Extended Abstract

Thymic tumors: impact of the TNM for medical oncologists: extended abstract

Nicolas Girard[1,2,3,4]

[1]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France; [2]EURACAN, Centre Léon Bérard, Lyon, France; [3]RYTHMIC, Gustave Roussy, Villejuif, France; [4]International Thymic Malignancy Interest Group, Mount Kisco, NY, USA

Correspondence to: Nicolas Girard. Département d'Oncologie Médicale, Institut Curie, 26 rue d'Ulm, 75248 Paris, Cedex 05, France.
Email: nicolas.girard2@curie.fr.

Received: 30 November 2021; Accepted: 24 February 2022; Published: 25 June 2022.
doi: 10.21037/med-21-56
View this article at: https://dx.doi.org/10.21037/med-21-56

Thymic tumors are rare thoracic malignancies that require comprehensive assessment and multidisciplinary management; these may be aggressive and difficult to treat (1). In the past decade, the scientific community has been increasingly interested in that field, with the creation of many dedicated working groups, including the International Thymic Malignancy Interest Group (ITMIG, www.itmig.org), or local organizations, such as the RYTHMIC (Réseau tumeurs THYMiques et Cancer; www.rythmic.org) network in France. At the 2021 ITMIG virtual annual meeting, a discussion focused on the impact of the 8th TNM classification for medical oncologists.

A key point in thymic tumors is that there is no formal clinical staging system, as stage grouping include pathological findings, especially for early stage tumors, and the treatment strategy is then primarily based on whether the tumor may be resected upfront or not, as complete resection represents the most significant prognostic factor on disease-free and overall survival (2,3). Correlation between clinical and final stage is better in advanced stages, given the identification at imaging of vessel invasion, enlarged lymph nodes, pleural/pericardial lesions, or even systemic metastases (4).

The management of patients with TETs is based on multidisciplinary expertise that is mandatory at all stages of the disease (1). The assessment of resectability is mostly based on the radiologist and the surgeon expertise, but may be complex, even if the 8th TNM staging provides a definition of resectable anatomical structures (stage IIIA). Ultimately, stage IV disease does not mean that the tumor is not amenable to complete surgical resection, especially in the setting of localized pleural implants (5,6). Multidisciplinary tumor board (MTB) is then recommended at any stage of the disease. In France, RYTHMIC is a nationwide network dedicated to thymic tumors, which was recognized by the French National Cancer Institute, in 2012. The treatment of all patients with TET is discussed on a real-time basis at a national MTB, which is organized twice a month basis using a web-based system. Decision-making is based on consensual recommendations, that were originally established based on available evidence, and are updated and approved each year by all members of the network (1). Similar thymoma-dedicated networks are now being implemented in France and in other European countries, such as Spain and Italy (the TYME collaborative group) (7,8). EURACAN is a European Reference Network that helps gathering expertise and organizing initiatives across European countries and expert centers.

In Masaoka-Koga stage III/IVA tumors (classified as stage IIIA/IIIB/IVA in the 8th TNM proposed system), complete resection is usually not achievable upfront. A biopsy is performed, followed by primary/induction chemotherapy, in a curative-intent setting with subsequent surgery or radiotherapy (1). Patients not eligible for any kind of local treatment receive definitive chemotherapy.

Chemotherapy should be offered as the single modality treatment in advanced, non-resectable, non-irradiable or metastatic (stage IVB) TETs. The aim is to improve tumor-related symptoms through obtention of tumor response, while prolonged survival is uncertain. Cisplatin-based combination regimen should be administered (9-12). No randomized studies have been conducted, and it is

unclear which regimens are best; multi-agent combination regimens and anthracycline-based regimens report higher response rates compared to others, especially the etoposide, ifosfamide and cisplatin combination; still response is hard to assess given the site of target lesions; criteria recommended for pleural lesions include the use of short axis as the measurement plane, and the unidimensional measurement of 2 pleural tumor sites at 3 different levels (13). Combinations of cisplatin, adriamycin, and cyclophosphamide is preferred. Combination of carboplatin and paclitaxel is an option for thymic carcinoma (11).

All consecutive patients for whom systemic treatment was discussed at the RYTHMIC MTB from 2012 to 2015 and who received at least one cycle of treatment were analysed in a landmark real world evidence study (12). A total of 236 patients were included in this analysis. 91 patients received primary chemotherapy, leading to a response rate of 79%, and a median progression-free survival (PFS) of 23.2 months. Predictors of longer PFS were histology of thymoma and cyclophosphamide, adriamycin and platin (PAC) regimen. Exclusive chemotherapy was delivered to 54 patients. Response rate was 35% and was higher with PAC regimen. Median PFS was 6.2 months, and was correlated to response rate.

In non-resectable recurrences, several consecutive lines of systemic treatment are delivered. PAC chemotherapy may be re-administered. Preferred regimens for second-line treatment include carboplatin plus paclitaxel (10), and platin plus etoposide. Options for subsequent lines include pemetrexed (500 mg/m^2/3 w) (11), oral etoposide (100 mg daily). In the RYTHMIC cohort, chemotherapy for 1st, 2nd, 3rd and 4th recurrence was delivered to 114, 81, 51 and 27 patients, respectively (12). Response rates ranged between 11 and 25%. Median PFS were 7.7, 6.2, 5.9, and 6.5 months, respectively.

Ultimately, a key question is whether the current delineation of stages has to be improved. A common agreement seems to exist to keep the M1a *vs.* M1b definitions, that are correlated with clinical management, with possible surgical resection in M1a, that is infrequently proposed in M1b with the exception of oligometastatic disease; also, there is a need, in the future analyses of databases, to assess outcomes in thymomas and thymic carcinomas separately. Within the M1a group, further distinction of patients with one metastatic site or implant *vs.* patients with multiple sites or implants will be valuable. Within the M1b group, similarly separating patients with oligometastases as there is some relevance in the clinic, maybe regarding outcomes, would better suit the treatment strategies and the outcomes; differentiating intrathoracic (lung) *vs.* extrathoracic lesions would be of interest. Finally, the N1/N2 disease may be grouped with stage III rather than with IV.

Thymic malignancies are rare cancers, with complex classifications and treatment strategies based on multidisciplinary expertise and consensus. The updating of the TNM represents a major initiative in this setting for patients and physicians.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Malgorzata Szolkowska, Mirella Marino, Katarzyna Blasinska, Magdalena Knetki-Wroblewska, and Giuseppe Cardillo) for "The Series Dedicated to the 11th International Thymic Malignancy Interest Group Annual Meeting (Virtual ITMIG 2021)" published in *Mediastinum*. The article has undergone external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-21-56/coif). "The Series Dedicated to the 11th International Thymic Malignancy Interest Group Annual Meeting (Virtual ITMIG 2021)" was commissioned by the editorial office without any funding or sponsorship. NG serves as an unpaid editorial board member of *Mediastinum* from October 2021 to September 2023. The author has no other conflicts of interest to declare.

Ethical Statement: The author is 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-21-56
Cite this article as: Girard N. Thymic tumors: impact of the TNM for medical oncologists: extended abstract. Mediastinum 2022;6:17.