Consensus

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

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

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

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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

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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

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

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

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

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

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

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

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

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

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

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

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

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

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Footnote

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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.

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