The rarity and heterogeneity of these tumors limits research and obviates the possibility of large randomized clinical trials. Surgery remains the mainstay of treatment, but often radiotherapy and/or chemotherapy is required. The role of neoadjuvant therapy is evolving. In the not too distant future, new therapies tailored to the molecular profile of the tumor will be available.

Thymic epithelial tumors are a morphologically heterogeneous group of tumors that continue to remain an intriguing multidisciplinary challenge. They represent 0.2% to 1.5% of all malignancies, with an incidence of 0.15 cases per 100,000 persons, and they range from relatively benign encapsulated thymomas to highly invasive carcinomas.

Thymic epithelial tumors usually are broadly classified into two main categories: thymoma and thymic carcinoma. In adults, thymomas are the most common primary tumor in the anterior mediastinum. A large variety of paraneoplastic or parathymic syndromes may suggest the presence of a thymoma. Myasthenia gravis coexists in approximately 30% to 40% of patients with thymoma. It is still unclear whether thymoma causes myasthenia gravis or vice versa. The definition, diagnosis, and treatment of thymomas have been periodically re-evaluated. Controversies persist regarding histological classification, staging, surgical approach, and adjuvant and neoadjuvant therapy.

In the foregoing article, Drs. Kalhor and Moran discuss still-unresolved issues in these uncommon tumors. First among these is the issue of histologic classification, which has always attracted the interest of pathologists. Controversies and confusion regarding the “traditional” and “histogenetic” proposed classifications persist, and both schemas remain open to challenge. However, despite the fact that certain histologies seem to correlate with certain outcomes, independent of surgical staging, multivariate analysis has almost invariably demonstrated that histology is not of independent prognostic value.

We consider correct the authors’ statement about tumor sampling, which is often neglected. Thymomas display different growth patterns; thus, at least five sections of the specimen are necessary to achieve a more reliable classification.

Staging represents a crucial prognosticator, and its definition is a challenge. Several staging systems have been proposed since the first was introduced by Berg in 1978. The developer of this system proposed that a proper stratification of patients was advantageous both for predicting prognosis and for choosing the best therapies. The staging system proposed by Masaoka in 1981 has been the most successful. Its greatest limitation is the fact that it assigns a fundamental role to macroscopic findings, which are easily detectable by the surgeon during the operation, but not by the pathologist, to whom it falls to determine the answer to the basic question of whether or not the tumor is encapsulated.

As thoracic surgeons, we for the most part appreciated the recent analysis by Moran et al., which proposed a staging system whose aim was not only to facilitate the work of pathologists, surgeons, and other clinicians, but also to offer key information for the stratification of patients, with the ultimate goal of more appropriate medical therapy. We hypothesize that additional elements for an optimal staging system can be derived via molecular techniques. At present, however, we can affirm that pathological staging seems to be the single most relevant factor in prognosis, together with the completeness of the resection.

We agree with the authors when they state that treatment of thymomas is primarily surgical. To date surgery through a total sternotomy appears irreplaceable and is used as part of a multimodality strategy. In experienced hands, complete surgical resection is easy to perform in encapsulated or limited invasive tumors. It assures the best chance for cure in approximately 90% of patients with localized tumors. Extended operations can be successfully carried out that include the lung, innominate vein, superior vena cava, aortic arch, main pulmonary artery, and chest wall. Recently, minimally invasive approaches have been used for early-stage thymomas. This modality is safe and feasible, with a shorter hospital stay and better patient acceptance. However, additional
experience and longer follow-up are needed to confirm the early favorable outcomes that presently appear equivalent in open and non-open resections.[14] At this time, the minimally invasive approach is not yet validated.

Is there a role for a partial resection in “deemed-invasive and/or technically irresectable thymomas”? Data are unclear. However, a partial resection provides slightly better survival compared to biopsy only, and it may enhance the effect of adjuvant chemotherapy or radiotherapy. Thus it is possible that a minimal residual disease status, as well as the predilection of these tumors to grow locally, may improve survival.

In patients with incomplete resection, radiotherapy or chemotherapy can be used postoperatively with benefit. However, there are no specific indications for this approach, and long-term results have yet to be analyzed.

The role of, or need for, postoperative radiotherapy is controversial. However, to date there is general agreement that in Masaoka stage I and stage IIa tumors no adjuvant treatment is recommended because the risk of recurrence is very low due to the possibility of complete extirpation. Postoperative radiation should be considered in high-risk patients: those with Masaoka stage IIb or WHO grade B type tumors, those with close surgical margins, and those with tumor adherent to the pericardium.

Radiation can also be utilized as a preoperative treatment, with or without chemotherapy, to reduce the tumor load. After a proper response, evaluated by appropriate imaging within 4 to 6 weeks, surgery can be performed. The authors discussed at length the role of neoadjuvant therapy in advanced thymomas and concluded that this approach may increase the chances of complete resection.

Adjuvant radiation can be used after induction chemotherapy or in patients who cannot undergo surgery. Chemotherapy is offered to patients with stage III or IV tumors.[15] Thymoma recurrence occurs in 10% to 30% of patients after complete resection[16] and in 40% of invasive tumors.[7] Recurrence does not necessarily imply a poor prognosis. When it is feasible, complete resection of the recurrence is the optimal solution. Usually reoperation is safe and easy to perform. Generally, a resected recurrence offers the same chances of survival as are associated with complete resection of a primary thymoma. Thus, an aggressive approach is justified. Chemotherapy is offered to patients with nonresectable recurrences. In our own experience, pleural and/or pulmonary recurrences were safely and successfully thrice resected in three patients.

Significant progress has been made in understanding the role of the cell cycle in the pathogenesis and prognosis of thymomas.[17] The cell cycle is modulated via small proteins called cell-cycle kinase inhibitors: p21 and p27. We found that low expressions of p21 and p27 were significantly correlated with reduced disease-free survival in cases of radically resected thymomas.[18] The same correlation was also seen in patients with recurrent intrathoracic thymomas.[16] We hypothesized that cell-cycle protein expression may influence the response to neoadjuvant chemotherapy, thus indirectly impacting survival.[19]

We conclude by congratulating Drs. Kalhor and Moran for having provided a comprehensive analysis of various aspects of the management of thymomas. Controversies still remain, but the rarity and heterogeneity of these tumors limits research and obviates the possibility of large randomized clinical trials. Surgery remains the mainstay of treatment, but often radiotherapy and/or chemotherapy is required. The role of neoadjuvant therapy is evolving. In the not too distant future, new therapies tailored to the molecular profile of the tumor will be available.[20] Thymomas will present new challenges.

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