Editorial Commentary

Best practices and guidelines for the management of thymic epithelial tumors

Giuseppe Giaccone, Jonathan W. Lischalk

Lombardi Comprehensive Cancer Center, Department of Oncology, Georgetown University Medical Center, Washington, DC, USA

Correspondence to: Giuseppe Giaccone, MD, PHD. Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3970 Reservoir Road, Washington, DC 20007, USA. Email: gg496@georgetown.edu.

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This is an Editorial comment to a position paper by Italian experts in thymic malignancies. Controversies in the managements of this heterogeneous and rare group of tumors and new findings are discussed in relation to current ESMO and NCCN guidelines.

The manuscript by Imbimbo *et al.* summarizes changes in clinical staging and treatment of thymic malignancies based on a multidisciplinary review by Italian experts who also attempt to quantify general clinical adherence to the ESMO guidelines (1). This cadre of experts was selected based on the volume of patients treated at their home institution (i.e. at least 15 patients per year), which of course gives a good indication of the experience of the individual center, although variability in expertise by discipline at a given institution exists. Their conclusion states that, for the most part, there was good agreement with the ESMO guidelines (2) regarding postoperative management strategies.

Thymic tumors are extremely rare malignancies, consequently standardized guidelines are challenging to establish and are oftentimes based on limited data. The published literature is in fact mainly retrospective and composed of relatively small institutional series. Despite this, in the past decade there have been several attempts to improve the histological classification of these tumors as well as the staging system. In 2015, the WHO classification was updated (3) and in 2017 the new TNM system for thymic tumors was introduced (4). The updated AJCC 8th edition classification will likely complement or even replace the longstanding Masaoka-Koga staging system, which has been in use for several decades.

The use of PET/CT scans for diagnostic staging and surveillance has become more ubiquitous for thymic malignancies in the modern era and although is optimal in more rapidly dividing tumors such as thymic carcinomas it can also be useful to detect more indolent thymomas. This modern imaging modality may guide the upfront treatment and assist in long term surveillance of patients with thymic cancers. Somatostatin scans are mainly indicated in neuroendocrine thymic tumors where positivity suggests potential effectiveness of somatostatin analogues or even radioactive somatostatin analogues (e.g., Lutathera).

One of the major conclusions of this expert panel was the importance of referral to an experienced oncologic center to evaluate and assist in the management of these uncommon cases. This is particularly important with respect to pathologic assessment and histologic classification, which can be challenging for community pathologists, given the rarity of these tumor types. Most notably, there are major differences in terms of prognosis and treatment between thymomas and thymic carcinomas—a critical decision point for subsequent management. Thymic carcinomas can metastasize to virtually all organs and usually exhibit local infiltration, which makes a radical resection more difficult. In addition, thymic carcinomas have distinct molecular characteristics relative to thymomas, common genetic alterations often seen in other carcinomas (e.g., p53, Ras mutations), and are rarely associated with paraneoplastic syndromes. The presence of combined histologies, however, needs to be emphasized and can only be assessed

on the resection specimen. In the case of resection after induction therapy, the different components may exhibit variable response to induction treatment depending on differential sensitivities. However, there is little data on the consequences of neoadjuvant therapy both surgically and pathologically, although it is well recognized in other tumor types including lung cancer where neoadjuvant chemotherapy is often used in locally advanced disease.

Immunohistochemistry is used to better categorize the various subtypes of thymoma and thymic carcinoma, however the authors highlight the limited role, at present, of molecular diagnostics. In fact, the mutational tumor burden seen in thymic malignancies is amongst the lowest observed in adult tumors (5). Given the difficulty in classifying these tumors, the use of molecular markers, such as GTF2I mutations may help discriminate indolent tumors from more aggressive ones, since these mutations are almost exclusively found in type A and AB thymomas (5,6). So far the molecular landscape of thymic tumors has not provided much in terms of potential targets, with the exception of c-Kit (7) and possibly PIK3CA (8). c-kit mutations are found in 10% or less of thymic carcinomas and may predict responses to Kit inhibitors in patients with advanced disease. However, epigenetic abnormalities have been found quite commonly in thymic malignancies and may represent a novel therapeutic target in the future (9).

Thymic malignancies continue to be a disease primarily managed with upfront surgical resection. Hence, access to an experienced cardiothoracic surgery team at a high-volume center is critical to optimize patient clinical outcomes. Minimally invasive surgical techniques at specialized centers appear to result in similar oncologic outcomes relative to more conventional surgical approaches with possible mitigation of surgical toxicity and minimization of hospitalization length (10,11). Adjuvant therapy following surgical resection is possibly the most controversial topic amongst experts and with few small prospective studies we are again left with primarily retrospective data upon which to base our treatment recommendations.

Adjuvant recommendations in the United States are reflected in the NCCN guidelines where postoperative treatment is almost entirely dictated by surgical margins status and to a lesser extent pathologic classification. For early stage completely resected thymoma and even thymic carcinoma, controversy exists regarding the benefit of postoperative radiotherapy (12-14). In cases of microscopically positive or grossly positive surgical margins, postoperative radiotherapy is recommended with or without chemotherapy. Historically the clinical efficacy of three-dimensional adjuvant radiotherapy has been dogged by the geometric location of the surgical cavity relative to critical normal structures such as the heart and lungs. Consequently, given the relatively high doses of radiation required, particularly for microscopic or gross positive margins, collateral damage to the heart and lungs was substantial using older radiation technologies. In the modern era, intensity modulated radiation therapy and proton beam radiation therapy have emerged as viable radiation modalities to deliver maximal radiation dose while minimizing adjacent normal tissue radiation exposure (14-17). Minimizing damage to adjacent heart and lungs is critical for patients with an extended life expectancy, such as those with thymic cancer, where late radiation toxicity could manifest itself as significant. With modern radiation modalities, the therapeutic window for adjuvant radiotherapy may widen enough to observe improvements not only in PFS but also survival.

Adjuvant chemotherapy is more controversial, since there is very little data to support its use. Although chemotherapy is relatively effective in advanced thymomas, its efficacy is much more limited in thymic carcinomas and therefore its use is indeed controversial despite the higher risk of recurrence. This is an area that poses important challenges, since randomized trials will likely be very difficult to mount, given the rarity of the disease and the heterogeneous prognosis.

Integrated therapies are indicated in borderline operable tumors, where systemic and radiation therapies may improve surgical resectability. However, there are important caveats to consider, particularly when chemotherapy and radiotherapy are given concurrently prior to surgery. There is little evidence supporting concomitant chemoradiation over chemotherapy alone, but there is considerable data in lung cancer for instance to suggest that this is feasible and potentially more effective than sequential treatments, though more toxic. However, as the Albain trial demonstrated in locally advanced lung cancer, patients must be carefully selected for this neoadjuvant approach to avoid untoward treatment-related toxicity (18). The choice of drugs is also important given doxorubicin's cardiotoxicity, thus left ventricular ejection fraction should be carefully monitored in these patients. Furthermore, doxorubicin should not be given concomitantly with radiation therapy making the selection of concurrent systemic therapy with radiation more limited.

The authors stated clearly that debulking surgery is not indicated in thymic tumors, however, we wonder whether this is really supported by the literature. Given the indolent nature of thymic tumors, debulking surgery as well as stereotactic body radiation may maintain locoregional control for many years and potentially have a positive impact on survival. There is a growing body of literature regarding the survival improvement with locally ablative strategies in cases of upfront oligometastatic stage IV disease and oligoprogressive malignancies (19,20). This data includes cancers with dramatically lower life expectancies than thymic malignancies. As a result, it would be reasonable to expect local ablative strategies in advanced thymic tumors to improve local symptomatology, disease progression, and survival with long term follow up.

There are presently several options for the treatment of unresectable advanced disease, but none appear to be curative. Nevertheless, recently pembrolizumab has been shown to have a 20% to 25% response rate in thymic carcinomas, with very prolonged control rates and potentially even cures (21,22). Interestingly, nivolumab, also a PD1 inhibitor, did not have any responses in a small Japanese study (23), suggesting that there may be differences in immune checkpoint inhibitors, as has been observed in other tumors types.

Overall, given the rarity of this disease and the limited number of specialized centers with experience, there is certainly value in expert meetings such as the one organized by the Italian consortium. Nonetheless, national and international guidelines are only as good as the authors writing them, and for challenging diseases where no randomized trials are available a network organization as that seen in France is ideal to not only homogenize treatment strategies and discuss difficult cases but also to foster research initiatives (24).

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Footnote

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