Editorial

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

Marcelo F. Benveniste[1], Edith M. Marom[2]

[1]Department of Diagnostic Radiology, MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Diagnostic Radiology, Chaim Sheba Medical Center, Ramat-Gan, Israel

Correspondence to: Edith M. Marom. Department of the Chaim Sheba Medical Center affiliated with the Tel Aviv University, Tel Aviv, Israel. Email: edith.marom@gmail.com.

Submitted Apr 12, 2016. Accepted for publication Apr 22, 2016.
doi: 10.21037/jtd.2016.05.34
View this article at: http://dx.doi.org/10.21037/jtd.2016.05.34

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

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

Prior to assessing CT's ability to correlate to Masaoka-Koga pathologic staging in TETs' one should question this gold standard. The staging of TET has been lagging decades behind that of more common malignancies such as lung cancer. The bodies responsible for defining stage classification, the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) have not declared a staging system for TET. Until recently, there were at least 15 different stage classifications created for these diseases, all based on single institution studies of less than 100 patients. Perhaps the most widely known were the Masaoka (20) and the Masaoka-Koga (21) staging systems, both suffer from similar ambiguities.

Well known from clinical practice and all imaging studies, the differentiation of Masaoka-Koga stage I to stage II, or even the differentiation between stage IIa and IIb is almost impossible, all requiring the identification of the microscopic relationship with a tumor capsule (14). It is because of this that some imaging studies grouped stage I and II together, as both require no neoadjuvant therapy and thus this preoperative differentiation was thought to be of lesser importance (7). However, this differentiation proved difficult at pathology as well as not all tumors have a capsule. It is ambiguities like this with the older staging systems, as well as other vague definitions, that prompted the ITMIG to join hands with the International Association for the Study of Lung Cancer (IASLC) and formulate a robust evidence based new staging system.

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

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

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: Shen Y, Gu Z, Ye J, *et al*. CT staging and preoperative assessment of resectability for thymic epithelial tumors. J Thorac Dis 2016;8:646-55.

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.
2. 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.
3. 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.
4. Hayes SA, Huang J, Plodkowski AJ, et al. Preoperative computed tomography findings predict surgical resectability of thymoma. J Thorac Oncol 2014;9:1023-30.
5. Jeong YJ, Lee KS, Kim J, et al. Does CT of thymic epithelial tumors enable us to differentiate histologic

subtypes and predict prognosis? AJR Am J Roentgenol 2004;183:283-9.
6. Liu Y. Characterization of thymic lesions with F-18 FDG PET-CT: an emphasis on epithelial tumors. Nucl Med Commun 2011;32:554-62.
7. Marom EM, Milito MA, Moran CA, et al. Computed tomography findings predicting invasiveness of thymoma. J Thorac Oncol 2011;6:1274-81.
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 G, Shi H, et al. Preoperative CT findings of thymoma are correlated with postoperative Masaoka clinical stage. Acad Radiol 2013;20:66-72.
10. Sadohara J, Fujimoto K, Müller NL, et al. Thymic epithelial tumors: comparison of CT and MR imaging findings of low-risk thymomas, high-risk thymomas, and thymic carcinomas. Eur J Radiol 2006;60:70-9.
11. Tomiyama N, Müller NL, Ellis SJ, et al. Invasive and noninvasive thymoma: distinctive CT features. J Comput Assist Tomogr 2001;25:388-93.
12. Totanarungroj K, Watcharaporn C, Muangman N. Helpful CT findings for giving specific diagnosis of anterior mediastinal tumors. J Med Assoc Thai 2010;93:489-96.
13. Yakushiji S, Tateishi U, Nagai S, et al. Computed tomographic findings and prognosis in thymic epithelial tumor patients. J Comput Assist Tomogr 2008;32:799-805.
14. Shen Y, Gu Z, Ye J, et al. CT staging and preoperative assessment of resectability for thymic epithelial tumors. J Thorac Dis 2016;8:646-55.
15. Ganeshan B, Miles KA. Quantifying tumour heterogeneity with CT. Cancer Imaging 2013;13:140-9.
16. Gripp S, Hilgers K, Wurm R, et al. Thymoma: prognostic factors and treatment outcomes. Cancer 1998;83:1495-503.
17. Elkiran ET, Abali H, Aksoy S, et al. Thymic epithelial neoplasia: a study of 58 cases. Med Oncol 2007;24:197-201.
18. 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.
19. 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.
20. 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.
21. 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.

Cite this article as: Benveniste MF, Marom EM. Only when all contribute their firewood can they build up a big fire. J Thorac Dis 2016;8(7):1391-1393. doi: 10.21037/jtd.2016.05.34

