Editorial

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

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Submitted Apr 28, 2016. Accepted for publication May 11, 2016.
doi: 10.21037/jtd.2016.05.66
View this article at: http://dx.doi.org/10.21037/jtd.2016.05.66

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

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

The paucity of TET and the in general good prognosis and favorable long-term outcome of most patients with the disease hampers the study of the efficacy of treatments other than surgery and large prospective randomized clinical trials become extremely challenging. Only a few retrospective studies have been performed, which were in general small. One of the largest studies was recently published by Wang *et al*. (13) that was comprised of 42 inoperable patients with TET. This single center, retrospective study from the Shanghai Chest Hospital included 11 patients with thymoma and 31 patients with thymic carcinoma collected over a 10-year period. The study encompassed patients with histologically proven TET, Masaoka stage III disease upon radiologic imaging, stage IV disease with only adjacent

pleural implant or lymph node enlargement which could be covered by one radiation field along with the primary tumor and no metastasis to distant organs. The best objective response rate (ORR) was achieved with concurrent chemoradiation with consolidation chemotherapy (ORR, 87%); patients who were treated with radiation therapy had a significantly lower ORR (44%). Sequential chemoradiation showed a trend towards an ORR (50%) that was lower than that of concurrent chemoradiation. Similarly, patients who were treated with concurrent chemoradiation had a significant better overall survival (5-year survival, 62%) than patients treated with radiation alone (30%) and showed a trend toward better survival than patients treated with sequential chemoradiation (50%). Moreover, concurrent chemoradiation was found to be a prognostic factor that was independent of age, Masaoka stage (stage III *vs*. IV) and histology (thymoma *vs*. thymic carcinoma). A similar 5-year survival of 68% was found by Chen *et al*. using concurrent chemoradiation in 16 patients with unresectable thymic carcinoma although the ORR was only 50% in that study (14). In studies by Wright *et al*. (10), including 10 patients with stage III and IV thymic malignancies and Korst *et al*. (9), including 21 patients with thymoma or thymic carcinoma, concomitant chemoradiation led to 40% and 48% ORR, respectively.

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

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

To validate the observations by Wang *et al*. (13), prospective randomized clinical trials are greatly needed. Given the rarity of these tumors, such clinical trials might only be possible as multicenter regional or global endeavors to accrue a higher number of patients to provide sufficient power for a meaningful statistical analysis of outcome. Furthermore, although PD-L1 expression has been shown in at least a subset of thymoma and thymic carcinoma (12,17,18), randomized prospective clinical trials using anti-PD-1 or anti-PD-L1 antibodies have not been reported. National organizations such as ChART or the Japanese Association for Research of the Thymus (JART) and international associations such as the International Thymic Malignancy Interest Group (ITMIG) that are committed to research of TET would be ideal leaders for this effort. For instance, with contribution from 18 tertiary referral centers in 14 provinces and cities, ChART has successfully built a large national database for thymic malignancies, which contains more than 2,500 cases of treated thymic malignancies during 1994–2012 (12). ITMIG established a retrospective database comprised of over 6,000 cases from 47 institutions from 15 countries from North and South America, Europe and Asia (19). This database was already of fundamental value for the 2015 WHO classification of thymic malignancies (20). Conclusions drawn from the analysis of this database also formed the basis for a staging system that was recently proposed by the International Association of the Study of Lung Cancer (IASLC) and ITMIG that might be useful for thymoma, thymic carcinoma and thymic neuroendocrine tumors as currently no such staging system exist that can be easily applied to all these tumors (21).

In summary, evidence from the study by Wang *et al*. (13) suggests that concomitant chemoradiation might lead to a better outcome in patients with inoperable TET than

subsequent chemoradiation or radiation only. These findings need to be validated in large, multicenter trials that would be most successful if headed by the existing national and international interest groups in TET that are dedicated to the research of these rare tumors and have established robust infrastructures that could facilitate such studies.

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 author has no conflicts of interest to declare.

Comment on: Wang CL, Gao LT, Lv CX, *et al*. Outcome of nonsurgical treatment for locally advanced thymic tumors. J Thorac Dis 2016;8:705-10.

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Cite this article as: Roden AC. Non-surgical treatment of locally advanced thymic epithelial tumors—a need for multicenter trials. J Thorac Dis 2016;8(8):1859-1862. doi: 10.21037/jtd.2016.05.66