Editorial

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

Pier Luigi Filosso, Francesco Guerrera, Alberto Sandri, Enrico Ruffini

Department of Thoracic Surgery, University of Torino, Turin, Italy

Correspondence to: Pier Luigi Filosso, MD. Department of Thoracic Surgery, University of Torino, San Giovanni Battista Hospital, Corso Dogliotti, 14 10126 Torino, Italy. Email: pierluigi.filosso@unito.it.

Submitted May 02, 2016. Accepted for publication May 15, 2016.
doi: 10.21037/jtd.2016.05.18
View this article at: http://dx.doi.org/10.21037/jtd.2016.05.18

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

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

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

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

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

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

latest study period, advanced tumors were more frequently treated with induction CT or RT, alone.

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

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

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

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

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

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

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

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Guest Editor Wentao Fang (Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: 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;8:665-72.

References

1. Ruffini E, Detterbeck F, Van Raemdonck D, et al. Tumours of the thymus: a cohort study of prognostic factors from the European Society of Thoracic Surgeons database. Eur J Cardiothorac Surg 2014;46:361-8.
2. 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.
3. Ruffini E, Detterbeck F, Van Raemdonck D, et al. Thymic carcinoma: a cohort study of patients from the European society of thoracic surgeons database. J Thorac Oncol 2014;9:541-8.
4. Leuzzi G, Rocco G, Ruffini E, et al. Multimodality therapy for locally advanced thymomas: A propensity score-matched cohort study from the European Society of Thoracic Surgeons Database. J Thorac Cardiovasc Surg 2016;151:47-57.e1
5. Filosso PL, Yao X, Ahmad U, et al. Outcome of primary neuroendocrine tumors of the thymus: a joint analysis of the International Thymic Malignancy Interest Group and the European Society of Thoracic Surgeons databases. J Thorac Cardiovasc Surg 2015;149:103-9.e2.
6. Filosso PL, Yao X, Ruffini E, et al. Comparison of outcomes between neuroendocrine thymic tumours and other subtypes of thymic carcinomas: a joint analysis of the European Society of Thoracic Surgeons and the International Thymic Malignancy Interest Group. Eur J Cardiothorac Surg 2016. [Epub ahead of print].
7. Thomas CR Jr, Bonomi P. Mediastinal tumors. Curr Opin Oncol 1990;2:359-67.
8. Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and association with subsequent malignancies. Int J Cancer 2003;105:546-51.
9. Venuta F, Anile M, Diso D, et al. Thymoma and thymic carcinoma. Eur J Cardiothorac Surg 2010;37:13-25.
10. Filosso PL, Ruffini E, Lausi PO, et al. Historical perspectives: The evolution of the thymic epithelial tumors staging system. Lung Cancer 2014;83:126-32.
11. 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.
12. Sandri A, Cusumano G, Lococo F, et al. Long-term results after treatment for recurrent thymoma: a multicenter analysis. J Thorac Oncol 2014;9:1796-804.
13. Detterbeck FC, Parson AM. Thymic tumors. Ann Thorac Surg 2004;77:1860-9.
14. Marulli G, Lucchi M, Margaritora S, et al. Surgical treatment of stage III thymic tumors: a multi-institutional review from four Italian centers. Eur J Cardiothorac Surg 2011;39:e1-7.
15. 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.
16. Loehrer PJ Sr, Kim K, Aisner SC, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. J Clin Oncol 1994;12:1164-8.
17. 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.
18. 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;8:665-72.
19. Venuta F, Rendina EA, Longo F, et al. Long-term outcome after multimodality treatment for stage III thymic tumors. Ann Thorac Surg 2003;76:1866-72.
20. 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.
21. 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.
22. 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.
23. 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.
24. Hamaji M, Ali SO, Burt BM. A meta-analysis of induction therapy for advanced Thymic Epithelial Tumors. Ann Thorac Surg 2015;99:1848-56.
25. Huang J, Riedly GJ, Rosenzweig KE, et al. Multimodality therapy for locally advanced Thymomas: state of the art or investigational therapy? Ann Thorac Surg 2008;85:365-7.

Cite this article as: Filosso PL, Guerrera F, Sandri A, Ruffini E. Multimodality therapy for locally-advanced thymic epithelial tumors: where are we now? J Thorac Dis 2016;8(7):1428-1430. doi: 10.21037/jtd.2016.05.18

