Editorial

Lymph nodes metastases in thymic malignancies: we need prospective studies

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Thymic epithelial tumors (TET) are rare malignancies of the anterior mediastinum with a wide spectrum of biologic behavior. It is generally accepted that thymomas become more invasive as their World Health Organization (WHO) histologic classification advances to B2 and B3. Thymic carcinomas and neuroendocrine tumors of the thymus (NETT) are more difficult to treat as these are often invasive and give rise to metastases earlier than thymomas. It is important for the practitioner to understand that thymomas, thymic carcinomas, and NETT are not a spectrum of worsening malignancy, but rather three different pathologies, with different behavior and different response to surgery, chemotherapy, and radiation therapy. The WHO recognized this and now separately classified thymoma, thymic carcinoma, and thymic neuroendocrine tumors as distinct diseases (1).

Until recently, the Masaoka-Koga classification was the most widely staging system used for TET (2). This staging system allowed for proper survival stratification of patients with TET but had one significant drawback as it was not based on a Tumor/Node/Metastases (TNM) but rather on the invasiveness of the primary tumor and the presence of local or distant metastases. Importantly, the Masaoka-Koga system did not require knowledge of nodal status for the final staging and generically classified all nodal metastases as stage IVB. This has likely discouraged surgeons from performing lymph node dissection in patients with TET. Over this background, it is easy to understand that nodal metastases in TET is a topic with much discussion but without high-quality data. The recently proposed TNM classification of TET by the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancies Interest Group (ITMIG) (3) includes a proposal for a nodal mapping for TET (4) and will likely increase awareness among surgeons to the importance of at least nodal sampling in this patient population.

Available literature is sparse on nodal metastases from TET. Kondo was one of the first to investigate this topic (5,6). Using a questionnaire sent to 185 institutions in Japan Kondo compiled a database of 1,320 patients (1,093 thymomas, 186 thymic carcinomas, 41 thymic carcinoids). The incidence of nodal metastases was 1.8% in thymomas, 26.8% in thymic carcinomas, and 27.5% in thymic carcinoids. Our own work with the Surveillance, Epidemiology, and End Results (SEER) registry revealed an incidence of nodal metastases in thymomas of 13.4% (7), 33.5% in thymic carcinomas, and 62.3% in thymic neuroendocrine tumors (8). These numbers must be interpreted with caution as part of the inclusion criteria for the study was the presence of at least one lymph node examined and the majority of resected patients were not included in the analysis. Why would some patients have nodal sampling while the majority does not? It is likely that in patients who had nodes sampled, surgeons must have identified a reason to sample nodes, possibly increase in size of a lymph node. It is likely that the true incidence of nodal metastases is lower than the reported by Weksler *et al.* Both Kondo's and Weksler's studies should be viewed with relative suspicion, as both are based on retrospective database without confirmation of pathology, besides other well-known deficiencies of large retrospective databases.

A somewhat higher quality data was offered by Park and

colleagues (9) which looked retrospectively at 37 patients with thymic carcinoma, 8 had no node dissection (Nx), 13 had limited node dissection and were N0, 10 had extensive node dissection and were N0, and 6 had nodal metastasis (N1). Twenty-nine patients had node dissection and the average nodal yield was 9.4. Six patients had nodal metastases to 19 nodes. The authors confirmed that nodal metastases were more common in patients who had invasion of adjacent organs, and interestingly, the majority of metastases were to the right paratracheal area, independent of the location of the tumor. The incidence of nodal metastases in this cohort of patients was 16.2% (6/37), but if only those patients who had nodal sampling are included, the incidence raises to 20.7% (6/29), a number not far from Kondo's study, but still significantly lower than Weksler's studies.

Recently, Gu and colleagues from the Chinese Alliance for Research in Thymoma (10) presented their work on the incidence of nodal metastases in patients with TET. Utilizing a large database maintained by the Chinese Alliance for Research in Thymoma, the authors identified 1,617 eligible cases, the majority (1,310, 81.0%) being thymomas. There were 265 (16.4%) patients with thymic carcinoma, and 42 (2.6%) with thymic neuroendocrine tumors. The overall incidence of nodal metastases was 2.2% and more specifically 0.5% in thymomas, 7.9% in thymic carcinomas, and 16.7% in thymic neuroendocrine tumors. Multivariable analysis showed that tumors other than thymomas, and T stage above T1 were risk for nodal metastases. Although survival was significantly lower in patients with nodal metastases, multivariable analysis revealed that only complete resection and histological grade were factors significantly affecting survival, while nodal status did not make the final multivariable model.

The study of Gu *et al.* adds important information to the current body of literature, mainly the very low incidence of nodal metastases in patient with thymoma. However, the study is fraught with the usual problems of a large retrospective database. The main piece of data that is missing is the number of lymph nodes harvested in patients with and without nodal metastases. It is well known from other thoracic malignancies that the incidence of nodal metastases increases with increasing number of harvested nodes. Is it possible that there were patients (in particular with thymic carcinoma and thymic neuroendocrine tumors) that had occult microscopic metastases to lymph nodes that were not detected during surgery as nodal sampling was not done? What is the prognostic implication of micrometastases? Finally, as in previous database studies, it is likely that pathology was not reviewed for all patients and there is data to suggest a significant disagreement among pathologists when it comes to the differentiation of B2 thymomas from B3, and B3 from thymic carcinoma (11,12).

The only way to know for sure the true incidence of nodal metastases in TET is with a prospective study in which all patients undergo a preset minimal nodal sampling, regardless of suspicious nodes on preoperative imaging, while standardizing the pathologic diagnosis and having pathology reviewed by at least two pathologists. Due to the rarity of the disease, this can and should be done within the aegis of a large multinational organization such as the ITMIG, which will allow collection of data prospectively and hopefully accrue patients at an expeditious pace. Until then, retrospective database studies will be unlikely to provide better data than what is already available in the literature.

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