Editorial Commentary

# Thymoma: does tumor size matter?

**Arya Amini[1], Chad G. Rusthoven[2]**

[1]Department of Radiation Oncology, City of Hope National Medical Center, Duarte, CA, USA; [2]Department of Radiation Oncology, University of Colorado Cancer Center, Aurora, CO, USA

*Correspondence to:* Arya Amini, MD. Department of Radiation Oncology, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010, USA. Email: aamini@coh.org.

*Provenance:* This is an invited article commissioned by the Section Editor Laura Chiara Guglielmetti (Cantonal Hospital Winterthur, Kantonsspital Winterthur, Winterthur, Switzerland).

*Comment on:* Okumura M, Yoshino I, Yano M, *et al.* Tumour size determines both recurrence-free survival and disease-specific survival after surgical treatment for thymoma†. Eur J Cardiothorac Surg 2019;56:174-81.

Submitted May 11, 2019. Accepted for publication Jun 13, 2019.
doi: 10.21037/jtd.2019.06.40
**View this article at:** http://dx.doi.org/10.21037/jtd.2019.06.40

Prior to the American Joint Committee on Cancer (AJCC) 8th edition, no AJCC or Union for International Cancer Control (UICC) stage classification system existed for thymic tumors. Historically, several staging systems have been used including the well-known Masaoka-Koga classification, which characterizes the anatomical extent of disease with respect to the tumor capsule and neighboring or distant structures (1). In a combined effort by the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancies Interest Group (ITMIG), a partnership was formed to develop the AJCC 8th edition classification with TNM staging (2). A total of 10,808 thymoma patients from 105 institutions across 22 countries were analyzed (3,4) to help generate the AJCC classification of thymoma, which mirrored the underlying principles of the Masaoka-Koga system in that tumor stage correlated with the involvement of nearby structures including pericardium (T2), lung/superior vena cava/brachiocephalic vein/chest wall/phrenic nerve (T3), and aorta/arch vessels/myocardium/trachea/esophagus (T4). A nodal staging system was also developed: N1 [anterior (perithymic) lymph nodes] and N2 (deep intrathoracic or cervical nodes). Tumor size was not incorporated into the staging criteria.

In the study recently published by Okumura *et al.* (5), the authors sought to evaluate the prognostic impact of tumor size on recurrence-free survival (RFS) and disease-specific survival (DSS) for patients with surgically resectable thymoma. A total of 2,083 patients were included in the analysis, treated over a period of 20 years, compiled retrospectively by the Japanese Association for Research of the Thymus (JART) from 32 institutions. Tumor size was evaluated based on the maximum diameters seen on computed tomography (CT) based images and ranged from 0.6 to 19.4 cm with a median size of 4.9 cm. The authors found in their analysis a significant tumor size cut-off value at 5 cm for RFS, generating three groups: ≤5 cm (A), 5.1–10 cm (B), and >10 cm (C). The total incidences of disease recurrence for the groups were 3.5%, 10.3%, and 16.7%, respectively. For those undergoing a complete resection, 10-year RFS was 93.8% and 84.3% for tumor size ≤5 cm and greater accordingly. The model developed for DSS incorporated a cutoff of 8 cm; 10-year DFS for those ≤8 and >8 cm was 98.8% and 90.1% respectively. Moreover, while tumor size was positively correlated with tumor stage, both size and stage remained independently associated of with RFS and DSS on multivariable analysis.

Overall, Okumura *et al.* concluded that tumor size represented a significant prognostic factor for local recurrence (5 cm) and DSS (8 cm) in thymoma patients in their series. The authors also point out that their results conflict with previous findings from the IASLC/ITMIG analysis representing the basis for the new AJCC 8th edition staging for thymoma, which included JART data (4). Among other factors, the IASLC/ITMIG project evaluated tumor size in the 5,796 cases with available data on tumor size and found that size was not prognostic; a recursive partitioning analysis was also used to account

for other tumor features and tumor size again appeared to play a very minor role, which is why tumor size was not included in the AJCC staging system. The IASLC/ITMIG project also evaluated whether size predicted for a R0 resection and found that tumor size did not predict for resectability. Tumor size only appeared to make a difference in OS postoperatively among those with R1 *vs.* R2 resections and was, therefore, not considered useful in staging. Okumura *et al.* discuss potential reasons that might underlie the discordant prognostic findings regarding tumor size between their analysis and the IASLC/ITMIG, which include the following: the IASLC/ITMIG analyzed a heterogeneous global dataset with mixed thymic tumor histologies (thymomas and thymic carcinomas) treated with a variety of modalities, whereas the JART analysis included only patients treated in Japan with surgically resected thymomas.

There are other studies that have suggested that tumor size may be a prognostic factor in thymoma. Bian *et al.* analyzed the Surveillance, Epidemiology, and End Results (SEER) database and found that tumor size was associated with postoperative DSS and overall survival (OS) (6). Fukui *et al.* analyzed patients treated with surgical resection at Nagoya University Hospital in Japan and found that tumor size >4 cm was an independent prognostic factor for RFS, similar to the findings of Okumura *et al.* (7). In the IASLC/ITMIG staging project described above, size did appear to predict the probability of a R1 versus R2 resection, suggesting that tumor size is associated with probability of residual disease postoperatively and the need for adjuvant therapy. The current National Comprehensive Cancer Network (NCCN) guidelines suggest postoperative radiation is indicated for R1 resected thymomas and postoperative radiation with or without chemotherapy is indicated following R2 resections (8).

Cancer stage is critical both to prognostication and to informing optimal management strategies for all cancers, including thymomas. Stage also plays an important role in the inclusion or exclusion of clinical trials. Across the field of oncology, rapid changes in diagnostic modalities, molecular classifications, and treatment options has led to relatively frequent incremental updates of the AJCC TNM staging manual, which occur approximately every 5–7 years. It can be challenging to develop simplified staging classifications for each cancer as we become increasingly aware that cancers cannot only be classified by clinical factors such as size and anatomic extension alone, but also require molecular characterizations that are often prognostic for outcomes and predictive of responses to tailored therapies. In addition, when these staging systems are created, one needs to account for the various environments and resources available throughout the world. For example, this has been appreciated in gynecologic oncology where the International Federation of Gynecology and Obstetrics (FIGO) staging historically utilized basic imaging techniques such as chest X-rays and intravenous pyelogram (IVP) in order to account for regions of the world where newer modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans are not readily available. Overall, staging classifications represent increasingly complex undertakings that attempt to account for evolving awareness of prognostic factors balanced with widely available staging technologies and a preference for simplicity of application for clinicians.

Today, thymoma staging and management is driven by the primacy of surgical resection. Adjuvant therapies are currently tailored to extent of resection and a tumor staging system which incorporates extension into surrounding anatomic structures, but not tumor size specifically. This large, thorough analysis of the JART dataset by Okumura and colleagues suggests that tumor size may represent an independent prognostic factor in resectable thymoma appropriate for consideration in future staging systems. Further efforts to validate tumor size as a prognostic factor in distinct populations are warranted, as are predictive analyses regarding the potential interaction of tumor size with adjuvant radiation and systemic therapies.

## Acknowledgments

None.

## Footnote

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

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## References

1. Yamakawa Y, Masaoka A, Hashimoto T, et al. A tentative

 

tumor-node-metastasis classification of thymoma. Cancer 1991;68:1984-7.
2. 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.
3. Huang J, Ahmad U, Antonicelli A, et al. Development of the international thymic malignancy interest group international database: an unprecedented resource for the study of a rare group of tumors. J Thorac Oncol 2014;9:1573-8.
4. 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.
5. Okumura M, Yoshino I, Yano M, et al. Tumour size determines both recurrence-free survival and disease-specific survival after surgical treatment for thymomadagger. Eur J Cardiothorac Surg 2019;56:174-81.
6. Bian D, Zhou F, Yang W, et al. Thymoma size significantly affects the survival, metastasis and effectiveness of adjuvant therapies: a population based study. Oncotarget 2018;9:12273-83.
7. Fukui T, Fukumoto K, Okasaka T, et al. Prognostic impact of tumour size in completely resected thymic epithelial tumours. Eur J Cardiothorac Surg 2016;50:1068-74.
8. Thymomas and Thymic Carcinomas. National Comprehensive Cancer Network (NCCN) Guidelines Version 2. 2019. Accessed May 2019.

**Cite this article as:** Amini A, Rusthoven CG. Thymoma: does tumor size matter? J Thorac Dis 2019;11(Suppl 15):S2005-S2007. doi: 10.21037/jtd.2019.06.40

 