Introduction

Surgical resection is considered the gold standard for the treatment of thymomas no matter what the histological type. Even when complete resection is achieved, however, recurrence of thymoma is not uncommon as it occurs in about 10-29% of patients. Recurrences affect subsequent treatment and final outcome but there is still no general consensus on how to manage them. Complete resection of recurrences should be attempted whenever possible to achieve long-term survival. When complete resection is not feasible, an iterative debulking approach may improve survival by reducing the size of these slow-growing tumors. Currently, a multimodality approach combining radiotherapy and/or chemotherapy with surgery may be considered the best treatment for thymoma recurrences.

State of the Art

Thymic tumors are relatively rare primary tumors originating from the thymic epithelium with an overall incidence of 0.15 cases per 100,000 [1]. These tumors include thymomas, thymic carcinomas, and thymic carcinoids (or neuroendocrine carcinomas). Thymomas represent by far the most common thymic tumor and are the most frequent tumors of the anterior or mediastinum, accounting for about 20% of all mediastinal masses in the adult population. They are a heterogeneous group of tumors that include encapsulated and benign lesions as well as highly invasive and malignant neoplasms (Fig. 25.1). Their heterogeneity has led to some confusion in distinguishing their clinical behavior and in identifying the most appropriate therapeutic approach. After many years of discussion on the prognostic accuracy of the Masaoka clinical staging system (Table 25.1), new insights have been offered by the recent WHO histological classification system, which divides thymic tumors into six different subtypes (A, AB, B1, B2, B3, and C), based on the morphology of the epithelium cell component (Table 25.2). The WHO classification system establishes a...
more reliable correlation between the histological patterns and the clinical course of the disease, thus improving the prognostic value of the clinical Masaoka staging system. Studies applying the WHO classification retrospectively have demonstrated that not only the tumor stage but also the histological subtype could be considered independent prognostic factors [2-4].

Currently the majority of thymomas are considered low-grade malignant tumors with a slow-growing and indolent natural history. However, even if the clinical course is generally benign, these tumors are able to induce local and regional invasion. Up to 33% of thymomas behave aggressively, penetrating the capsule and extending into the mediastinal fat and adjacent organs such as the pleura, pericardium, lung, chest wall, and great vessels. Typical findings are drop metastases into the homolateral pleura and pericardium, whereas lymph node and hematogenous metastases are rare [5-7]. Invasive thymomas may also infiltrate the diaphragm and overrun into the abdomen as well as the retro peritoneum space [8].

Surgical resection is considered the gold standard for the treatment of thymomas no matter what the histological type [9-12]. The mainstay of thymoma treatment is to achieve complete macroscopic resection and microscopic clearance, by removing en bloc all the involved tissue. Several studies have demonstrated that complete resection of thymomas has a significantly favorable effect on long-term outcome [13-15]. In their retrospective analysis, Strobel et al. [16] found that long-term survival was related to completeness of surgical resection and evidence of recurrence as well as Masaoka tumor stage and WHO histological subtype. However, variables such as patients’ age, sex, presence of myasthenia gravis (MG), and tumor size were not statistically correlated with survival.

Recurrence of thymoma is not uncommon even when complete resection is achieved and a long-term follow-up should therefore be envisaged. Thymoma recurrences occur in about 10-29% of patients [17, 18], who therefore require further treatment. Most recurrences occur in the thoracic cavity. In 1997, before the introduction of the WHO classification, Regnard reported a 10% recurrence rate in a series of 285 patients who had undergone complete thymoma resection. Most of the recurrences were intrathoracic and resectable; only two patients had concomitant extrathoracic metastases [15]. Local recurrences may occur in early stage thymoma patients (mainly Masaoka stage I and II) who do not have adjuvant treatment after initial surgery. This reveals that recurrences are likely to occur where microscopic tumor residuals are left in place during surgery [15]. Pleural, pericardial, and pulmonary metastases are more frequent in stage III and IV thymomas even if patients have been treated postoperatively with mediastinal radiation therapy since radiation is able to prevent local mediastinal recurrences but obviously not pleural and pulmonary metastases. Histological subtyping has generated animated discussions during the last decade and it has recently been suggested that the cortical differentiation of the tumor is related to a higher degree of malignancy and consequently with a worse survival. In their retrospective study, Ciccone and Rendina [19] report that all the recurrences in their series occurred in cortical differentiated thymomas (B1, B2, and B3 subtype according to the WHO histological staging system), which may point to an adverse prognostic role of these histological subtypes. Besides, a histological change was noted between primary tumors and the recurrences in about 45% of the patients, mainly towards a higher malignancy, within the cortical differentiation subtypes [19]. Wright et al. [20] showed that recurrence rate, correlated with WHO tumor type, was respectively 27% for B2 thymomas and 50% for B3, demonstrating that WHO and Masaoka stage systems were independent predictors of relapses.

As thymomas are infrequent tumors, there is as yet no well-defined approach to the management of their recurrences, due to the small number of patients in published series [11, 13-15, 21]. Regnard et al. [15] emphasized that the best therapeutic approach for thymoma recurrences was difficult to determine, as no control group was available for comparison. Ruffini et al. [13] demonstrated that the best option for long-term survival was complete surgical resection of recurrences. When resection was necessarily incomplete, it was related to a poor prognosis even if followed by radiation. Haniuda et al. [20] suggest that an iterative debulking approach should be attempted if complete resection is not feasible, to reduce tumor size and improve survival, considering the slow growth of these tumors [21]. Conflicting results are reported by Okumura et al. [22] who found that the overall 10-year survival rate in their reresected patients was significantly higher than in the patients in whom surgical treatment was not performed. Increasingly gaining consensus is the conviction that early stage tumors (stage I) are successfully treated by surgery alone whereas a multimodality treatment is the best approach for unresectable and advanced stage thymomas (stage III or IV), as well as for tumors with a cortical subtype differentiation and for patients with recurrences. Shin et al. [23] showed that locally advanced and unresectable thymoma could be effectively treated by an aggressive multimodal treatment. In a multicenter study Loehrer et al. [24] demonstrated a 50% response rate to chemotherapy treatment...