



# Commentary on “Multidisciplinary tumor board decision-making for postoperative radiotherapy in thymic epithelial tumors: insights from the RYTHMIC prospective cohort”

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*Comment on:* Basse C, Thureau S, Bota S, *et al.* Multidisciplinary Tumor Board Decision Making for Postoperative Radiotherapy in Thymic Epithelial Tumors: Insights from the RYTHMIC Prospective Cohort. *J Thorac Oncol* 2017;12:1715-22.

Received: 02 November 2017; Accepted: 01 March 2018; Published: 16 March 2018.

doi: 10.21037/med.2018.03.11

View this article at: <http://dx.doi.org/10.21037/med.2018.03.11>

Thymic epithelial neoplasms, including thymoma, thymic carcinoma, and thymic neuroendocrine tumors, are rare intrathoracic malignancies that may act in an aggressive manner (1,2). At least 15 different stage classification systems for these lesions have been proposed and used to varying degrees clinically, most of which have been derived from small data sets (3). Until recently, the most widely used staging classifications were the Masaoka and Masaoka-Koga staging systems, both based on a single institution cohort of less than 100 patients. The Masaoka-Koga staging system has historically been recommended for use in staging of thymic epithelial neoplasms by the International Thymic Malignancy Interest Group (ITMIG) (4). Recently, a tumor-node-metastasis (TNM) staging system has been implemented after being recognized by the American Joint Committee on Cancer and the Union for International Cancer Control, the groups responsible for defining stage classifications for neoplasms. This staging system was the product of analyses performed on a large retrospective database of 10,000 patients created by ITMIG and the International Association for the Study of Lung Cancer (IASLC) (5,6). As with other thoracic malignancies, work on future iterations of the staging system is constantly underway, with the emphasis currently on prospective data collection. This prospective collection of data is only possible with such a rare disease through multi-institutional collaboration. There is no single institution which can gather a sufficiently large cohort of patients

with thymic epithelial malignancies to establish meaningful and statistically significant insight as to the understanding predictors of survival.

As for the treatment of these rare malignancies, surgical resection remains the treatment of choice; however, these cancers are often difficult to treat and neoadjuvant chemotherapy may be administered when it is determined that complete resection may not be achievable (1,2). Research has revealed recurrence rates following surgery, based on the Masaoka-Koga staging system, of 10% in stage I-II thymomas, 30% in stage III thymomas and stage I-II thymic carcinomas, and 60% in stage IV thymomas and stage III thymic carcinomas (7). The role of radiation therapy in the treatment of thymic epithelial neoplasms continues to evolve. Historically, it has been recommended that radiation therapy be administered to the surgical bed in the anterior/prevascular mediastinum following resection; however, the available guidelines are of low levels of evidence given the lack of a randomized or even prospective clinical study to evaluate the impact on recurrence rate or survival (8). Recent analyses of databases and retrospective studies have demonstrated no survival benefit following radiation therapy in stage I thymoma, questionable survival benefit after complete (R0) surgical resection of stage II-III thymoma, and similar recurrence rate regardless of whether patients received radiation therapy following complete surgical resection of thymoma (9-16). However, there was a recurrence-free and overall survival benefit after surgical

resection of thymic carcinoma (10,12,13,16).

In an effort to overcome the lack of expertise in treating rare diseases in smaller institutions and to overcome erratic treatment decisions, national, international and subspecialty guidelines for many neoplasms recommend that treatment decisions be made in a multidisciplinary tumor board setting. Schmidt *et al.* prospectively evaluated the actual impact of case presentation at a dedicated tumor board on decision making in patients with lung and esophageal cancer (17). Of 724 assessments of 479 patients (85 with esophageal cancer and 294 with lung cancer), the recommendations of the multidisciplinary tumor board differed from the initial treatment plan in 26% and 40% of esophageal and lung cancer patients, respectively, with an overall change in 46% of cases. The authors concluded that treatment recommendations in this setting can be successfully initiated in most patients, and that patients with complex thoracic neoplasms benefit from review at multidisciplinary tumor boards. Foster and colleagues assessed the utility of multidisciplinary case conferences on decision making in cases of benign and malignant breast disease (18). Of 76 patients presented (43 with malignant diagnosis and 33 with benign diagnoses), treatment recommendations differed from the initial plan in 41% of cases due to new and/or clarified diagnostic information. The authors concluded that presentation of clinical cases at multidisciplinary case conferences should be encouraged, especially for difficult diagnostic or management issues.

Despite the advantage of conducting multidisciplinary treatment conferences prior to treatment implementation, such conferences do have their limitations. Decision making, in single institutions, is often swayed by individual factors, related to the treating clinician's individual ability and preferences as well as individual patient factors. Such conferences do not result in the prospective collection of the data that lead to the selection of a certain treatment modality. Thus, any future retrospective study on such patient cohorts and their treatment is limited. Additionally, decision making on chemotherapy or radiation therapy in the treatment of thymic epithelial malignancies is not based on high level evidence as no prospective randomized study has been conducted so far on such patients. As pointed out by Basse *et al.*, published in this issue, it is not possible to reach conclusions as to whether radiation benefits a patient population or not, while studying a patient cohort retrospectively (19).

Before embarking on any randomized novel treatment for this disease, the question remains as to which of the

treatment arms currently available is the correct arm for each patient population. To answer this question, one would have to actively implement a systematic treatment approach while gathering all patient information and all decision making information prospectively. Similar to the staging project, such collection of data would have to be on a large scale, with multi-institutional involvement. Such an approach would enable future insights that cannot be acquired with a retrospective approach, single institution multidisciplinary conferences and prior to implementing a costly randomized multi-institutional trial.

The creation of a nationwide network for France titled "Réseau tumeurs THYMIques et Cancer" (RYTHMIC) is a leap forward in our understanding of this rare disease and has opened a window of opportunity from which the whole world may benefit. RYTHMIC was established in 2012 for the prospective collection of data for all patients for whom clinical management is discussed at a national multidisciplinary tumor board (20). At the local level, it solves the issue of treating a rare disease in a large country, where expertise may vary from major centers in larger cities to the more rural areas. For patients with these neoplasms, clinical management decisions are based on national recommendations and those from the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (2). At a higher level, the strict adherence to treatment guidelines, creating a more homogenous treatment algorithm while prospectively gathering all patient information and treatment decision information, has opened up possibilities to study the effect of a specific treatment on specific patient cohorts. An additional benefit is to more readily quantify the success rate of adherence to treatment decisions and assessing the causes for failing to do so. The study of such failure helps shed light into mass implementation of any future guideline on the population at large not that limited to specialty large hospitals. Basse *et al.* evaluated whether decisions made at this multidisciplinary tumor board regarding treatment with postoperative radiation therapy were in accordance with ESMO/RYTHMIC guidelines (19). Additionally, the authors determined how ITMIG definitions and recommendations for dose-volume constraints were adhered to in an actual practice setting. A total of 274 patients, 243 (89%) with thymoma and 31 (11%) with thymic carcinoma, prospectively evaluated by the multidisciplinary tumor board from 2012 to 2015 were identified from the RYTHMIC database. The ultimate treatment decision of the national multidisciplinary tumor board corresponded

with the established guidelines in 221 (92%) of the 241 patients with stage I–III disease. It was recommended that 117 (43%) of patients be treated with radiation therapy following surgical resection, with this modality ultimately initiated in 101 patients. Several causes were identified for instances in which patients did not actually receive radiation therapy, the most frequent of which was excessive (>3 months) delay after surgical resection. For those patients treated with radiation therapy, the dose-volume constraints defined by ITMIG were followed in all but 4 patients. In conclusion, this study by Basse and colleagues offers insight into the decision-making process for postoperative radiation therapy in the management of thymic epithelial neoplasm and emphasizes the necessity of methodical discussion at expert multidisciplinary tumor boards within the context of expert guidelines currently available. We look forward to future outcome studies from RYTHMIC, as its systematic well controlled approach will certainly enable us to learn more in the future how to best tailor treatment to each patient.

### Acknowledgments

*Funding:* None.

### Footnote

*Provenance and Peer Review:* This article was commissioned and reviewed by Section Editor Xiaomin Niu (Department of Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/med.2018.03.11>). BWC serves as an unpaid editorial board member of *Mediastinum* from May 2017 - Apr 2019. The authors have no other 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.

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doi: 10.21037/med.2018.03.11

**Cite this article as:** Carter BW, Marom EM. Commentary on “Multidisciplinary tumor board decision-making for postoperative radiotherapy in thymic epithelial tumors: insights from the RYTHMIC prospective cohort”. *Mediastinum* 2018;2:18.