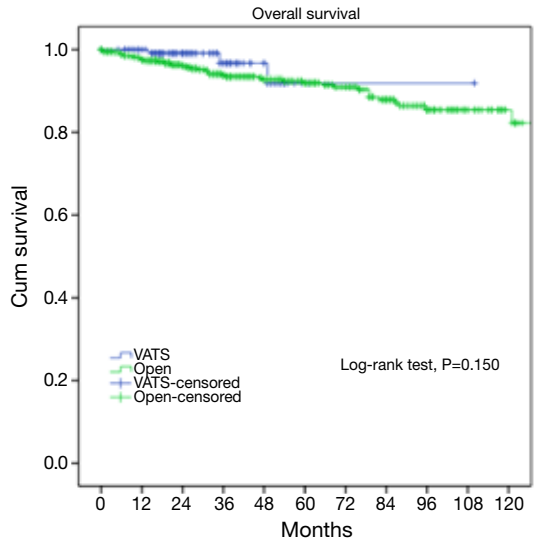


Figure 3 Overall survivals of the VATS and the Open groups. VATS, video-assisted thoracoscopic surgery.

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.

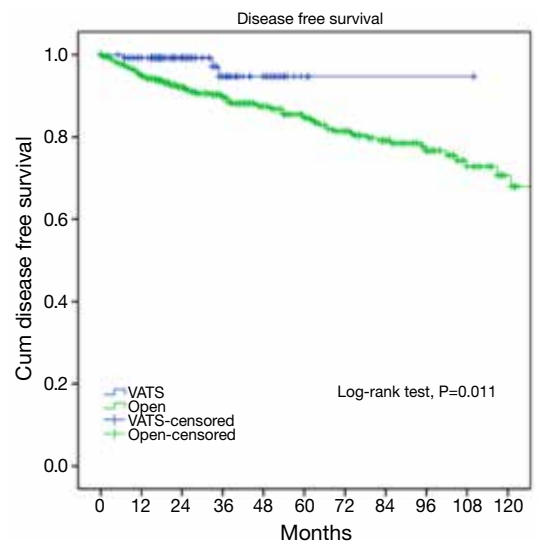


Figure 4 Disease-free survivals of the VATS and the Open groups. VATS, video-assisted thoracoscopic surgery.

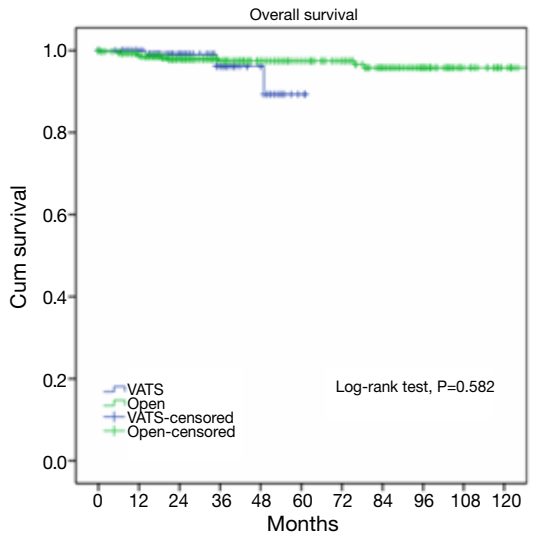


Figure 5 Five-year overall survivals of the VATS and the Open groups (89.4% *vs.* 96.7%, P=0.582) in Masaoka-Koga pStage I-II tumors. VATS, video-assisted thoracoscopic surgery.

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

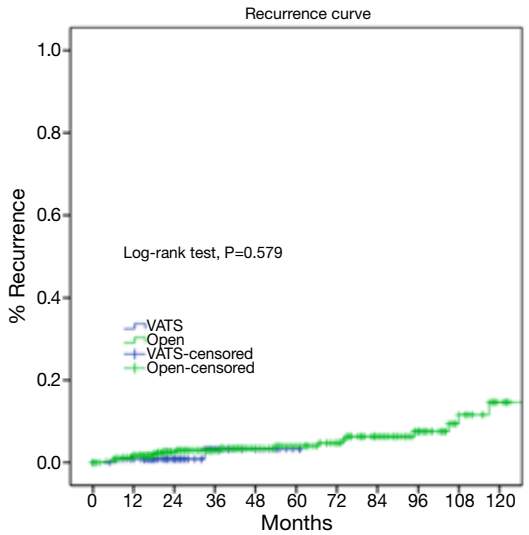


Figure 6 Cumulative incidence of recurrence of the VATS and the Open groups (3.3% *vs.* 4.7%, P=0.579) in Masaoka-Koga pStage I-II tumors. VATS, video-assisted thoracoscopic surgery.

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

[a]*Members of the Chinese Alliance for Research in Thymomas (ChART):* Yi Shen, Yucheng Wei, Affiliated Hospital of Qingdao University, Qingdao, China; Yin Li, Guanghui Liang, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Keneng Chen, Hao Fu, Beijing Cancer Hospital, Beijing, China; Hezhong Chen, Shihua Yao, Changhai Hospital, Shanghai, China; Youbin Cui and Yanzhong Xin, First Affiliated Hospital of Jilin University, Changchun, China; Renquan Zhang, Ningning Kang, First Hospital of Anhui Medical University, Hefei, China; Lijie Tan, Jianyong Ding, Hao Wang, Gang Chen, Jie Wu, Zhongshan Hospital, Fudan University, Shanghai, China; Chun Chen, Wei Zheng, Fujian Medical University Union Hospital, Fuzhou, China; Liewen Pang, Fangrui Wang, Huashan Hospital, Fudan University, Shanghai, China; Yangchun Liu, Qing Lin, Jiangxi People's Hospital, Nanchang, China; Yongyu Liu, Yongkai Wu, Liaoning Cancer Hospital, Shenyang, China; Wentao Fang, Jie Zhang, Yan Shen, Changlu Wang, Lei Zhu, Zhitao Gu, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Yongtao Han, Lin Peng, Sichuan Cancer Hospital, Chengdu, China; Jianhua Fu, Qianwen Liu, Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Zhentao Yu, Jie Yue, Tianjin Cancer Hospital, Tianjin, China; Peng Zhang, Yuan Chen, Tianjin Medical University General Hospital, Tianjin, China; Yun Wang and Yingcai Geng, West China Hospital, Sichuan University, Chengdu, China; Xinming Zhou, Hongguang Zhao, Zhejiang Cancer Hospital, Hangzhou, China.

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

References

1. Odaka M, Akiba T, Yabe M, et al. Unilateral thoracoscopic subtotal thymectomy for the treatment of stage I and II thymoma. Eur J Cardiothorac Surg 2010;37:824-6.
2. Ng CS, Wan IY, Yim AP. Video-assisted thoracic surgery thymectomy: the better approach. Ann Thorac Surg 2010;89:S2135-41.
3. Jurado J, Javidfar J, Newmark A, et al. Minimally invasive thymectomy and open thymectomy: outcome analysis of 263 patients. Ann Thorac Surg 2012;94:974-81; discussion 981-2.
4. Ye B, Tantai JC, Ge XX, et al. Surgical techniques for early-stage thymoma: video-assisted thoracoscopic thymectomy versus transsternal thymectomy. J Thorac Cardiovasc Surg 2014;147:1599-603.
5. Davenport E, Malthaner RA. The role of surgery in the management of thymoma: a systematic review. Ann Thorac Surg 2008;86:673-84.
6. Kohman LJ. Controversies in the management of malignant thymoma. Chest 1997;112:296S-300S.
7. Takeo S, Fukuyama S. Video-assisted thoracoscopic resection of a giant anterior mediastinal tumor (lipoma) using an original sternum-lifting technique. Jpn J Thorac Cardiovasc Surg 2005;53:565-8.
8. Whitson BA, Andrade RS, Mitiek MO, et al. Thoracoscopic thymectomy: technical pearls to a 21st century approach. J Thorac Dis 2013;5:129-34.
9. Ye B, Tantai JC, Li W, et al. Video-assisted thoracoscopic

surgery versus robotic-assisted thoracoscopic surgery in the surgical treatment of Masaoka stage I thymoma. World J Surg Oncol 2013;11:157.
10. Mu JW, Chen GY, Sun KL, et al. Application of video-assisted thoracic surgery in the standard operation for thoracic tumors. Cancer Biol Med 2013;10:28-35.
11. Singhal S, Shrager JB, Rosenthal DI, et al. Comparison of stages I-II thymoma treated by complete resection with or without adjuvant radiation. Ann Thorac Surg 2003;76:1635-41; discussion 1641-2.
12. Murakawa T, Nakajima J, Kohno T, et al. Results from surgical treatment for thymoma. 43 years of experience. Jpn J Thorac Cardiovasc Surg 2000;48:89-95.
13. Gu ZT, Mao T, Chen WH, et al. Comparison of video-assisted thoracoscopic surgery and median sternotomy approaches for thymic tumor resections at a single institution. Surg Laparosc Endosc Percutan Tech 2015;25:47-51.
14. Kirschner PA. Reoperation on the thymus. A critique. Chest Surg Clin N Am 2001;11:439-45.
15. Yuan ZY, Cheng GY, Sun KL, et al. Comparative study of video-assisted thoracic surgery versus open thymectomy for thymoma in one single center. J Thorac Dis 2014;6:726-33.
16. Pennathur A, Qureshi I, Schuchert MJ, et al. Comparison of surgical techniques for early-stage thymoma: feasibility of minimally invasive thymectomy and comparison with open resection. J Thorac Cardiovasc Surg 2011;141:694-701.
17. Chen G, Marx A, Chen WH, et al. New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. Cancer 2002;95:420-9.
18. Ströbel P, Bauer A, Puppe B, et al. Tumor recurrence and survival in patients treated for thymomas and thymic squamous cell carcinomas: a retrospective analysis. J Clin Oncol 2004;22:1501-9.
19. Safieddine N, Liu G, Cuningham K, et al. Prognostic factors for cure, recurrence and long-term survival after surgical resection of thymoma. J Thorac Oncol 2014;9:1018-22.
20. Gawrychowski J, Rokicki M, Gabriel A, et al. Thymoma--the usefulness of some prognostic factors for diagnosis and surgical treatment. Eur J Surg Oncol 2000;26:203-8.
21. Detterbeck FC. Clinical value of the WHO classification system of thymoma. Ann Thorac Surg 2006;81:2328-34.
22. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878-84; discussion 884-5.

Cite this article as: Wang H, Gu Z, Ding J, Tan L, Fu J, Shen Y, Wei Y, Zhang P, Han Y, Chen C, Zhang R, Li Y, Chen K, Chen H, Liu Y, Cui Y, Wang Y, Pang L, Yu Z, Zhou X, Liu Y, Liu Y, Fang W; Members of the Chinese Alliance for Research in Thymomas. Perioperative outcomes and long-term survival in clinically early-stage thymic malignancies: video-assisted thoracoscopic thymectomy versus open approaches. J Thorac Dis 2016;8(4):673-679. doi: 10.21037/jtd.2016.03.05

Original Article

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

Zhitao Gu[1], Jianhua Fu[2], Yi Shen[3], Yucheng Wei[3], Lijie Tan[4], Peng Zhang[5], Yongtao Han[6], Chun Chen[7], Renquan Zhang[8], Yin Li[9], Keneng Chen[10], Hezhong Chen[11], Yongyu Liu[12], Youbing Cui[13], Yun Wang[14], Liewen Pang[15], Zhentao Yu[16], Xinming Zhou[17], Yangchun Liu[18], Yuan Liu[1], Wentao Fang[1]; Members of the Chinese Alliance for Research in Thymomas[a]

[1]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [2]Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China; [3]Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266001, China; [4]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [5]Department of Endocrinology, Tianjin Medical University General Hospital, Tianjin 300052, China; [6]Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu 610041, China; [7]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou 350001, China; [8]Department of Thoracic Surgery, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [9]Department of Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, China; [10]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing 100142, China; [11]Department of Cardiothoracic Surgery, Changhai Hospital, Shanghai 200433, China; [12]Department of Thoracic Surgery, Liaoning Cancer Hospital, Shenyang 110042, China; [13]Department of Thoracic Surgery, First Affiliated Hospital of Jilin University, Changchun 130021, China; [14]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China; [15]Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200032, China; [16]Department of Esophageal Cancer, Tianjin Cancer Hospital, Tianjin 300060, China; [17]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China; [18]Department of Thoracic Surgery, Jiangxi People's Hospital, Nanchang 330006, China

Contributions: (I) Conception and design: W Fang; (II) Administrative support: W Fang, Z Gu; (III) Provision of study materials or patients: All authors; (IV) Collection ad assembly of data: Z Gu; (V) Data analysis and interpretation: Z Gu, Y Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Wentao Fang, MD. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 Huaihai Road West, Shanghai 200030, China. Email: vwtfang12@shchest.org.

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

Submitted Jan 22, 2016. Accepted for publication Feb 12, 2016.
doi: 10.21037/jtd.2016.03.16
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.16

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

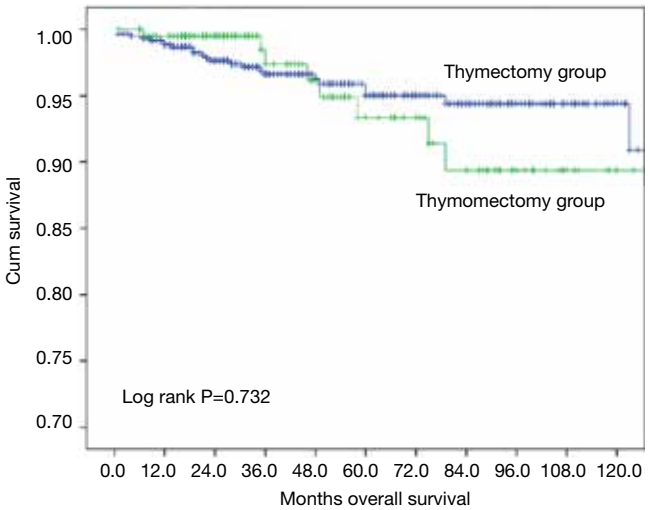


Figure 1 Comparison of overall survival between thymectomy and thymomectomy (P=0.732).

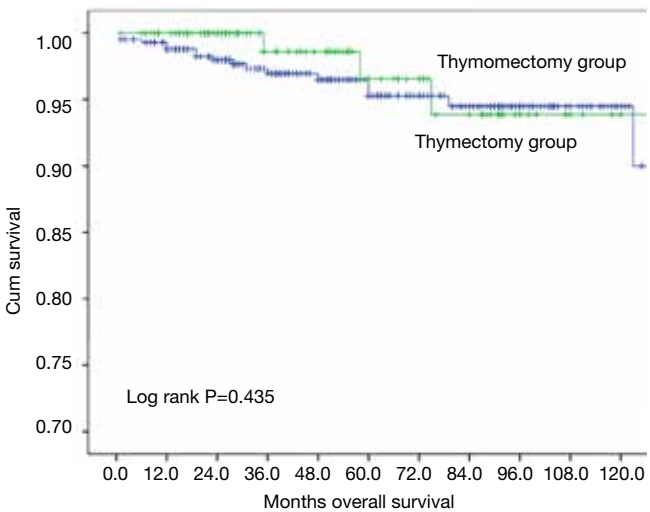


Figure 2 Comparison of overall survival between thymectomy and thymomectomy among patients with Masaoka-Koga stage I tumors (P=0.435).

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

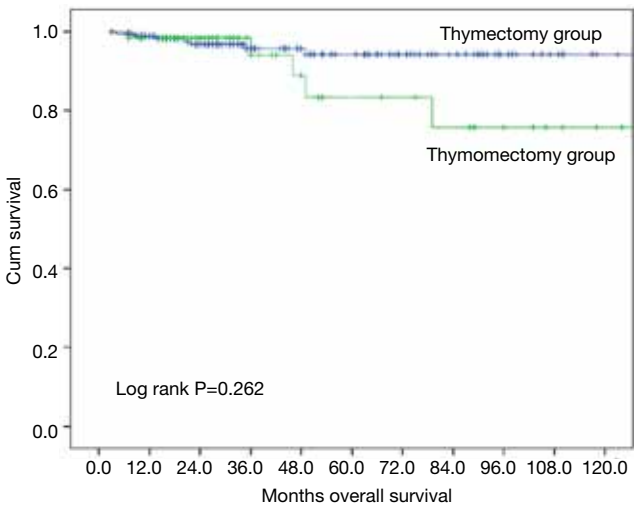


Figure 3 Comparison of overall survival between thymectomy and thymomectomy among patients with Masaoka-Koga stage II tumors (P=0.262).

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.

Acknowledgements

None.

Footnote

[a]*Members of Chinese Alliance for Research in Thymomas* (*ChART*)*:* Yi Shen, Yucheng Wei, Affiliated Hospital of Qingdao University, Qingdao, China; Yin Li, Guanghui Liang, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Keneng Chen, Hao Fu, Beijing Cancer Hospital, Beijing, China; Hezhong Chen, Shihua Yao, Changhai Hospital, Shanghai, China; Youbin Cui, Yanzhong Xin, First Affiliated Hospital of Jilin University, Changchun, China; Renquan Zhang, Ningning Kang, First Hospital of Anhui Medical University, Hefei, China; Lijie Tan, Jianyong Ding, Hao Wang, Gang Chen, Jie Wu, Zhongshan Hospital, Fudan University, Shanghai, China; Chun Chen, Wei Zheng, Fujian Medical University Union Hospital, Fuzhou, China; Liewen Pang, Fangrui Wang, Huashan Hospital, Fudan University, Shanghai, China; Yangchun Liu, Qing Lin, Jiangxi People's Hospital, Nanchang, China; Yongyu Liu, Yongkai Wu, Liaoning Cancer Hospital, Shenyang, China; Wentao Fang, Jie Zhang, Yan Shen, Changlu Wang, Lei Zhu, Zhitao Gu, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Yongtao Han, Lin Peng, Sichuan Cancer Hospital, Chengdu, China; Jianhua Fu, Qianwen Liu, Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Zhentao Yu, Jie Yue, Tianjin Cancer Hospital, Tianjin, China; Peng Zhang, Yuan Chen, Tianjin Medical University General Hospital, Tianjin, China; Yun Wang, Yingcai Geng, West China Hospital Sichuan University, Chengdu, China; Xinming Zhou, Hongguang Zhao, Zhejiang Cancer Hospital, Hangzhou, China.

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

References

1. Toker A, Sonett J, Zielinski M, et al. Standard terms, definitions, and policies for minimally invasive resection of thymoma. J Thorac Oncol 2011;6:S1739-42.
2. Onuki T, Ishikawa S, Iguchi K, et al. Limited thymectomy for stage I or II thymomas. Lung Cancer 2010;68:460-5.
3. Tseng YC, Hsieh CC, Huang HY, et al. Is thymectomy necessary in nonmyasthenic patients with early thymoma? J Thorac Oncol 2013;8:952-8.
4. Sakamaki Y, Kido T, Yasukawa M. Alternative choices of total and partial thymectomy in video-assisted resection of noninvasive thymomas. Surg Endosc 2008;22:1272-7.
5. Nakajima J, Murakawa T, Fukami T, et al. Postthymectomy myasthenia gravis: relationship with thymoma and antiacetylcholine receptor antibody. Ann Thorac Surg 2008;86:941-5.
6. Kondo K, Monden Y. Myasthenia gravis appearing after thymectomy for thymoma. Eur J Cardiothorac Surg

2005;28:22-5.
7. Pennathur A, Qureshi I, Schuchert MJ, et al. Comparison of surgical techniques for early-stage thymoma: feasibility of minimally invasive thymectomy and comparison with open resection. J Thorac Cardiovasc Surg 2011;141:694-701.
8. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology 2000;55:16-23.
9. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485-92.
10. Wright CD, Wain JC, Wong DR, et al. Predictors of recurrence in thymic tumors: importance of invasion, World Health Organization histology, and size. J Thorac Cardiovasc Surg 2005;130:1413-21.
11. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878-84; discussion 884-5.
12. Marom EM, Rosado-de-Christenson ML, Bruzzi JF, et al. Standard report terms for chest computed tomography reports of anterior mediastinal masses suspicious for thymoma. J Thorac Oncol 2011;6:S1717-23.
13. Marom EM, Milito MA, Moran CA, et al. Computed tomography findings predicting invasiveness of thymoma. J Thorac Oncol 2011;6:1274-81.
14. Priola AM, Priola SM, Di Franco M, et al. Computed tomography and thymoma: distinctive findings in invasive and noninvasive thymoma and predictive features of recurrence. Radiol Med 2010;115:1-21.
15. Benveniste MF, Moran CA, Mawlawi O, et al. FDG PET-CT aids in the preoperative assessment of patients with newly diagnosed thymic epithelial malignancies. J Thorac Oncol 2013;8:502-10.
16. Roth T, Ackermann R, Stein R, et al. Thirteen years follow-up after radical transsternal thymectomy for myasthenia gravis. Do short-term results predict long-term outcome? Eur J Cardiothorac Surg 2002;21:664-70.
17. Buckingham JM, Howard FM Jr, Bernatz PE, et al. The value of thymectomy in myasthenia gravis: a computer-assisted matched study. Ann Surg 1976;184:453-8.
18. Ito M, Fujimura S, Monden Y, et al. A retrospective group study on post-thymectomy myasthenia gravis. Nihon Kyobu Geka Gakkai Zasshi 1992;40:189-93.
19. Sonett JR, Jaretzki A 3rd. Thymectomy for nonthymomatous myasthenia gravis: a critical analysis. Ann N Y Acad Sci 2008;1132:315-28.

Cite this article as: Gu Z, Fu J, Shen Y, Wei Y, Tan L, Zhang P, Han Y, Chen C, Zhang R, Li Y, Chen K, Chen H, Liu Y, Cui Y, Wang Y, Pang L, Yu Z, Zhou X, Liu Y, Liu Y, Fang W; Members of the Chinese Alliance for Research in Thymomas. Thymectomy versus tumor resection for early-stage thymic malignancies: a Chinese Alliance for Research in Thymomas retrospective database analysis. J Thorac Dis 2016;8(4):680-686. doi: 10.21037/jtd.2016.03.16

Original Article

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

Qianwen Liu[1*], Zhitao Gu[2*], Fu Yang[3], Jianhua Fu[1], Yi Shen[4], Yucheng Wei[4], Lijie Tan[5], Peng Zhang[6], Yongtao Han[7], Chun Chen[8], Renquan Zhang[9], Yin Li[10], Keneng Chen[11], Hezhong Chen[12], Yongyu Liu[13], Youbing Cui[14], Yun Wang[15], Liewen Pang[16], Zhentao Yu[17], Xinming Zhou[18], Yangchun Liu[19], Jin Xiang[20], Yuan Liu[2], Wentao Fang[2]; Members of the Chinese Alliance for Research in Thymomas[a]

[1]Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China; [2]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [3]Department of Thoracic Surgery, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai 200080, China; [4]Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266001, China; [5]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [6]Department of Endocrinology, Tianjin Medical University General Hospital, Tianjin 300052, China; [7]Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu 610041, China; [8]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou 350001, China; [9]Department of Thoracic Surgery, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [10]Department of Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, China; [11]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing 100142, China; [12]Department of Cardiothoracic Surgery, Changhai Hospital, Shanghai 200433, China; [13]Department of Thoracic Surgery, Liaoning Cancer Hospital, Shenyang 110042, China; [14]Department of Thoracic Surgery, First Affiliated Hospital of Jilin University, Changchun 130021, China; [15]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China; [16]Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200032, China; [17]Department of Esophageal Cancer, Tianjin Cancer Hospital, Tianjin 300060, China; [18]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China; [19]Department of Thoracic Surgery, Jiangxi People's Hospital, Nanchang 330006, China; [20]Department of Pathology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China

Contributions: (I) Conception and design: J Fu, W Fang; (II) Administrative support: W Fang, Z Gu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Q Liu, F Yang, J Xiang, Z Gu; (V) Data analysis and interpretation: Y Liu, Z Gu, W Fang, J Fu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Jianhua Fu. Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, 561 Dongfeng Road East, Guangzhou, Guangdong 510060, China. Email: fujh@sysucc.org.cn; Wentao Fang. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 Huaihai Road West, Shanghai 200030, China. Email: vwtfang12@shchest.org.

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)

Submitted Jan 18, 2016. Accepted for publication Feb 25, 2016.
doi: 10.21037/jtd.2016.03.28
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.28

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,

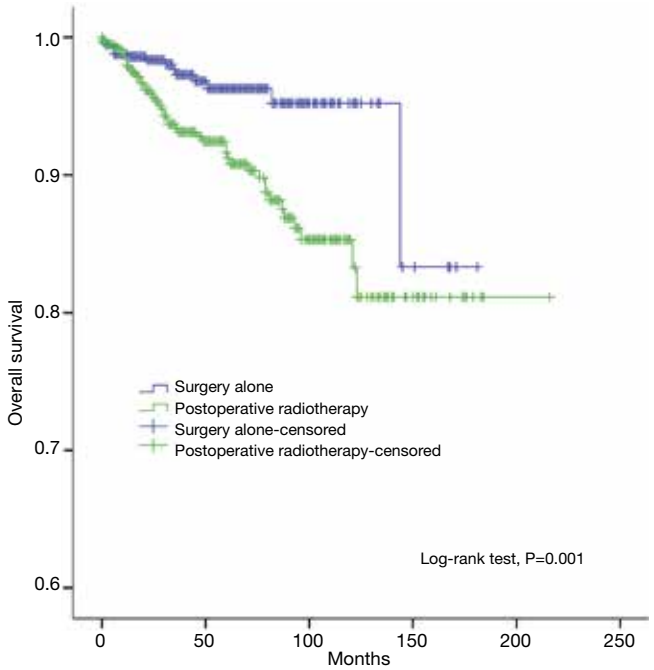


Figure 1 Kaplan-Meir overall survival curve of patients treated with surgery alone, and those treated with PORT. PORT decreased OS of stage I/II/III thymic epithelial tumor (P=0.001).

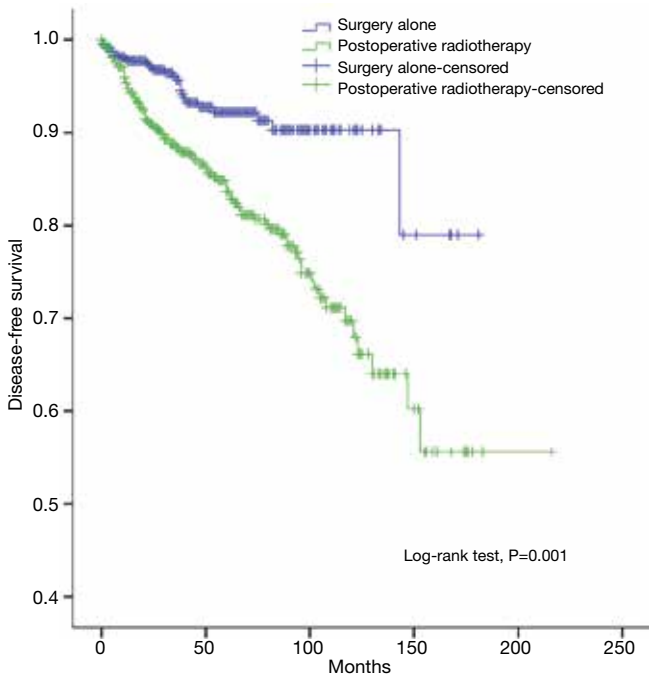


Figure 2 Kaplan-Meir disease-free survival curve of patients treated with surgery alone, and those treated with PORT. PORT decreased DFS of stage I/II/III thymic epithelial tumor (P<0.001).

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.

Acknowledgements

None.

Footnote

[a]*Members of The Chinese Alliance for Research in Thymomas* (*ChART*): Yi Shen, Yucheng Wei, Affiliated Hospital of Qingdao University, Qingdao, China; Yin Li, and Guanghui Liang, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Keneng Chen and Hao Fu, Beijing Cancer Hospital, Beijing, China; Hezhong Chen and Shihua Yao, Changhai Hospital, Shanghai, China; Youbin Cui and Yanzhong Xin, First Affiliated Hospital of Jilin University, Changchun, China; Renquan Zhang and Ningning Kang, First Hospital of Anhui Medical University, Hefei, China; Lijie Tan, Jianyong Ding, Hao Wang, Gang Chen, and Jie Wu, Zhongshan Hospital, Fudan University, Shanghai, China; Chun Chen and Wei Zheng, Fujian Medical University Union Hospital, Fuzhou, China; Liewen Pang and Fangrui Wang, Huashan Hospital, Fudan University, Shanghai, China; Yangchun Liu and Qing Lin, Jiangxi People's Hospital, Nanchang, China; Yongyu Liu and Yongkai Wu, Liaoning Cancer Hospital, Shenyang, China; Wentao Fang, Jie Zhang, Yan Shen, Changlu Wang, Lei Zhu and Zhitao Gu, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Yongtao Han, Lin Peng, Sichuan Cancer Hospital, Chengdu, China; Jianhua Fu and Qianwen Liu, Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Zhentao Yu and Jie Yue, Tianjin Cancer Hospital, Tianjin, China; Peng Zhang and Yuan Chen, Tianjin Medical University General Hospital, Tianjin, China; Yun Wang and Yingcai Geng, West China Hospital, Sichuan University, Chengdu, China; Xinming Zhou and Hongguang Zhao, Zhejiang Cancer Hospital, Hangzhou, China.

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

References

1. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol 2010;5:S260-5.
2. Qu YJ, Liu GB, Shi HS, et al. Preoperative CT findings of thymoma are correlated with postoperative Masaoka clinical stage. Acad Radiol 2013;20:66-72.
3. Detterbeck F, Youssef S, Ruffini E, et al. A review of prognostic factors in thymic malignancies. J Thorac Oncol 2011;6:S1698-704.

4. Detterbeck FC, Zeeshan A. Thymoma: current diagnosis and treatment. Chin Med J (Engl) 2013;126:2186-91.
5. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878-84; discussion 884-5.
6. Rea F, Marulli G, Girardi R, et al. Long-term survival and prognostic factors in thymic epithelial tumours. Eur J Cardiothorac Surg 2004;26:412-8.
7. Detterbeck FC, Parsons A. Thymic tumors: a review of current diagnosis, classification, and treatment. In: Patterson GA, Cooper JD, Deslauriers J, et al, (editors). Thoracic and esophageal surgery. Philadelphia: Elsevier, 2008:1589-1614.
8. Tomaszek S, Wigle DA, Keshavjee S, et al. Thymomas: review of current clinical practice. Ann Thorac Surg 2009;87:1973-80.
9. Falkson CB, Bezjak A, Darling G, et al. The management of thymoma: a systematic review and practice guideline. J Thorac Oncol 2009;4:911-9.
10. Maggi G, Casadio C, Cavallo A, et al. Thymoma: results of 241 operated cases. Ann Thorac Surg 1991;51:152-6.
11. Loehrer PJ Sr, Jiroutek M, Aisner S, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. Cancer 2001;91:2010-5.
12. Rena O, Papalia E, Maggi G, et al. World Health Organization histologic classification: an independent prognostic factor in resected thymomas. Lung Cancer 2005;50:59-66.
13. Kundel Y, Yellin A, Popovtzer A, et al. Adjuvant radiotherapy for thymic epithelial tumor: treatment results and prognostic factors. Am J Clin Oncol 2007;30:389-94.
14. Lucchi M, Ambrogi MC, Duranti L, et al. Advanced stage thymomas and thymic carcinomas: results of multimodality treatments. Ann Thorac Surg 2005;79:1840-4.
15. Nakahara K, Ohno K, Hashimoto J, et al. Thymoma: results with complete resection and adjuvant postoperative irradiation in 141 consecutive patients. J Thorac Cardiovasc Surg 1988;95:1041-7.
16. Chen G, Marx A, Chen WH, et al. New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. Cancer 2002;95:420-9.
17. Ogawa K, Uno T, Toita T, et al. Postoperative radiotherapy for patients with completely resected thymoma: a multi-institutional, retrospective review of 103 patients. Cancer 2002;94:1405-13.
18. Weksler B, Shende M, Nason KS, et al. The role of adjuvant radiation therapy for resected stage III thymoma: a population-based study. Ann Thorac Surg 2012;93:1822-8; discussion 1828-9.
19. Utsumi T, Shiono H, Kadota Y, et al. Postoperative radiation therapy after complete resection of thymoma has little impact on survival. Cancer 2009;115:5413-20.
20. Korst RJ, Kansler AL, Christos PJ, et al. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. Ann Thorac Surg 2009;87:1641-7.
21. Mangi AA, Wain JC, Donahue DM, et al. Adjuvant radiation of stage III thymoma : is it necessary? Ann Thorac Surg 2005;79:1834-9.
22. Detterbeck FC, Nicholson AG, Kondo K, et al. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. J Thorac Oncol 2011;6:S1710-6.
23. Kuo TT. Tumours of the thymus. In: Travis WD, Brambilla E, Burke AP, et al, editors. World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press, 2004:146-248.
24. Myojin M, Choi NC, Wright CD, et al. Stage III thymoma: pattern of failure after surgery and postoperative radiotherapy and its implication for future study. Int J Radiat Oncol Biol Phys 2000;46:927-33.
25. Ruffini E, Mancuso M, Oliaro A, et al. Recurrence of thymoma: analysis of clinicopathologic features, treatment, and outcome. J Thorac Cardiovasc Surg 1997;113:55-63.
26. Shulimzon T, Apter S, Weitzen R, et al. Radiation pneumonitis complicating mediastinal radiotherapy postpneumonectomy. Eur Respir J 1996;9:2697-9.
27. Yeoh E, Holloway RH, Russo A, et al. Effects of mediastinal irradiation on oesophageal function. Gut 1996;38:166-70.
28. Velissaris TJ, Tang AT, Millward-Sadler GH, et al. Pericardial mesothelioma following mantle field radiotherapy. J Cardiovasc Surg (Torino) 2001;42:425-7.
29. Johansson S, Svensson H, Denekamp J. Timescale of evolution of late radiation injury after postoperative radiotherapy of breast cancer patients. Int J Radiat Oncol Biol Phys 2000;48:745-50.
30. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol 2004;22:3139-48.
31. Weksler B, Dhupar R, Parikh V, et al. Thymic carcinoma: a multivariate analysis of factors predictive of survival in 290 patients. Ann Thorac Surg 2013;95:299-303.
32. Hsu CP, Chen CY, Chen CL, et al. Thymic carcinoma.

Ten years' experience in twenty patients. J Thorac Cardiovasc Surg 1994;107:615-20.
33. Omasa M, Date H, Sozu T, et al. Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: the Japanese Association for Research on the Thymus Database Study. Cancer 2015;121:1008-16.
34. Ahmad U, Yao X, Detterbeck F, et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. J Thorac Cardiovasc Surg 2015;149:95-100, 101.e1-2.

Cite this article as: Liu Q, Gu Z, Yang F, Fu J, Shen Y, Wei Y, Tan L, Zhang P, Han Y, Chen C, Zhang R, Li Y, Chen K, Chen H, Liu Y, Cui Y, Wang Y, Pang L, Yu Z, Zhou X, Liu Y, Xiang J, Liu Y, Fang W; Members of the Chinese Alliance for Research in Thymomas. The role of postoperative radiotherapy for stage I/II/III thymic tumor—results of the ChART retrospective database. J Thorac Dis 2016;8(4):687-695. doi: 10.21037/jtd.2016.03.28

Original Article

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

Ke Ma[1*], Zhitao Gu[2*], Yongtao Han[1], Jianhua Fu[3], Yi Shen[4], Yucheng Wei[4], Lijie Tan[5], Peng Zhang[6], Chun Chen[7], Renquan Zhang[8], Yin Li[9], Keneng Chen[10], Hezhong Chen[11], Yongyu Liu[12], Youbing Cui[13], Yun Wang[14], Liewen Pang[15], Zhentao Yu[16], Xinming Zhou[17], Yangchun Liu[18], Yuan Liu[2], Wentao Fang[2]; Members of the Chinese Alliance for Research in Thymomas[a]

[1]Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu 610041, China; [2]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [3]Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China; [4]Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266001, China; [5]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [6]Department of Endocrinology, Tianjin Medical University General Hospital, Tianjin 300052, China; [7]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou 350001, China; [8]Department of Thoracic Surgery, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [9]Department of Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, China; [10]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing 100142, China; [11]Department of Cardiothoracic Surgery, Changhai Hospital, Shanghai 200433, China; [12]Department of Thoracic Surgery, Liaoning Cancer Hospital, Shenyang 110042, China; [13]Department of Thoracic Surgery, First Affiliated Hospital of Jilin University, Changchun 130021, China; [14]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China; [15]Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200032, China; [16]Department of Esophageal Cancer, Tianjin Cancer Hospital, Tianjin 300060, China; [17]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China; [18]Department of Thoracic Surgery, Jiangxi People's Hospital, Nanchang 330006, China

Contributions: (I) Conception and design: Y Han, W Fang; (II) Administrative support: W Fang, Z Gu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Z Gu, K Ma; (V) Data analysis and interpretation: Y Liu, Z Gu, W Fang, Y Han; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Dr. Yongtao Han. Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu Medical College, Chengdu 610041, China. Email: hanyongt@aliyun.com; Dr. Wentao Fang. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China. Email: vwtfang12@shchest.org.

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

Submitted Oct 05, 2015. Accepted for publication Nov 12, 2015.
doi: 10.21037/jtd.2016.03.31
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.31

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*).

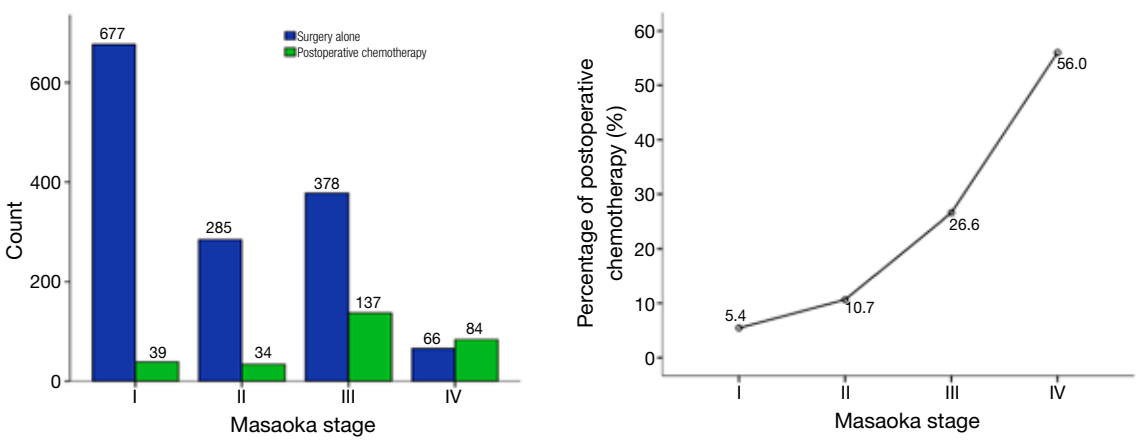


Figure 1 Percentage of postoperative chemotherapy in patients with different stage tumors.

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		

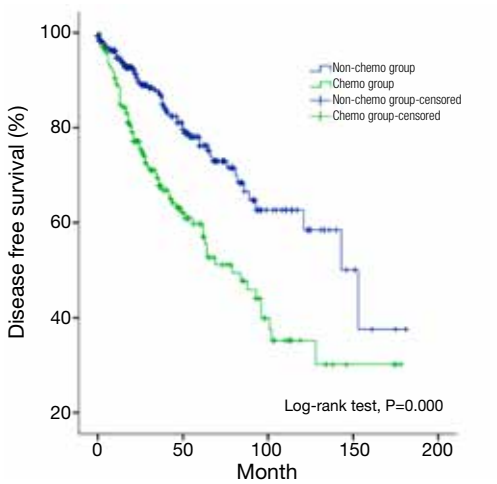


Figure 2 Five- and ten-year disease free survivals (non-chemo group *vs.* chemo group, P=0.000).

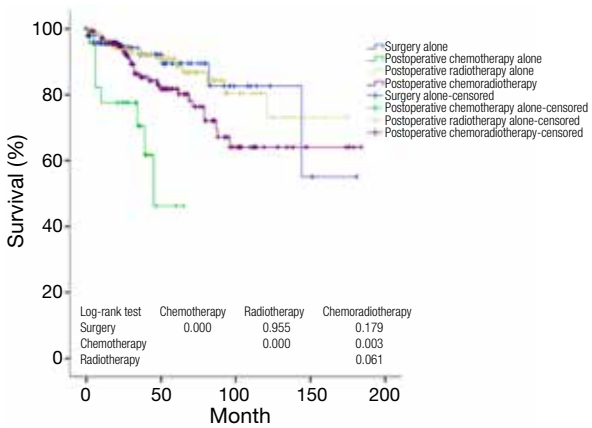


Figure 3 Survival curves for subgroups of patients with surgery alone, postoperative chemotherapy alone, postoperative radiotherapy alone, and postoperative chemoradiotherapy.

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.

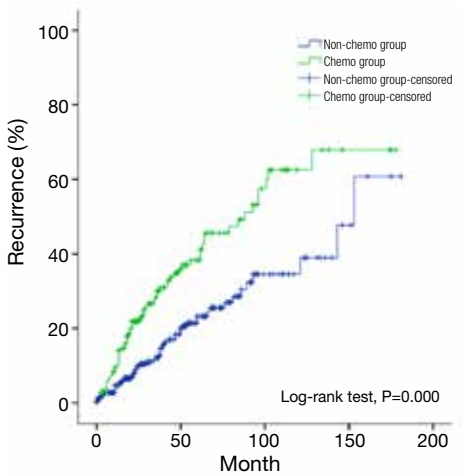


Figure 4 Five- and ten-year recurrence rates (chemo group *vs.* non-chemo group, P=0.000).

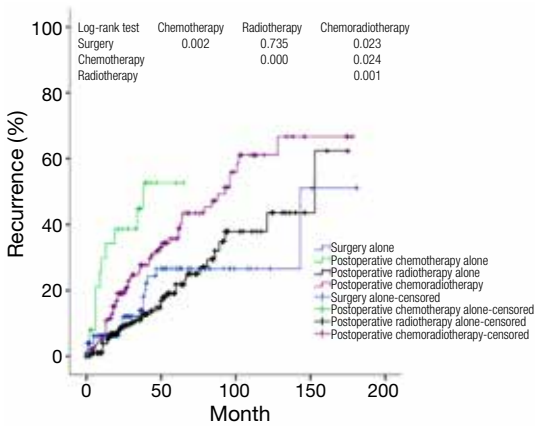


Figure 5 Cumulative incidence of recurrence for subgroups of patients with surgery alone, chemotherapy alone, radiotherapy alone, and chemoradiotherapy.

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.

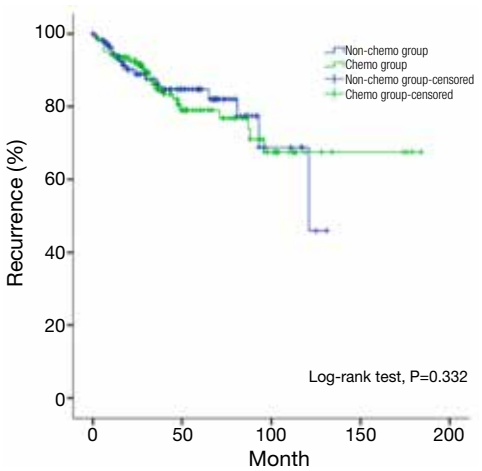


Figure 6 Survival curves of the two groups in the propensity-matched study.

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.

Acknowledgements

None.

Footnote

[a]*Members of Chinese Alliance for Research in Thymomas* (*ChART*): Yi Shen, Yucheng Wei, Affiliated Hospital of Qingdao University, Qingdao, China; Yin Li, Guanghui Liang, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Keneng Chen, Hao Fu, Beijing Cancer Hospital, Beijing, China; Hezhong Chen, Shihua Yao, Changhai Hospital, Shanghai, China; Youbin Cui, Yanzhong Xin, First Affiliated Hospital of Jilin University, Changchun, China; Renquan Zhang, Ningning Kang, First Hospital of Anhui Medical University, Hefei, China; Lijie Tan, Jianyong Ding, Hao Wang, Gang Chen, Jie Wu, Zhongshan Hospital, Fudan University, Shanghai, China; Chun Chen, Wei Zheng, Fujian Medical University Union Hospital, Fuzhou, China; Liewen Pang, Fangrui Wang, Huashan Hospital, Fudan University, Shanghai, China; Yangchun Liu, Qing Lin, Jiangxi People's Hospital, Nanchang, China; Yongyu Liu, Yongkai Wu, Liaoning Cancer Hospital, Shenyang, China; Wentao Fang, Jie Zhang, Yan Shen, Changlu Wang, Lei Zhu, Zhitao Gu, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Yongtao Han, Lin Peng, Sichuan Cancer Hospital, Chengdu, China; Jianhua Fu, Qianwen Liu, Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Zhentao Yu, Jie Yue, Tianjin Cancer Hospital, Tianjin, China; Peng Zhang, Yuan Chen, Tianjin Medical University General Hospital, Tianjin, China; Yun Wang, Yingcai Geng, West China Hospital, Sichuan University, Chengdu, China; Xinming Zhou, Hongguang Zhao, Zhejiang Cancer Hospital, Hangzhou, China.

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

References

1. Girard N, Mornex F, Van Houtte P, et al. Thymoma: a focus on current therapeutic management. J Thorac Oncol 2009;4:119-26.
2. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485-92.
3. Detterbeck FC, Nicholson AG, Kondo K, et al. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. J Thorac Oncol 2011;6:S1710-6.
4. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878-84; discussion 884-5.
5. Singhal S, Shrager JB, Rosenthal DI, et al. Comparison of stages I-II thymoma treated by complete resection with or without adjuvant radiation. Ann Thorac Surg 2003;76:1635-41; discussion 1641-2.
6. Mangi AA, Wright CD, Allan JS, et al. Adjuvant radiation therapy for stage II thymoma. Ann Thorac Surg 2002;74:1033-7.
7. Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy of invasive thymoma. J Clin Oncol 1990;8:1419-23.
8. Bretti S, Berruti A, Loddo C, et al. Multimodal management of stages III-IVa malignant thymoma. Lung Cancer 2004;44:69-77.
9. Loehrer PJ Sr, Jiroutek M, Aisner S, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. Cancer 2001;91:2010-5.
10. Berruti A, Borasio P, Roncari A, et al. Neoadjuvant chemotherapy with adriamycin, cisplatin, vincristine and cyclophosphamide (ADOC) in invasive thymomas: results in six patients. Ann Oncol 1993;4:429-31.
11. Berruti A, Borasio P, Gerbino A, et al. Primary chemotherapy with adriamycin, cisplatin, vincristine and cyclophosphamide in locally advanced thymomas: a single institution experience. Br J Cancer 1999;81:841-5.
12. Ströbel P, Bauer A, Puppe B, et al. Tumor recurrence and survival in patients treated for thymomas and thymic squamous cell carcinomas: a retrospective analysis. J Clin Oncol 2004;22:1501-9.
13. Kim BK, Cho BC, Choi HJ, et al. A single institutional experience of surgically resected thymic epithelial tumors over 10 years: clinical outcomes and clinicopathologic features. Oncol Rep 2008;19:1525-31.
14. Attaran S, McCormack D, Pilling J, et al. Which stages of thymoma benefit from adjuvant chemotherapy post-thymectomy? Interact Cardiovasc Thorac Surg 2012;15:273-5.

Cite this article as: Ma K, Gu Z, Han Y, Fu J, Shen Y, Wei Y, Tan L, Zhang P, Chen C, Zhang R, Li Y, Chen K, Chen H, Liu Y, Cui Y, Wang Y, Pang L, Yu Z, Zhou X, Liu Y, Liu Y, Fang W; Members of the Chinese Alliance for Research in Thymomas. The application of postoperative chemotherapy in thymic tumors and its prognostic effect. J Thorac Dis 2016;8(4):696-704. doi: 10.21037/jtd.2016.03.31

Original Article

Outcome of nonsurgical treatment for locally advanced thymic tumors

Chang-Lu Wang[1], Lan-Ting Gao[1], Chang-Xing Lv[1], Lei Zhu[2], Wen-Tao Fang[3]

[1]Department of Radiation Oncology, [2]Department of Pathology, [3]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China

Contributions: (I) Conception and design: CL Wang, WT Fang; (II) Administrative support: CX Lv; (III) Provision of study materials or patients: CX Lv, CL Wang, L Zhu; (IV) Collection and assembly of data: CL Wang, LT Gao; (V) Data analysis and interpretation: CL Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Professor Wen-Tao Fang. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 West Huaihai Road, Shanghai 200030, China. Email: vwtfang@hotmail.com.

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

Submitted Oct 05, 2015. Accepted for publication Nov 10, 2015.
doi: 10.21037/jtd.2016.01.79
View this article at: http://dx.doi.org/10.21037/jtd.2016.01.79

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.

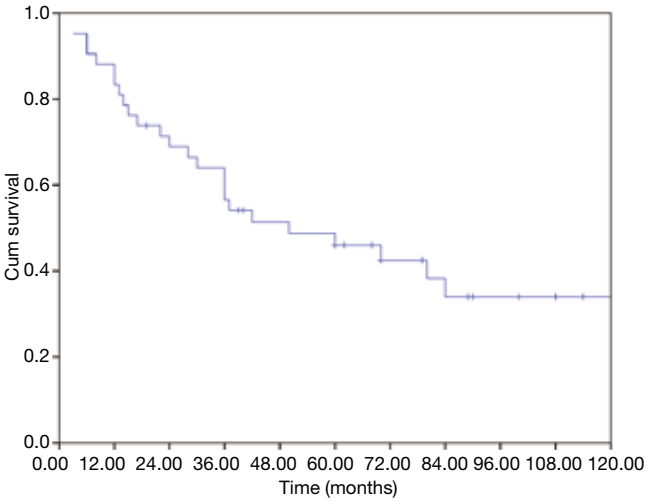


Figure 1 Overall survival (OS) of all 42 patients.

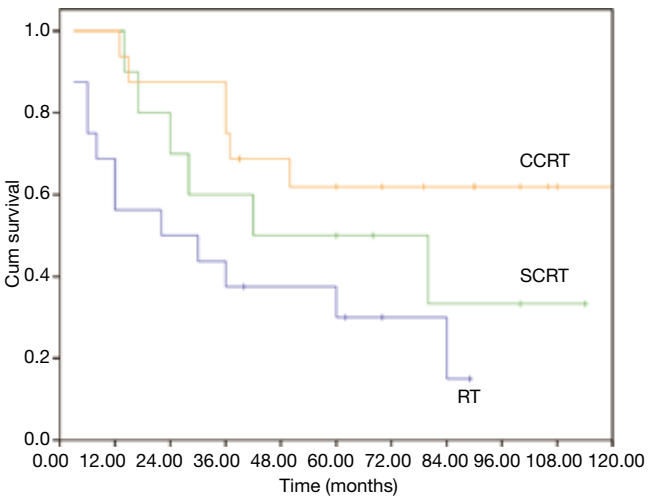


Figure 2 Survival curves of three treatment regimens (CCRT *vs.* SCRT, P=0.282; CCRT *vs.* RT, P=0.011; SCRT *vs.* RT, P=0.230). CCRT, concurrent chemoradiation; SCRT, sequential chemoradiation; RT, radiotherapy.

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%).

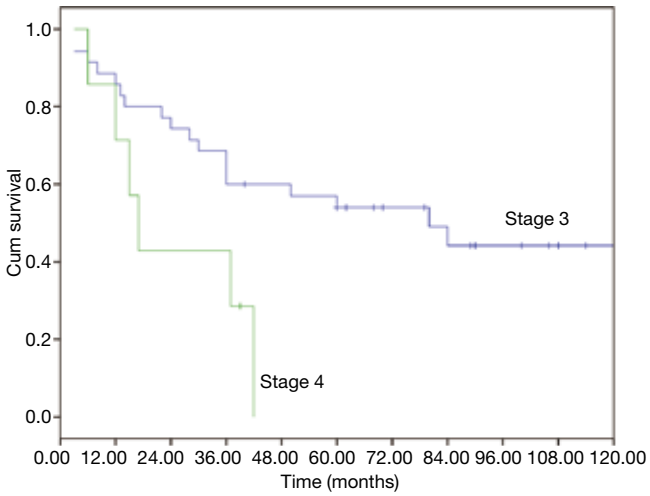


Figure 3 Overall survival (OS) of patients with Masaoka III and IV tumors (P=0.009).

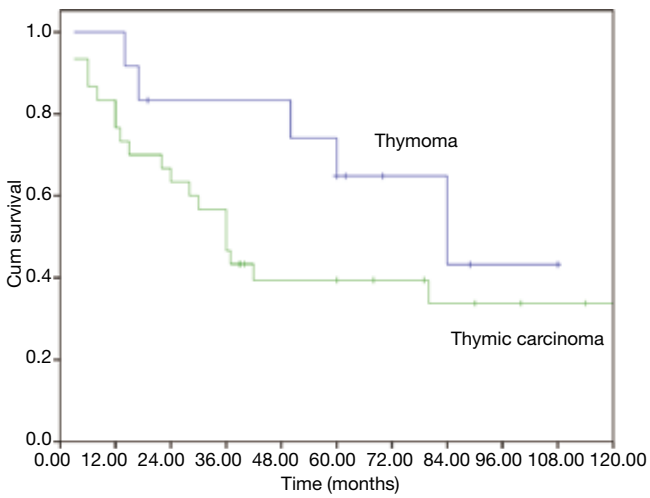


Figure 4 Overall survival (OS) of patients with thymoma and thymic carcinoma (P=0.163).

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.

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

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.

Acknowledgements

The authors want to thank Ms. Yuan Liu for her support in statistics.

Footnote

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

References

1. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol 2010;5:S260-5.

2. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878-84; discussion 884-5.
3. Riely GJ, Huang J. Induction therapy for locally advanced thymoma. J Thorac Oncol 2010;5:S323-6.
4. Benveniste MF, Korst RJ, Rajan A, et al. A practical guide from the International Thymic Malignancy Interest Group (ITMIG) regarding the radiographic assessment of treatment response of thymic epithelial tumors using modified RECIST criteria. J Thorac Oncol 2014;9:S119-24.
5. Fang W, Chen W, Chen G, et al. Surgical management of thymic epithelial tumors: a retrospective review of 204 cases. Ann Thorac Surg 2005;80:2002-7.
6. Vokes EE, Weichselbaum RR. Concomitant chemoradiotherapy: rationale and clinical experience in patients with solid tumors. J Clin Oncol 1990;8:911-34.
7. Trott KR. Radiobiological mechanisms for new strategies in radiochemotherapy. Strahlenther Onkol 1998;174:421-6.
8. Bartelink H, Schellens JH, Verheij M. The combined use of radiotherapy and chemotherapy in the treatment of solid tumours. Eur J Cancer 2002;38:216-22.
9. Slampa P. Overview of concomitant chemoradiotherapy of solid tumors. Cas Lek Cesk 2003;142 Suppl 1:4-8.
10. Chen YY, Huang CH, Tang Y, et al. Concurrent chemoradiotherapy for unresectable thymic carcinoma. Chang Gung Med J 2004;27:515-22.
11. Suster S, Rosai J. Thymic carcinoma. A clinicopathologic study of 60 cases. Cancer 1991;67:1025-32.
12. Liu HC, Hsu WH, Chen YJ, et al. Primary thymic carcinoma. Ann Thorac Surg 2002;73:1076-81.
13. Ogawa K, Toita T, Uno T, et al. Treatment and prognosis of thymic carcinoma: a retrospective analysis of 40 cases. Cancer 2002;94:3115-9.
14. Wright CD, Choi NC, Wain JC, et al. Induction chemoradiotherapy followed by resection for locally advanced Masaoka stage III and IVA thymic tumors. Ann Thorac Surg 2008;85:385-9.
15. Korst RJ, Bezjak A, Blackmon S, et al. Neoadjuvant chemoradiotherapy for locally advanced thymic tumors: a phase II, multi-institutional clinical trial. J Thorac Cardiovasc Surg 2014;147:36-44, 46.e1.
16. Lucchi M, Ambrogi MC, Duranti L, et al. Advanced stage thymomas and thymic carcinomas: results of multimodality treatments. Ann Thorac Surg 2005;79:1840-4.
17. Rea F, Sartori F, Loy M, et al. Chemotherapy and operation for invasive thymoma. J Thorac Cardiovasc Surg 1993;106:543-9.
18. Onuki T, Ishikawa S, Yamamoto T, et al. Pathologic radioresponse of preoperatively irradiated invasive thymomas. J Thorac Oncol 2008;3:270-6.
19. Watanabe N, Umemura S, Niho S, et al. Docetaxel for platinum-refractory advanced thymic carcinoma. Jpn J Clin Oncol 2015;45:665-9.

Cite this article as: Wang CL, Gao LT, Lv CX, Zhu L, Fang WT. Outcome of nonsurgical treatment for locally advanced thymic tumors. J Thorac Dis 2016;8(4):705-710. doi: 10.21037/jtd.2016.01.79

Original Article

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

Fangrui Wang[1], Liewen Pang[1], Jianhua Fu[2], Yi Shen[3], Yucheng Wei[3], Lijie Tan[4], Peng Zhang[5], Yongtao Han[6], Chun Chen[7], Renquan Zhang[8], Yin Li[9], Keneng Chen[10], Hezhong Chen[11], Yongyu Liu[12], Youbing Cui[13], Yun Wang[14], Zhentao Yu[15], Xinming Zhou[16], Yangchun Liu[17], Yuan Liu[18], Zhitao Gu[18], Wentao Fang[18]; Members of the Chinese Alliance for Research in Thymomas[a]

[1]Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200040, China; [2]Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China; [3]Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266001, China; [4]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [5]Department of Endocrinology, Tianjin Medical University General Hospital, Tianjin 300052, China; [6]Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu 610041, China; [7]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou 350001, China; [8]Department of Thoracic Surgery, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [9]Department of Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, China; [10]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing 100142, China; [11]Department of Cardiothoracic Surgery, Changhai Hospital, Shanghai 200433, China; [12]Department of Thoracic Surgery, Liaoning Cancer Hospital, Shenyang 110042, China; [13]Department of Thoracic Surgery, First Affiliated Hospital of Jilin University, Changchun 130021, China; [14]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China; [15]Department of Esophageal Cancer, Tianjin Cancer Hospital, Tianjin 300060, China; [16]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China; [17]Department of Thoracic Surgery, Jiangxi People's Hospital, Nanchang 330006, China; [18]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China

Contributions: (I) Conception and design: L Pang, F Wang, Z Gu; (II) Administrative support: W Fang, Z Gu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Z Gu, F Wang; (V) Data analysis and interpretation: Y Liu, Z Gu, F Wang, L Pang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Liewen Pang. Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200040, China. Email: plwmd1967@126.com; Wentao Fang. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 Huaihai Road West, Shanghai 200030, China. Email: vwtfang12@shchest.org.

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

Submitted Oct 05, 2015. Accepted for publication Nov 12, 2015.
doi: 10.21037/jtd.2016.02.07
View this article at: http://dx.doi.org/10.21037/jtd.2016.02.07

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.

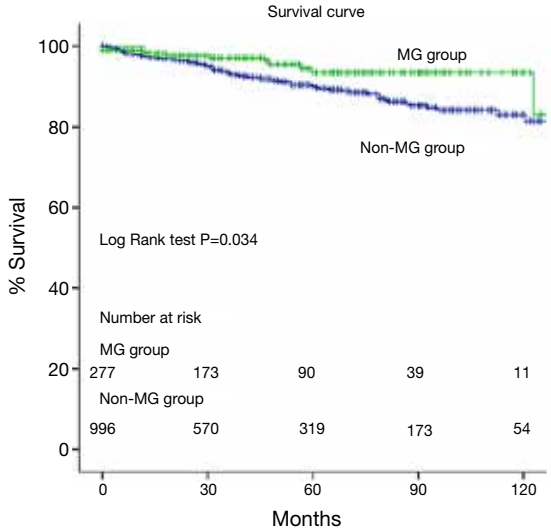


Figure 1 Comparison of overall survival between MG group and non-MG group. MG, myasthenia gravis.

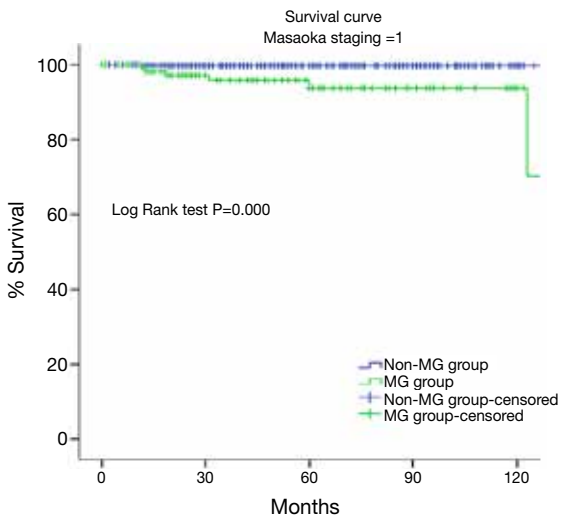


Figure 2 Comparison of overall survival between MG group and non-MG group in Masaoka stage I. MG, myasthenia gravis.

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

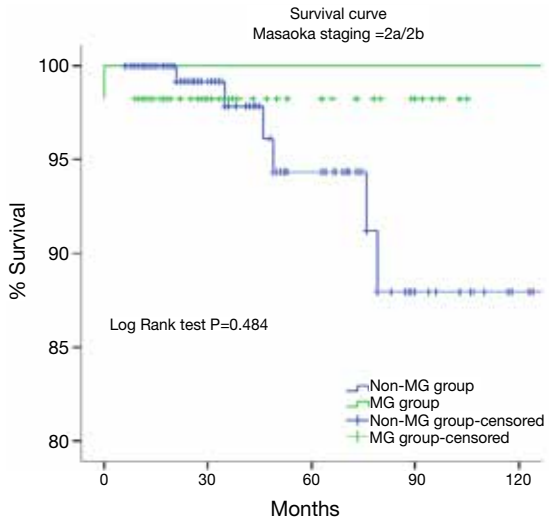


Figure 3 Comparison of overall survival between MG group and non-MG group in Masaoka stage II. MG, myasthenia gravis.

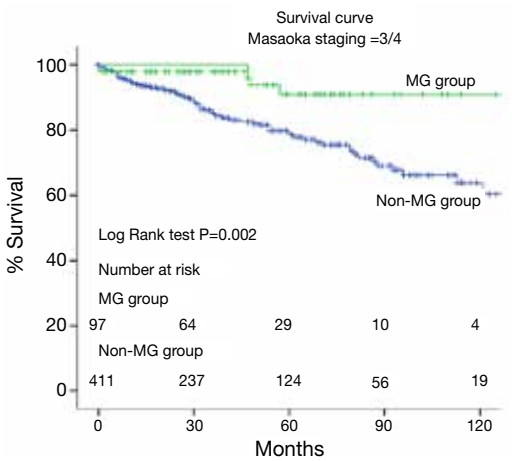


Figure 4 Comparison of overall survival between MG group and non-MG group in Masaoka stage III and IV. MG, myasthenia gravis.

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.

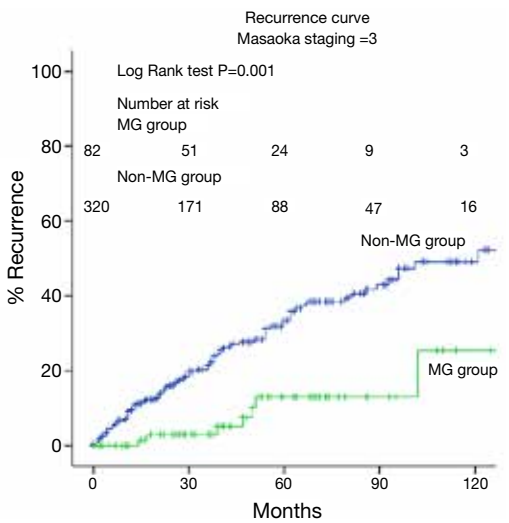


Figure 5 Comparison of tumor recurrence between MG group and non-MG group in advanced stage. MG, myasthenia gravis.

group (*Figures 5,6*).

Discussion

The appearance of MG in patients with thymoma makes them stand out from the population not only because of

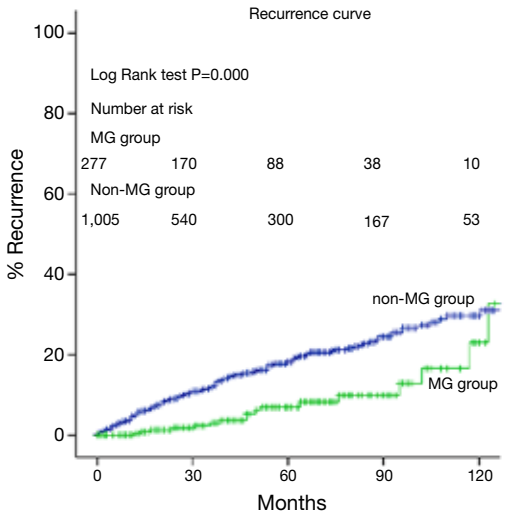


Figure 6 Comparison of tumor recurrence between MG group and non-MG group. MG, myasthenia gravis.

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.

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.

Acknowledgements

None.

Footnote

[a]*Members of Chinese Alliance for Research in Thymomas* (*ChART*): Yi Shen, Yucheng Wei, Affiliated Hospital of Qingdao University, Qingdao, China; Yin Li, Guanghui Liang, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Keneng Chen, Hao Fu, Beijing Cancer Hospital, Beijing, China; Hezhong Chen, Shihua Yao, Changhai Hospital, Shanghai, China; Youbin Cui, Yanzhong Xin, First Affiliated Hospital of Jilin University, Changchun, China; Renquan Zhang, Ningning Kang, First Hospital of Anhui Medical University, Hefei, China; Lijie Tan, Jianyong Ding, Hao Wang, Gang Chen, Jie Wu, Zhongshan Hospital, Fudan University, Shanghai, China; Chun Chen, Wei Zheng, Fujian Medical University Union Hospital, Fuzhou, China; Liewen Pang, Fangrui Wang, Huashan Hospital, Fudan University, Shanghai, China; Yangchun Liu, Qing Lin, Jiangxi People's Hospital, Nanchang, China; Yongyu Liu, Yongkai Wu, Liaoning Cancer Hospital, Shenyang, China; Wentao Fang, Jie Zhang, Yan Shen, Changlu Wang, Lei Zhu, Zhitao Gu, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Yongtao Han, Lin Peng, Sichuan Cancer Hospital, Chengdu, China; Jianhua Fu, Qianwen Liu, Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Zhentao Yu, Jie Yue, Tianjin Cancer Hospital, Tianjin, China; Peng Zhang, Yuan Chen, Tianjin Medical University General Hospital, Tianjin, China; Yun Wang, Yingcai Geng, West China Hospital, Sichuan University, Chengdu, China; Xinming Zhou, Hongguang Zhao, Zhejiang Cancer Hospital, Hangzhou, China.

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

References

1. Maggi G, Casadio C, Cavallo A, et al. Thymoma: results of 241 operated cases. Ann Thorac Surg 1991;51:152-6.
2. Okumura M, Miyoshi S, Takeuchi Y, et al. Results of surgical treatment of thymomas with special reference to the involved organs. J Thorac Cardiovasc Surg 1999;117:605-13.
3. de Perrot M, Liu J, Bril V, et al. Prognostic significance of thymomas in patients with myasthenia gravis. Ann Thorac Surg 2002;74:1658-62.
4. Maggi G, Casadio C, Cavallo A, et al. Thymectomy in myasthenia gravis. Results of 662 cases operated upon in 15 years. Eur J Cardiothorac Surg 1989;3:504-9; discussion 510-1.
5. Kondo K, Monden Y. Thymoma and myasthenia gravis:

a clinical study of 1,089 patients from Japan. Ann Thorac Surg 2005;79:219-24.
6. Ruffini E, Filosso PL, Mossetti C, et al. Thymoma: inter-relationships among World Health Organization histology, Masaoka staging and myasthenia gravis and their independent prognostic significance: a single-centre experience. Eur J Cardiothorac Surg 2011;40:146-53.
7. Filosso PL, Venuta F, Oliaro A, et al. Thymoma and inter-relationships between clinical variables: a multicentre study in 537 patients. Eur J Cardiothorac Surg 2014;45:1020-7.

Cite this article as: Wang F, Pang L, Fu J, Shen Y, Wei Y, Tan L, Zhang P, Han Y, Chen C, Zhang R, Li Y, Chen K, Chen H, Liu Y, Cui Y, Wang Y, Yu Z, Zhou X, Liu Y, Liu Y, Gu Z, Fang W; Members of the Chinese Alliance for Research in Thymomas. Postoperative survival for patients with thymoma complicating myasthenia gravis—preliminary retrospective results of the ChART database. J Thorac Dis 2016;8(4): 711-717. doi: 10.21037/jtd.2016.02.07

Original Article

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

Lei Zhu[1], Jie Zhang[1], Alexander Marx[2], Christel Weiss[3], Wen-Tao Fang[4]

[1]Department of Pathology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200032, China; [2]Institute of Pathology, [3]Department of Medical Statistics and Biomathematics, University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany; [4]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200032, China

Contributions: (I) Conception and design: J Zhang, WT Fang; (II) Administrative support: None; (III) Provision of study materials or patients: L Zhu; (IV) Collection and assembly of data: L Zhu, J Zhang, A Marx; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: all authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jie Zhang, MD, MS. Department of Pathology, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 Huaihai Road(W), Shanghai 200032, China. Email: jiezhang49@hotmail.com; Wen-Tao Fang, MD, PhD. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 Huaihai Road(W), Shanghai 200032, China. Email: vwtfang@hotmail.com.

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

Submitted Jan 21, 2016. Accepted for publication Feb 23, 2016.
doi: 10.21037/jtd.2016.03.24
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.24

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.

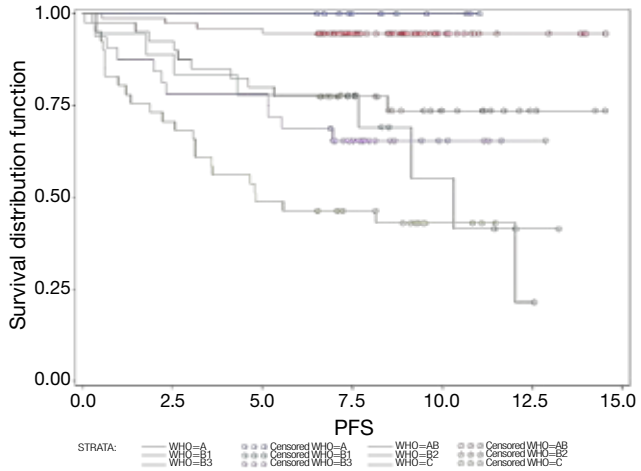


Figure 1 PFS by thymoma subgroup. The total number of cases was 241 (A, n=12; AB, n=74; B1, n=18; B2, n=46; B3, n=33; TCs, n=58). PFS, progression free survival.

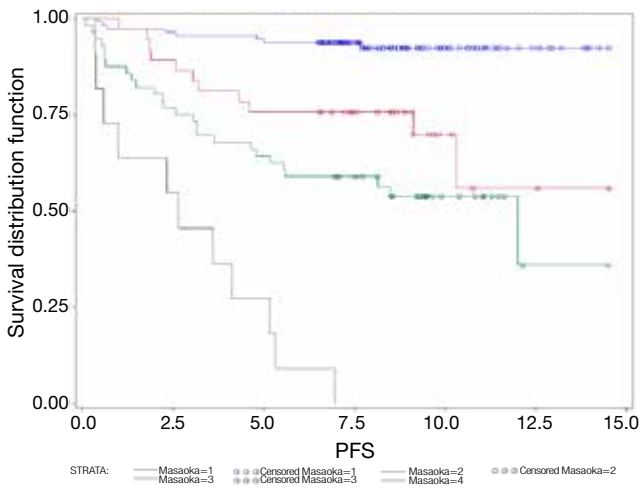


Figure 2 PFS by Masaoka stage. Total number of cases was 241 (stage I, n=115; stage II, n=38; stage III, n=74; stage IV, n=14). PFS, progression free survival.

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.

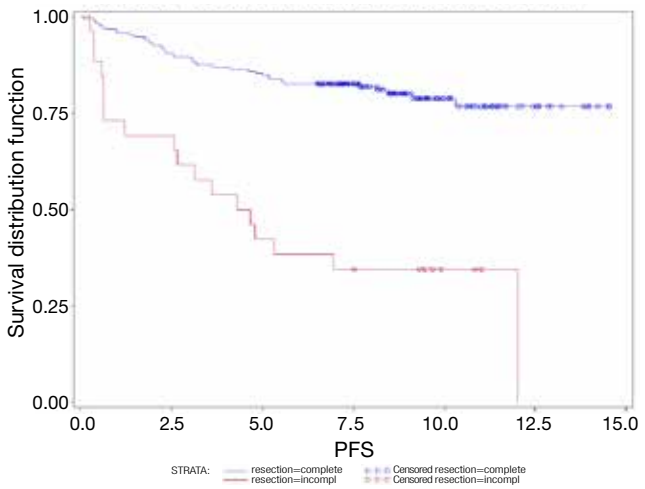


Figure 3 PFS of A, AB, B1, B2 and B3 thymomas and TCs by resection status. Total number of cases was 241 (complete resection: n=206; incomplete resection: n=35). PFS, progression free survival; TCs, thymic carcinomas.

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.

Acknowledgements

None.

Footnote

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

References

1. Marchevsky AM, Gupta R, McKenna RJ, et al. Evidence-based pathology and the pathologic evaluation of thymomas: the World Health Organization classification can be simplified into only 3 categories other than thymic carcinoma. Cancer 2008;112:2780-8.
2. Marino M, Müller-Hermelink HK. Thymoma and thymic carcinoma. Relation of thymoma epithelial cells to the cortical and medullary differentiation of thymus. Virchows Arch A Pathol Anat Histopathol 1985;407:119-49.
3. Rosai J, Sobin LH. Histological Typing of Tumors of the Thymus. 2nd ed. Berlin: Springer, 1999.
4. Travis WD, Brambilla E, Müller-Hermerlink Hk., et al. WHO Classification of tumors of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press, 2004.
5. Suster S, Moran CA. Histologic classification of thymoma: the World Health Organization and beyond. Hematol Oncol Clin North Am 2008;22:381-92.
6. Rieker RJ, Hoegel J, Morresi-Hauf A, et al. Histologic classification of thymic epithelial tumors: comparison of established classification schemes. Int J Cancer 2002;98:900-6.
7. Chalabreysse L, Roy P, Cordier JF, et al. Correlation of the WHO schema for the classification of thymic epithelial neoplasms with prognosis: a retrospective study of 90 tumors. Am J Surg Pathol 2002;26:1605-11.
8. Chen G, Marx A, Chen WH, et al. New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. Cancer 2002;95:420-9.
9. Detterbeck FC. Clinical value of the WHO classification system of thymoma. Ann Thorac Surg 2006;81:2328-34.
10. Verghese ET, den Bakker MA, Campbell A, et al. Interobserver variation in the classification of thymic tumours--a multicentre study using the WHO classification system. Histopathology 2008;53:218-23.
11. Kim DJ, Yang WI, Choi SS, et al. Prognostic and clinical relevance of the World Health Organization schema for the classification of thymic epithelial tumors: a clinicopathologic study of 108 patients and literature review. Chest 2005;127:755-61.
12. Park MS, Chung KY, Kim KD, et al. Prognosis of thymic epithelial tumors according to the new World Health Organization histologic classification. Ann Thorac Surg 2004;78:992-7; discussion 997-8.
13. Ströbel P, Bauer A, Puppe B, et al. Tumor recurrence and survival in patients treated for thymomas and thymic squamous cell carcinomas: a retrospective analysis. J Clin Oncol 2004;22:1501-9.
14. Kondo K, Yoshizawa K, Tsuyuguchi M, et al. WHO histologic classification is a prognostic indicator in thymoma. Ann Thorac Surg 2004;77:1183-8.
15. Okumura M, Ohta M, Tateyama H, et al. The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. Cancer 2002;94:624-32.
16. Nakagawa K, Asamura H, Matsuno Y, et al. Thymoma: a clinicopathologic study based on the new World Health Organization classification. J Thorac Cardiovasc Surg 2003;126:1134-40.
17. Rea F, Marulli G, Girardi R, et al. Long-term survival and prognostic factors in thymic epithelial tumours. Eur J Cardiothorac Surg 2004;26:412-8.
18. Rena O, Papalia E, Maggi G, et al. World Health Organization histologic classification: an independent prognostic factor in resected thymomas. Lung Cancer 2005;50:59-66.
19. Marx A, Rieker R, Toker A, et al. Thymic carcinoma: is it a separate entity? From molecular to clinical evidence. Thorac Surg Clin 2011;21:25-31. v-vi.
20. Jain RK, Mehta RJ, Henley JD, et al. WHO types A and AB thymomas: not always benign. Mod Pathol 2010;23:1641-9.
21. Fang W, Chen W, Chen G, et al. Surgical management of thymic epithelial tumors: a retrospective review of 204 cases. Ann Thorac Surg 2005;80:2002-7.
22. Masaoka A. Staging system of thymoma. J Thorac Oncol 2010;5:S304-12.
23. Zettl A, Ströbel P, Wagner K, et al. Recurrent genetic aberrations in thymoma and thymic carcinoma. Am J Pathol 2000;157:257-66.
24. Girard N, Shen R, Guo T, et al. Comprehensive genomic analysis reveals clinically relevant molecular distinctions between thymic carcinomas and thymomas. Clin Cancer Res 2009;15:6790-9.
25. Kaira K, Murakami H, Serizawa M, et al. MUC1

expression in thymic epithelial tumors: MUC1 may be useful marker as differential diagnosis between type B3 thymoma and thymic carcinoma. Virchows Arch 2011;458:615-20.
26. Wright CD, Wain JC, Wong DR, et al. Predictors of recurrence in thymic tumors: importance of invasion, World Health Organization histology, and size. J Thorac Cardiovasc Surg 2005;130:1413-21.
27. Marx A, Willcox N, Leite MI, et al. Thymoma and paraneoplastic myasthenia gravis. Autoimmunity 2010;43:413-27.
28. Detterbeck FC, Parsons AM. Management of stage I and II thymoma. Thorac Surg Clin 2011;21:59-67, vi-vii.

Cite this article as: Zhu L, Zhang J, Marx A, Weiss C, Fang WT. Clinicopathological analysis of 241 thymic epithelial tumors—experience in the Shanghai Chest Hospital from 1997–2004. J Thorac Dis 2016;8(4):718-726. doi: 10.21037/jtd.2016.03.24

Original 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

Guanghui Liang[1*], Zhitao Gu[2*], Yin Li[1], Jianhua Fu[3], Yi Shen[4], Yucheng Wei[4], Lijie Tan[5], Peng Zhang[6], Yongtao Han[7], Chun Chen[8], Renquan Zhang[9], Keneng Chen[10], Hezhong Chen[11], Yongyu Liu[12], Youbing Cui[13], Yun Wang[14], Liewen Pang[15], Zhentao Yu[16], Xinming Zhou[17], Yangchun Liu[18], Yuan Liu[2], Wentao Fang[2]; Members of the Chinese Alliance for Research in Thymomas[a]

[1]Department of Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, China; [2]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [3]Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China; [4]Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266001, China; [5]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [6]Department of Endocrinology, Tianjin Medical University General Hospital, Tianjin 300052, China; [7]Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu 610041, China; [8]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou 350001, China; [9]Department of Thoracic Surgery, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [10]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing 100142, China; [11]Department of Cardiothoracic Surgery, Changhai Hospital, Shanghai 200433, China; [12]Department of Thoracic Surgery, Liaoning Cancer Hospital, Shenyang 110042, China; [13]Department of Thoracic Surgery, First Affiliated Hospital of Jilin University, Changchun 130021, China; [14]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China; [15]Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200032, China; [16]Department of Esophageal Cancer, Tianjin Cancer Hospital, Tianjin 300060, China; [17]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China; [18]Department of Thoracic Surgery, Jiangxi People's Hospital, Nanchang 330006, China

Contributions: (I) Conception and design: Y Li, W Fang; (II) Administrative support: W Fang, Z Gu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Z Gu, G Liang; (V) Data analysis and interpretation: Y Liu, Z Gu, W Fang, Yin Li, G Liang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Yin Li. Department of Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University, 127 Dongming Road, Zhengzhou 450008, China. Email: liyin825@aliyun.com; Wentao Fang. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 Huaihai Road West, Shanghai 200030, China. Email: vwtfang12@shchest.org.

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

Submitted Feb 21, 2016. Accepted for publication Mar 12, 2016.
doi: 10.21037/jtd.2016.03.22
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.22

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

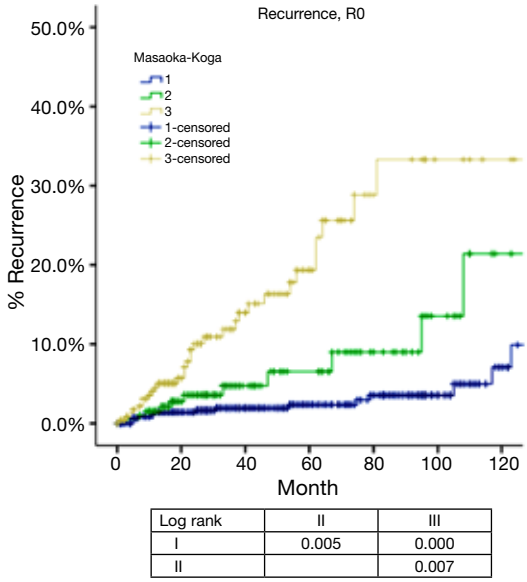


Figure 1 Kaplan-Meier survival curves: cumulative recurrence rate of patients with R0 resection in different stage by the Masaoka-Koga staging (log-rank). R0, complete resection.

Table 3 Differences between Masaoka-Koga categories

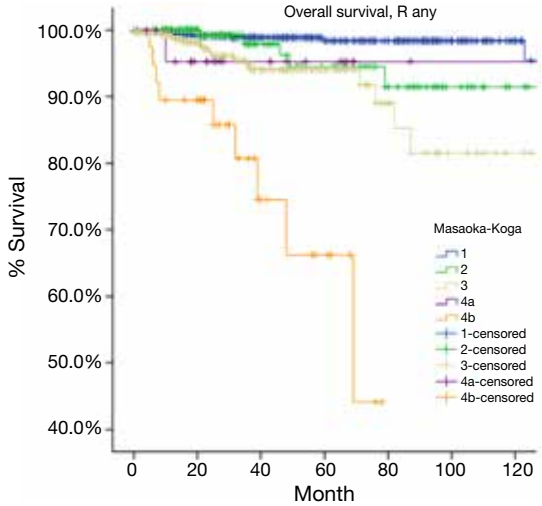
HR *vs.* adjacent Masaoka-Koga staging category	CIR, R0 (67/1,060)*		OS, R0 (23/1,085)*		OS, any R (39/1,198)*	
	HR	P	HR	P	HR	P
II *vs.* I	2.762	0.008	1.932	0.284	2.422	0.122
III *vs.* II	2.428	0.009	1.904	0.286	2.265	0.113
IV *vs.* III	—	—	—	—	3.506	0.002
IVb *vs.* IVa	—	—	—	—	6.482	0.078

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.

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

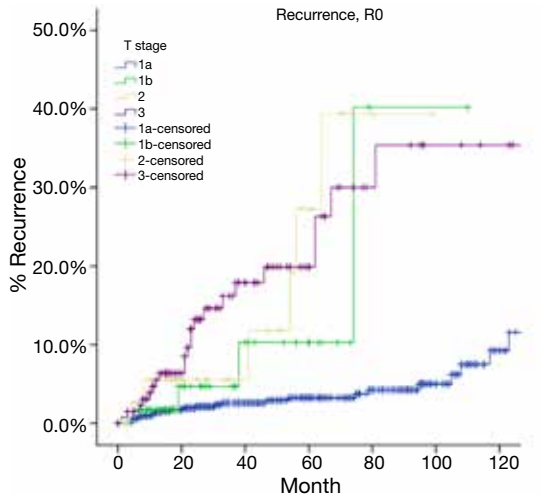
Stage	Recurrences		Deaths	
	%	N	%	N
I	4	36/870	2	17/886
T1aN0M0	4	30/798	1	12/814
T1bN0M0	8	6/72	7	5/72
II	13	6/47	2	1/48
III	19	38/195	5	11/205
IIIa	18	32/178	4	7/188
IIIb	35	6/17	24	4/17
IVa	39	15/38	13	5/38
TxN1M0	43	6/14	29	4/14
TxN0M1a	36	8/22	5	1/22
TxN1M1a	50	1/2	0	0/2
IVb	24	5/21	24	5/21
TxN2M0,1a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

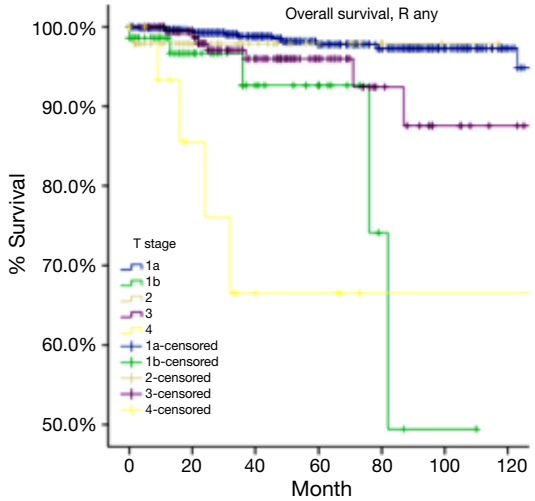
For N categories, CIR in R0 patients was shown in *Figure 6* and OS in R any patients was shown in *Figure 7*. CIR and OS in N negative patients were both better than those of N positive patients (P<0.05), whereas no statistical difference was detected between N1 and N2 (P>0.05). Upon COX analysis, N 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 patients with M positive diseases (P<0.05), whereas no



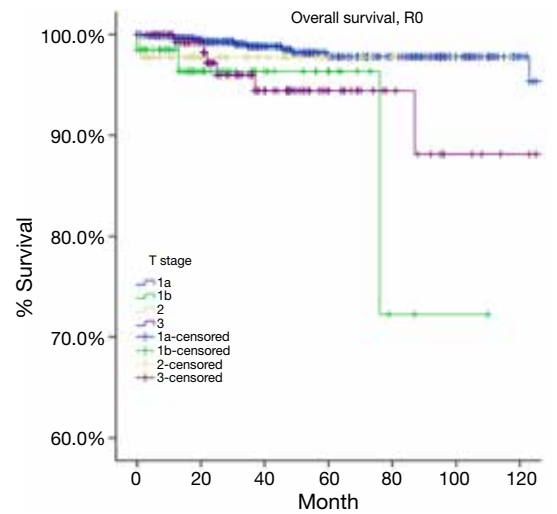
Log rank	T1b	T2	T3
T1a	0.021	0.000	0.000
T1b		0.315	0.215
T2			0.963

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	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.



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.

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*).

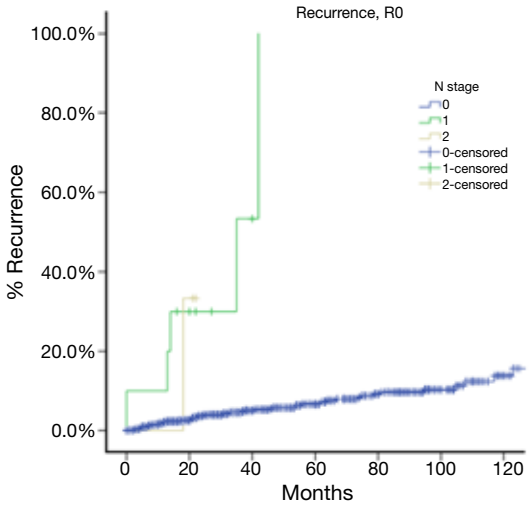
Discussion

Almost a dozen of different staging systems have been proposed for thymic malignancies (6-17). But few have

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

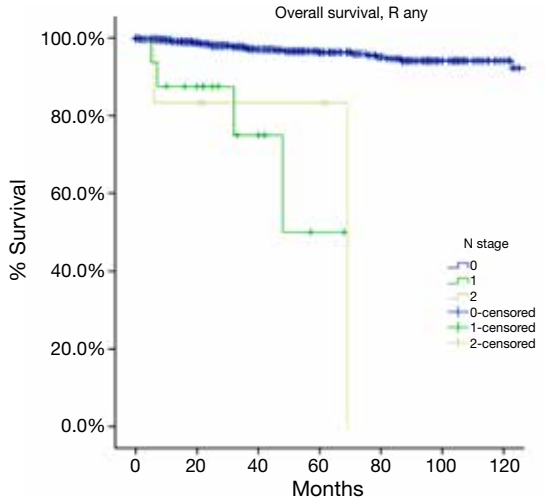
HR *vs.* adjacent T category	CIR, R0 (60/1,039)*		OS, R0 (21/1,064)*		OS, any R (29/1,139)*	
	HR	P	HR	P	HR	P
T1b *vs.* T1a	3.299	0.029	5.574	0.010	8.624	0.000
T2 *vs.* T1b	1.898	0.323	0.410	0.443	0.266	0.227
T3 *vs.* T1b	1.941	0.225	0.607	0.485	0.330	0.061
T2 *vs.* T1	6.299	0.000	1.837	0.558	1.497	0.696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

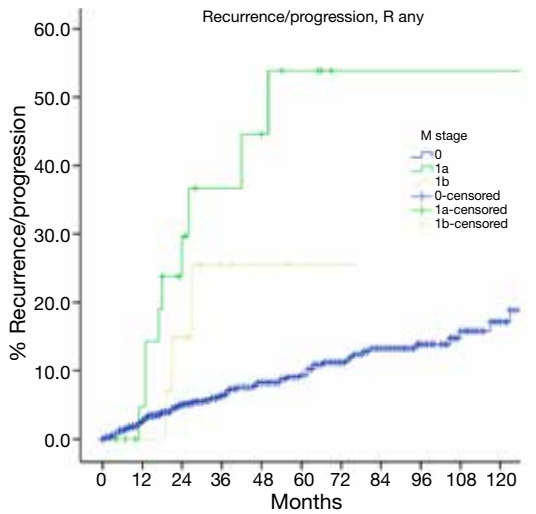
adopted the TNM approach as in most other solid tumors. The IASLC/ITMIG proposal for the new UICC staging of thymic malignancy is mostly based on the widely used Masaoka-Koga system, but using the TNM components instead. As can be seen from *Table 9*, stages I–IIIb in this new staging system are classified 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-Koga stage I and II together to become T1a (stage I)

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

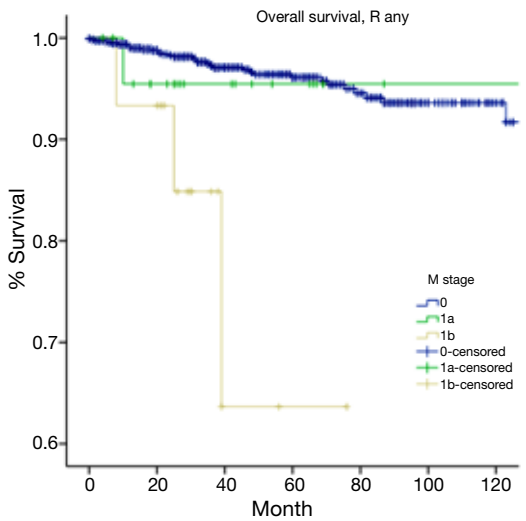
HR *vs.* adjacent N category	CIR, R0 (67/1,060)*		OS, R0 (23/1,085)*		OS, any R (39/1,198)*	
	HR	P	HR	P	HR	P
N1 *vs.* N0	15.66	0.000	6.817	0.062	13.034	0.000
N2 *vs.* N0	10.99	0.018	0.050	0.876	14.074	0.000
N2 *vs.* N1	0.893	0.922	0.033	0.737	0.515	0.559
N1 + N2 *vs.* N0	14.77	0.000	4.968	0.119	8.617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

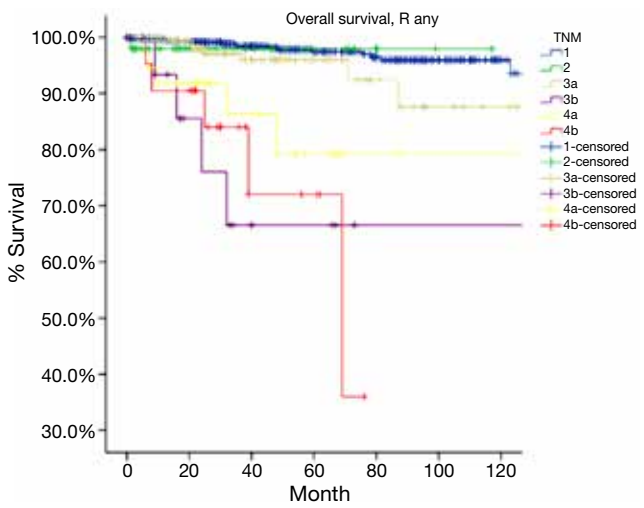
as in the ITMIG proposed system may be warranted (18). Still, the difference between recurrence rates in tumors with or without invasion into the capsule or mediastinal fat (Masaoka-Koga stage I and II) leaves the question whether they should be further subdivided in the future, as recurrence is also 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*) from the ChART database. Pleural invasion theoretically

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).

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 failed to find any significant difference between stage I and

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.

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.

Acknowledgements

None.

Footnote

[a]*Members of Chinese Alliance for Research in Thymomas* (*ChART*): Yi Shen, Yucheng Wei, Affiliated Hospital of Qingdao University, Qingdao, China; Yin Li, and Guanghui Liang, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Keneng Chen and Hao Fu, Beijing Cancer Hospital, Beijing, China; Hezhong Chen and Shihua Yao, Changhai Hospital, Shanghai, China; Youbin Cui and Yanzhong Xin, First Affiliated Hospital of Jilin University, Changchun, China; Renquan Zhang and Ningning Kang, First Hospital of Anhui Medical University, Hefei, China; Lijie Tan, Jianyong Ding, Hao Wang, Gang Chen, and Jie Wu, Zhongshan Hospital, Fudan University, Shanghai, China; Chun Chen and Wei Zheng, Fujian Medical University Union Hospital, Fuzhou, China; Liewen Pang and Fangrui Wang, Huashan Hospital, Fudan University, Shanghai, China; Yangchun Liu and Qing Lin, Jiangxi People's Hospital, Nanchang, China; Yongyu Liu and Yongkai Wu, Liaoning Cancer Hospital, Shenyang, China; Wentao Fang, Jie Zhang, Yan Shen, Changlu Wang, Lei Zhu and Zhitao Gu, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; Yongtao Han, Lin Peng, Sichuan Cancer Hospital, Chengdu, China; Jianhua Fu and Qianwen Liu, Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Zhentao Yu and Jie Yue, Tianjin Cancer Hospital, Tianjin, China; Peng Zhang and Yuan Chen, Tianjin Medical University General Hospital, Tianjin, China; Yun Wang and Yingcai Geng, West China Hospital, Sichuan University, Chengdu, China; Xinming Zhou and Hongguang Zhao, Zhejiang Cancer Hospital, Hangzhou, China.

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

References

1. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485-92.
2. Koga K, Matsuno Y, Noguchi M, et al. A review of 79

thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. Pathol Int 1994;44:359-67.
3. Detterbeck F, Youssef S, Ruffini E, et al. A review of prognostic factors in thymic malignancies. J Thorac Oncol 2011;6:S1698-704.
4. Detterbeck FC, Asamura H, Crowley J, et al. The IASLC/ITMIG thymic malignancies staging project: development of a stage classification for thymic malignancies. J Thorac Oncol 2013;8:1467-73.
5. Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol 2014;9:S65-72.
6. Bergh NP, Gatzinsky P, Larsson S, et al. Tumors of the thymus and thymic region: I. Clinicopathological studies on thymomas. Ann Thorac Surg 1978;25:91-8.
7. Wilkins EW Jr, Castleman B. Thymoma: a continuing survey at the Massachusetts General Hospital. Ann Thorac Surg 1979;28:252-6.
8. Verley JM, Hollmann KH. Thymoma. A comparative study of clinical stages, histologic features, and survival in 200 cases. Cancer 1985;55:1074-86.
9. Regnard JF, Magdeleinat P, Dromer C, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. J Thorac Cardiovasc Surg 1996;112:376-84.
10. Weydert JA, De Young BR, Leslie KO, et al. Recommendations for the reporting of surgically resected thymic epithelial tumors. Am J Clin Pathol 2009;132:10-5.
11. Gamondès JP, Balawi A, Greenland T, et al. Seventeen years of surgical treatment of thymoma: factors influencing survival. Eur J Cardiothorac Surg 1991;5:124-31.
12. Yamakawa Y, Masaoka A, Hashimoto T, et al. A tentative tumor-node-metastasis classification of thymoma. Cancer 1991;68:1984-7.
13. Tsuchiya R, Koga K, Matsuno Y, et al. Thymic carcinoma: proposal for pathological TNM and staging. Pathol Int 1994;44:505-12.
14. Travis WD, Brambilla E, Muller-Hermelink H, et al. Pathology and genetics of tumors of the lung, pleura, thymus and heart. In: Kleihues P, Sobin L, editors. WHO Classification of Tumors. Second Edition. Lyon: IARC Press, 2004:145-97.
15. Bedini AV, Andreani SM, Tavecchio L, et al. Proposal of a novel system for the staging of thymic epithelial tumors. Ann Thorac Surg 2005;80:1994-2000.
16. Kondo K, Monden Y. Lymphogenous and hematogenous metastasis of thymic epithelial tumors. Ann Thorac Surg 2003;76:1859-64; discussion 1864-5.
17. Kondo K. Tumor-node metastasis staging system for thymic epithelial tumors. J Thorac Oncol 2010;5:S352-6.
18. Nicholson AG, Detterbeck FC, Marino M, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposals for the T Component for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol 2014;9:S73-80.
19. Huang J, Detterbeck FC, Wang Z, et al. Standard outcome measures for thymic malignancies. J Thorac Oncol 2010;5:2017-23.
20. Fang W, Chen W, Chen G, et al. Surgical management of thymic epithelial tumors: a retrospective review of 204 cases. Ann Thorac Surg 2005;80:2002-7.
21. Bhora FY, Chen DJ, Detterbeck FC, et al. The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: A Proposed Lymph Node Map for Thymic Epithelial Tumors in the Forthcoming 8th Edition of the TNM Classification of Malignant Tumors. J Thorac Oncol 2014;9:S88-96.
22. Kondo K, Van Schil P, Detterbeck FC, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposals for the N and M components for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol 2014;9:S81-7.

Cite this article as: Liang G, Gu Z, Li Y, Fu J, Shen Y, Wei Y, Tan L, Zhang P, Han Y, Chen C, Zhang R, Chen K, Chen H, Liu Y, Cui Y, Wang Y, Pang L, Yu Z, Zhou X, Liu Y, Liu Y, Fang W; Members of the Chinese Alliance for Research in Thymomas. 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. J Thorac Dis 2016;8(4):727-737. doi: 10.21037/jtd.2016.03.22

Review Article

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

Jie Wu[1], Wentao Fang[2], Gang Chen[1]

[1]Department of Pathology, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [2]Department of Thoracic Surgery, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200030, China

Contributions: (I) Conception and design: G Chen, W Fang; (II) Administrative support: W Fang; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: J Wu; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Gang Chen. Department of Pathology, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China. Email: chestpathology@126.com.

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

Submitted Oct 05, 2015. Accepted for publication Nov 10, 2016.
doi: 10.21037/jtd.2016.01.84
View this article at: http://dx.doi.org/10.21037/jtd.2016.01.84

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%

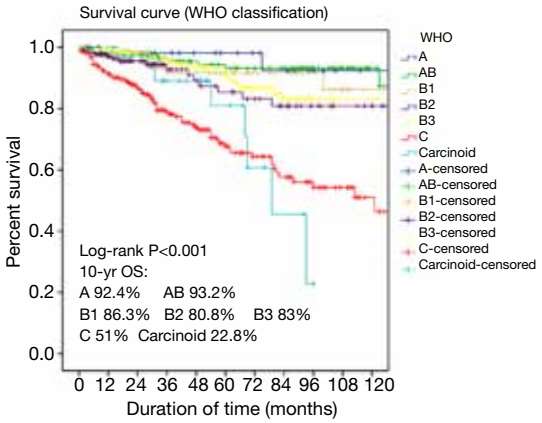


Figure 1 The 10-year overall survival of 1,930 cases of TETs from 10 hospitals from 1994 to 2012.

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.

Acknowledgements

Funding: This study was supported by the Shanghai Science and Technique Committee (134119a3200).

Footnote

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

References

1. Suster S, Moran CA. Problem areas and inconsistencies in the WHO classification of thymoma. Semin Diagn Pathol 2005;22:188-97.
2. Rieker RJ, Hoegel J, Morresi-Hauf A, et al. Histologic classification of thymic epithelial tumors: comparison of established classification schemes. Int J Cancer 2002;98:900-6.
3. Verghese ET, den Bakker MA, Campbell A, et al. Interobserver variation in the classification of thymic tumours--a multicentre study using the WHO classification system. Histopathology 2008;53:218-23.
4. Marx A, Ströbel P, Badve SS, et al. ITMIG consensus

statement on the use of the WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting. J Thorac Oncol 2014;9:596-611.
5. Jain RK, Mehta RJ, Henley JD, et al. WHO types A and AB thymomas: not always benign. Mod Pathol 2010;23:1641-9.
6. Moran CA, Kalhor N, Suster S. Invasive spindle cell thymomas (WHO Type A): a clinicopathologic correlation of 41 cases. Am J Clin Pathol 2010;134:793-8.
7. Wick MR. Histopathologic prognosis of thymomas: another example of medical surrogacy. Am J Clin Pathol 2010;134:703-5.
8. Müller-Hermelink HK, Engel P, Kuo TT, et al. Tumoursofthethymus. In: Travis WD, Brambilla E, Müller-Hermelink HK, eds. World Health Organization Classification of Tumours: Pathology and Genetics. Tumours of the lung, pleura, thymus and heart. Lyon: IARC Press, 2004.
9. Nonaka D, Rosai J. Is there a spectrum of cytologic atypia in type a thymomas analogous to that seen in type B thymomas? A pilot study of 13 cases. Am J Surg Pathol 2012;36:889-94.
10. Ströbel P, Hartmann E, Rosenwald A, et al. Corticomedullary differentiation and maturational arrest in thymomas. Histopathology 2014;64:557-66.
11. Ströbel P, Hohenberger P, Marx A. Thymoma and thymic carcinoma: molecular pathology and targeted therapy. J Thorac Oncol 2010;5:S286-90.
12. Marx A, Rieker R, Toker A, et al. Thymic carcinoma: is it a separate entity? From molecular to clinical evidence. Thorac Surg Clin 2011;21:25-31. v-vi.
13. Weissferdt A, Moran CA. Thymic carcinoma, part 1: a clinicopathologic and immunohistochemical study of 65 cases. Am J Clin Pathol 2012;138:103-14.
14. Moran CA, Suster S. Thymic carcinoma: current concepts and histologic features. Hematol Oncol Clin North Am 2008;22:393-407.
15. Kojika M, Ishii G, Yoshida J, et al. Immunohistochemical differential diagnosis between thymic carcinoma and type B3 thymoma: diagnostic utility of hypoxic marker, GLUT-1, in thymic epithelial neoplasms. Mod Pathol 2009;22:1341-50.
16. Kaira K, Endo M, Abe M, et al. Biologic correlation of 2-[18F]-fluoro-2-deoxy-D-glucose uptake on positron emission tomography in thymic epithelial tumors. J Clin Oncol 2010;28:3746-53.
17. Hishima T, Fukayama M, Fujisawa M, et al. CD5 expression in thymic carcinoma. Am J Pathol 1994;145:268-75.
18. Henley JD, Cummings OW, Loehrer PJ Sr. Tyrosine kinase receptor expression in thymomas. J Cancer Res Clin Oncol 2004;130:222-4.

Cite this article as: Wu J, Fang W, Chen G. The enlightenments from ITMIG Consensus on WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting. J Thorac Dis 2016;8(4):738-743. doi: 10.21037/jtd.2016.01.84

LUNG CANCER

Honorary Editors: Jie He, Rafael Rosell, Nanshan Zhong

Editors: Jianxing He, Thomas A. D'Amico, Xiuyi Zhi

Associate Editors: Qun Wang, Tristan D. Yan, Calvin S.H. Ng, Caicun Zhou, Heather A. Wakelee, Wenhua Liang

FEATURES

- Easy access both online and in print
- With English and Chinese version
- Comprised of contributions by the most accomplished scientists and clinicians internationally
- Illustrate from the basic science of lung cancer to the most advanced therapeutic technique

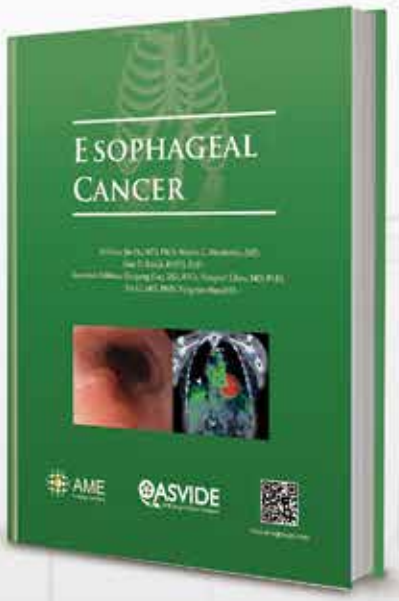
AME Publishing Company

www.amegroups.org

ASVIDE AME Surgical Video Database

AME Publishing Company

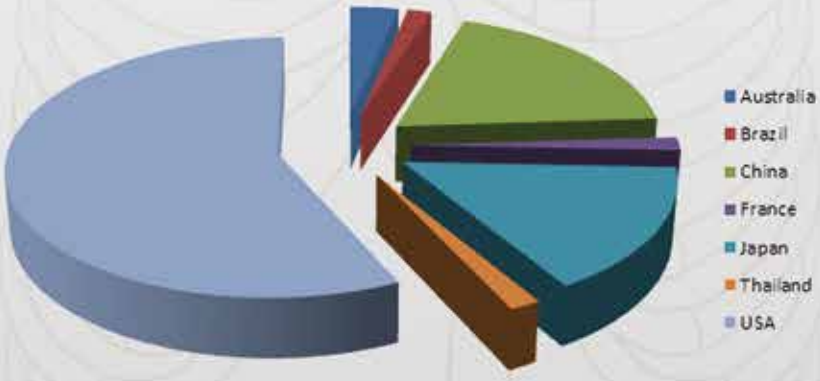
Esophageal Cancer



Editors: Jie He, MD, PhD; Wayne L. Hofstetter, MD;
Guy D. Eslick, DrPH, PhD
Associate Editors: Shugeng Gao, MD, PhD; Haiquan Chen, MD, PhD;
Yin Li, MD, PhD; Yong tao Han,MD

Contents include:

- Molecular Biology
- Overview of Diagnosis and Treatment
- Therapeutic Endoscopy
- Surgery
- Radiotherapy and Medical Treatment
- Prognosis and Prediction



来自Memorial Sloan-Kettering Cancer Center，MD Anderson Cancer Center，Duke University Medical Center, Yale University School of Medicine和Chinese National Cancer Center等众多国际著名癌症研究中心共120多位国际专家联手打造食管癌著作《Esophageal Cancer》

ASVIDE

amazon

www.amegroups.com