Thymoma and thymic carcinoma

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Summary

Thymoma and thymic carcinoma are an extremely heterogeneous group of neoplastic lesions with an exceedingly wide spectrum of morphologic appearances. They show different presentations with a variable and unpredictable evolution ranging from an indolent non-invasive attitude to a highly infiltrative and metastasising one. Prognosis can be predicted on the basis of a number of variables, mainly staging, the WHO histological pattern and diameter of the tumour. Complete surgical resection is certainly the gold standard to achieve cure. However, especially in patients with lesions at advanced stage, complete resection may be difficult and recurrence often occurs; at these stages, disease-free long-term survival may be difficult to be accomplished. Chemo- and radiotherapy protocols have been designed to complete surgical treatment and improve results in inoperable patients as well, based on the reported sensitivity of thymic tumours to these treatment modalities. The integration of clinical staging and histology, with the new histogenetic morphological classification, has contributed to design multimodality treatment protocols that help to improve prognosis. Induction therapy can now be applied before surgery in patients with tumours considered inoperable, improving resectability and outcome without adding morbidity and mortality to the surgical procedure. This newly developed approach helps to reduce the recurrence rate and to ameliorate disease-free survival. New therapies are now being evaluated as for many other tumours; however, they still need confirmation in prospective randomised studies. In the future, integrated treatment modality should be incorporated in a standardised approach that goes from a careful assessment of histology, staging and lymph node status, and a constructive and non-empirical cooperation between medical and radiation oncologists, pathologists and thoracic surgeons.

Keywords: Thymoma; Thymic carcinoma; Mediastinal tumours; Myasthenia gravis

1. Introduction

Thymic epithelial tumours are rare human neoplasms accounting for 50% of the anterior mediastinal masses; they are the most frequent mediastinal tumours in the adult population, with an incidence of 0.05 per 100 000 person-years [1,2]. This is an extremely heterogeneous group of lesions with a wide spectrum of morphologic appearances [1,3–5]. Thymoma and thymic carcinoma are certainly the most frequent histologic subtypes, and they are the only exhibiting differentiation towards the thymic epithelium. Nonetheless, there are other histological subtypes that seldom occur, such as carcinoids, thymolipomas, lymphomas and germ cell tumours; these subtypes show different clinical implications and will not be included in this review.

Thymomas have been found to occur at all ages, from patients of 8 months [6] to 90 years [7], with a mean age of about 53 years [8–14]; tumours accompanied by paraneoplastic syndromes, and in particular myasthenia gravis (MG), tend to occur at younger ages; however, there is a large overlap between MG and non-MG patients. The ratio between men and women is approximately equal.

These tumours show a variable and unpredictable evolution, ranging from an indolent non-invasive attitude to a highly infiltrative and metastasising one. However, even patients with invasive lesions tend to show a prolonged clinical course studded with multiple operations performed for diagnosis, primary resection and treatment of recurrences; surgery is usually alternated to cycles of chemo-/radiotherapy administered in an attempt to improve outcome. This group of patients is generally younger and more fit than those with other thoracic malignancies (lung, oesophagus, pleura), and they can withstand aggressive medical and surgical treatments; nevertheless, long-term survival often does not correspond to cure and disease-free survival.

The frequently indolent clinical course of these tumours is often associated with vague and subtle symptoms. Approximately 30% of patients are asymptomatic; 30% of them present with MG; local symptoms, when present, include pain, cough, hoarseness and dyspnoea; superior vena cava
Tumours occur in 2—5% of the patients (conversely, 10—15% of patients with MG have thymoma). Pure occurs in approximately 30—45% of the patients. The diagnosis of thymoma is usually made clinically, on the basis of symptoms (when they exist) and radiological appearance, and is subsequently confirmed by histology. Computed tomography (CT) usually shows the presence of a lesion located in the anterior mediastinum. These tumours usually appear at CT as well-defined round or oval masses located anterior to the great vessels and heart, just below the left innominate vein, and abutting the sternum; however, larger lesions may drape around the mediastinal vessels and extend caudally to abut either cardiac border or towards the right or left pulmonary hilum. Although thymomas are of soft tissue density, calcifications may be seen in about 15% of the patients (Fig. 1); a small percentage of them may be cystic. Extension of the tumour into the mediastinal fat and surrounding structures may be suggested by CT; however, this finding carries a false-positive rate of 20% and a false-negative rate of 7% [22]. Features suggestive of malignancy include vascular invasion, encasement and pleural dissemination [23]. Attempts to radiologically differentiate thymoma from thymic carcinoma and well-differentiated thymic carcinoma have been reported, but false-negative and false-positive rates are excessively high [24]. Magnetic resonance imaging has not yet become the standard practice to assess vascular involvement.

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Positron emission tomography (PET) has been investigated in the diagnosis and preoperative work-up of patients with thymic tumours. Some studies have been published [25] on the ability to differentiate hyperplasia from neoplasia and, within neoplasia, to distinguish thymoma from thymic carcinoma; however, there is no large database of outcomes to offer guidance for decision making. Liu and colleagues [26] reported the preliminary findings on a small cohort of 10 patients with thymoma and two with thymic hyperplasia. The findings suggested diffuse uptake of 18F fluorodeoxyglucose (FDG) in thymic hyperplasia, confined focal uptake in stages I and II thymoma and multiple discrete foci of FDG uptake in stages III and IV thymoma. Similarly, another small study showed that the pattern of uptake could reliably predict hyperplasia versus thymoma in patients with MG [27]. The use of semi-quantitative SUV max can help differentiate between thymoma and thymic carcinoma, but PET has been inconsistent in distinguishing non-invasive from invasive thymoma [25]. Despite these small studies suggesting value in PET imaging, it has not yet become the standard practice to evaluate thymic tumours with this technique.

2. Staging and histology

Classifications and staging systems are set for the purpose of standardising treatment and predicting the clinical course and prognosis of the disease; they certainly help to plan the most appropriate treatment strategy for each patient. Clinical (surgical) staging has long been considered the only variable able to predict outcome for patients with thymic tumours. Many staging systems have been proposed in the past [2,28,29] and also an attempt to employ the TNM (tumour, necrosis, metastasis) classification was performed without success [30—32]. The only classification that has gained widespread acceptance and stood the test of time is the one proposed by Masaoka and colleagues [28] in 1981 and subsequently modified in 1994 (Table 2) [32]. This classification is based on the detection of microscopic and macroscopic invasion into the capsule of the tumour and adjacent mediastinal fat and structures and on the evidence of distant metastases; in fact, local aggressiveness (even microscopic invasion of the capsule) could make a difference in the clinical course. Metastatic spread occurs less often than in other tumours and is predominantly directed to the
pericardium, pleura and lung parenchyma; extrathoracic dissemination as well as lymphogenous spread might occur although it is unusual at the time of presentation [30,33]. For this reason the TNM staging system of thymic tumours has never gained acceptance [30]. The Masaoka staging system has been repeatedly validated as an independent prognostic factor; however, if we rely only upon this classification, there are still some controversies that could bear on the design of the most appropriate therapeutic programme for each patient. In France, the GETT (Groupe d’Etude des Tumeurs Thymiques) staging system has been proposed (Table 3) [29]; the distinguishing feature of this system is that it takes into account not only the invasion into the capsule and surrounding structures, but also the extent and completeness of surgical resection; the latter may be of prognostic value postoperatively, but unfortunately it is obviously unpredictable before surgery and does not help to select the ideal approach.

Thymic tumours are often capsulated and, for this reason, many of them have been called ‘benign thymoma’ independently from their clinical course; however, some of these capsulated and apparently indolent lesions show cytological and histological features identical to those typical of invasive ‘malignant’ thymomas (identified as stages III and IV according to the Masaoka classification) and develop delayed recurrence. For these reasons, it is not accurate enough to assess prognosis and plan treatment only on the basis of clinical staging; if only this variable is considered as a prognostic factor, we may miss the real nature of the lesion, especially at early stages, understimating the potential growth, local invasiveness, recurrence and onset of metastases. In fact, despite the repeatedly stressed indolent behaviour of these tumours, recurrence and metastases have been observed in all large series after resection [17,18,32,34–37]; this is true even for stage I thymomas [6,7,9,10,17,18,32,35–43] and for each histological subtype [6,7,17,29,32,36,39–41], even if some authors demonstrated the lack of recurrence in some histological types (medullary or type A) [34,37,45–49]. For this reason other variables should be considered besides staging, matching all the information when assessing prognosis. Many histological classifications historically failed to reach a significant prognostic value at multivariate analysis until the modern histogenetic model was proposed. The problem concerning the value of histology was also related to the fact that morphology was usually available only after surgery without any impact on treatment planning; thus, up to the late 1980s, most of the management decisions have traditionally been taken on the basis of preoperative radiological work-up and clinical staging.

Regardless of the several proposed classifications, it is now generally agreed that the epithelial cell is the malignant component (the cell of origin) of thymoma and thymic carcinoma while the lymphocytic part (usually T cell) of the tumour is considered benign and reactive, and vary quantitatively in the different subtypes. Verley and Hallman [35] proposed a classification based on tumour architecture, cellular differentiation and predominant cell type; Lewis and colleagues [7] proposed a classification based on the percentage of epithelial cells and lymphocytes. In both systems the predominance of epithelial cells seemed to be associated with an increased incidence of macroscopic aggressiveness and worse prognosis. When the modern histogenetic classifications were developed the weight of this variable on decision making changed, giving more importance to preoperative tissue diagnosis. In fact, the Marino and Muller-Hermelink classification (medullary, cortical and mixed types) [41,50] and, more recently, the World Health Organization (WHO) system (Table 4) [51] rapidly gained acceptance and were repeatedly validated by multivariate analysis [37,39,49,52–54]; they consistently correlated with the Masaoka staging, prognosis and long-term outcome. These new classifications relate thymoma epithelial cells to the differentiation of thymic cells into medullary and cortical types in the normal gland architecture. The original Marino and Muller-Hermelink classification, subsequently confirmed by the observations of Kirschner and colleagues [50] and Pescarmona and colleagues [34,41], included six subtypes: medullary, mixed, predominately cortical, cortical, well-differentiated carcinoma and true thymic carcinoma. This new vision of thymoma histology progressively gained acceptance and was subsequently correlated with outcome [41,42,55]: in fact, medullary and mixed tumours are ‘benign’, usually they are not locally

| Table 2 |
| Masaoka staging system. |
| Stage I: | Macroscopically and microscopically completely encapsulated |
| Stage IIA: | Microscopic transcapsular invasion |
| Stage IIB: | Macroscopic invasion into the surrounding mediastinal fat tissue or grossly adherent to but not through the mediastinal pleura |
| Stage III: | Invasion into the neighbouring organs |
| Stage IVA: | Pleural or pericardial dissemination |
| Stage IVB: | Lymphogenous or haematogenous metastases |

| Table 3 |
| Groupe d’Etude des Tumeurs Thymiques (GETT) staging system. |
| Stage I: |
| IA: Encapsulated tumour completely resected |
| IB: Macroscopically encapsulated tumour totally resected; presence of mediastinal adhesion/invasion or suspected microscopic capsular invasion |
| Stage II: |
| Invasive tumour totally resected |
| Stage III: |
| IIIA: Invasive tumour subtotally resected |
| IIIB: Invasive tumour; simple biopsy |
| Stage IV: |
| IVA: Supraclavicular metastasis or distant pleural implant |
| IVB: Distant metastases |

<p>| Table 4 |
| Histology: World Health Organization classification synonyms. |</p>
<table>
<thead>
<tr>
<th>WHO type</th>
<th>Synonyms</th>
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<tbody>
<tr>
<td>Type A</td>
<td>Spindle cell thymoma; medullary thymoma</td>
</tr>
<tr>
<td>Type AB</td>
<td>Mixed thymoma</td>
</tr>
<tr>
<td>Type B1</td>
<td>Lymphocyte-rich thymoma; lymphocytic thymoma; predominantly cortical thymoma</td>
</tr>
<tr>
<td>Type B2</td>
<td>Cortical thymoma</td>
</tr>
<tr>
<td>Type B3</td>
<td>Well-differentiated thymic carcinoma; epithelial thymoma; squamoid thymoma</td>
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<tr>
<td>Type C</td>
<td>Thymic carcinoma (heterogeneous)</td>
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aggressive and have little chance to recur; however, cortical thymoma, well-differentiated thymic carcinoma and thymic carcinoma are aggressive tumours and tend to invade the adjacent structures and metastasise. These findings will show clear implications in the design of multimodality treatment of these tumours.

The most recent classification system has been proposed in 1999 by an international committee assembled by the WHO [51]. This system shows some similarities with the Marino and Muller-Hermelink classification with six subtypes (types A, AB, B1, B2, B3 and C): it is now accepted as the official one and is considered as an independent prognostic variable. Type A tumours are relatively uncommon and account for 4–19% of thymomas; they show a higher age at presentation (61 years vs 50 years for all thymoma patients) and 24% of them are associated with MG. They are usually capsulated and the vast majority of them are in Masaoka stage I. They are composed of neoplastic spindle-shaped epithelial cells without atypia or lymphocytes; the tumour cells show bland nuclei, dispersed chromatin and inconspicuous nucleoli; they are strongly positive for AE1-defined acid cytokeratins and negative for AE3-defined basic cytokeratins (CKs), while CK20 is negative. These tumours may show cystic or glandular structures expressing stronger CK. The overall survival of patients with type A thymomas has been reported to exceed 80% at 5 and 10 years [37,56].

Type AB thymoma is similar to type A but has some foci of lymphocytes; it has been postulated to derive from the normal thymic medullary epithelial cells; this theory is supported by the similar immunohistochemical expression of CD20, CKs, metallothionein and PE-35, as well as the relative paucity of immune T cells. Type AB thymoma is usually composed of a mixture of a lymphocyte-poor type A thymoma component and another one more lymphocyte-rich type B-like component. The tumour cells in the type B-like component are predominantly small and polygonal with small round, oval or spindle pale nuclei showing dispersed chromatin and inconspicuous nucleoli, and are smaller and paler than those of B1 or B2 thymomas; lymphocytes are more numerous than in the typical type A pattern but may be less represented than in B1 thymoma. There is a great variation in the proportion of the two components, and while both components are usually present in most sections, either type A or type B areas can be scanty.

Type B thymoma consists of plump epithelioid cells and is further subdivided in three subtypes defined by an increasing proportion of epithelial cells and atypia. B1 type show predominant areas resembling the normal thymic cortex architecture, with epithelial cells scattered in a prominent population of immature lymphocytes, and pale areas of medullary differentiation, with or without Hassal’s corpuscles. The postulated cell of origin is a thymic epithelial cell capable of differentiating towards both cortical and medullary type. The neoplastic epithelial cells are scant, small, with very little atypia and are surrounded by non-neoplastic T lymphocytes; they are dispersed and do not form cellular groupings. Perivascular spaces are not as frequent as in other type B thymomas. This type is often associated with MG and other immunological disorders, as well as the other B type thymomas. B1 thymoma is slightly more aggressive than A and AB types but less malignant than B2 and B3. B2 thymoma is composed of large, polygonal neoplastic cells arranged in a loose network; they show large vesicular nucleoli and closely resemble the epithelial cells of the normal thymic cortex. A background population of immature T cells is always present and usually outnumbers the neoplastic epithelial cells; the latter are large and polygonal, and their large nuclei display an open chromatin pattern with prominent central nucleoli, similar to the appearance of normal cortical thymic epithelial cells; they form a delicate loose network with palisades around perivascular spaces and along septa; large, confluent sheets of tumour cells may be present, although they are not a usual feature. B2 thymoma show higher malignant potential than B1 tumours, but appear to be slightly less aggressive than type B3; it is often invasive although completely resectable. B3 thymomas, previously described as well-differentiated thymic carcinoma, are predominantly composed by medium-sized round or polygonal cells with slight atypia. The epithelial cells are mixed with a very minor component of intra-epithelial lymphocytes, resulting in a sheet-like growth pattern. Tumour cells form lobules that are separated by thick fibrous and hyalinised septa; they are polygonal, medium-sized and the round or elongated nuclei are often folded or grooved and characteristically smaller with less prominent nucleoli than B2 thymoma. Palisades around perivascular spaces and along septa are often conspicuous; medullary islands are usually absent. These tumours are often not encapsulated and tend to invade the mediastinal fat and adjacent organs.

Thymic carcinoma is designated as type C by the WHO and accounts for less than 10% of thymic tumours; it is typically not associated with MG [37,42,44,47,57–59]. This category has been further divided into subtypes, including keratinising and non-keratinising squamous cell carcinoma, mucoid-epidermoid, basaloid, lympho-epithelioma-like, small cell/neuroendocrine, sarcomatoid, clear cell and undifferentiated/anaplastic [5,57]. Some cases of thymic squamous cell carcinoma are thought to arise from pre-existing thymomas based on the observation of combined thymic epithelial tumours that harbour squamous cell carcinoma and conventional (usually B3) thymoma components [4,60,61]. The two components may be widely separated or mixed with a gradual transition within the same mass. This hypothesis is also confirmed by the reported evidence of histological progression when recurrence occurs within the cortical histological differentiation [62]. The prognosis of type C lesions is clearly worse when compared to all the other epithelial thymic tumours and greatly depends on stage, histology and grading. The peculiar histological and prognostic characteristics of this group of lesions have recently encouraged to keep them completely separated from the other types of thymoma [29,63].

Thus, from type A to type C, there is a clear deterioration of prognosis; A, AB, B1 and B2 show a progressively worse outcome; B3 (the old ‘well-differentiated thymic carcinoma’) is more aggressive and shows intermediate survival, while patients with type C lesions present the worse outcome, with poor survival and high recurrence rate.

Although the WHO system describes a number of well-defined tumour types with clear diagnostic criteria, the overall level of agreement is moderate with recognised intra- and inter-observer discrepancies [64]; however, it could be improved if some groups are amalgamated. A meta-analysis
of the English literature from 1999 to the present demonstrated that, with the exclusion of thymic carcinoma, only three WHO categories are associated with significant survival differences: A/AB/B1, B2 and B3; thus, the classification could be simplified into fewer classes with significant prognostic value [65]. Both intra- and inter-observer reproducibility can be poor for the WHO system, particularly among pathologists with limited exposure to these tumours. Most of the discrepancies are related to group B thymomas, but difficulties also exist for types AB and for distinguishing B3 from well-differentiated squamous cell carcinoma. Such difficulties are related to the fact that this classification involves complex categories with extensive overlap among the different histological subtypes; in fact, thymic epithelial neoplasms are often characterised by a morphological heterogeneity and variations in morphology from field to field within the same tumour. To overcome these problems, Suster and Moran have proposed a simple classification based on the premise that primary epithelial thymic tumours offer a continuous spectrum of lesions ranging from well-differentiated to moderately differentiated to poorly differentiated tumours. Suster and Moran [66] proposed that well-differentiated tumours correspond to those conventionally designated as thymoma, the poorly differentiated neoplasms are designed as thymic carcinoma and tumours showing intermediate features of differentiation are designed as atypical thymoma. This approach was supported by the observation of tumour progression in thymoma, whereby tumour recurrences have shown transformation of low-grade histological type to that of a higher-grade histology and demonstration of transition among well-, moderately and poorly differentiated areas within the same neoplasm. According to these authors, this classification would not only simplify histological characterisation, but also fulfil the prediction of outcome capability.

Other prognostic factors have been elaborated during the years. As mentioned before, completeness of resection is a consistent independent prognostic factor. In stages III and IV tumours, the recurrence rate appears to be lower after complete resection when compared to microscopically or grossly incomplete resection [67]. Even survival after partial resection is slightly better than after simple biopsy [6,8,18,28,40], although this benefit is still debated because only one study attempted to correct for the stage when comparing partial resection with biopsy [9]; this was one of the studies that reported substantial survival differences: 10-year disease-free survival was significantly higher for partially resected stages III and IV thymoma compared with those undergoing biopsy only (80%, 62% and 0%, respectively). In addition, the diameter of the tumour is considered a reliable prognostic factor: the larger is the tumour the higher is the probability of recurrence [68].

The presence of MG is no longer considered a negative prognostic factor [40,53] as it was in older studies [69]; in fact, most of the recent reports have suggested either a trend [9,17,70,71] or significantly better survival in this group of patients when compared with those without MG [10,18,72]. This is probably related to the fact that the work-up for MG favours earlier diagnosis of thymoma; in fact, in most of the studies, MG patients have predominantly stages I and II tumours [6,9,35,39,73].

An attempt to use lymph node status as a prognostic factor has been reported [52]. However, even if lymph node involvement clearly acts as a negative prognostic index, the rarity of this presentation (less than 2%) indicates that the ‘N’ factor would not be a good candidate for stratifying survival in a staging system. However, knowing the lymph node status certainly contributes to improve staging (Masaoka IVB), assess prognosis and design the most appropriate treatment plan for each patient.

Involvement of the great vessels (stage III) has been found to be an independent negative prognostic factor by multivariate analysis [9] and favours the onset of recurrence [74]. Furthermore, recurrence has been stressed as a poor outcome predictor and is more frequent at advanced stages and with less differentiated histology. Early recurrence should be considered as an ominous predictive sign [54,75].

3. Surgical treatment

Complete surgical resection is the most effective treatment modality for thymic tumours; therefore, all patients with potentially resectable lesions should be carefully evaluated by an expert team. The operation is usually performed through median sternotomy and the whole thymus and surrounding mediastinal fat should be removed. The operative mortality does not exceed 2% in most of the recent series [53,70,76—78], even if it should be correlated with the extent of the resection when the tumour is removed en bloc with the surrounding structures.

However, up to 40% of the thymic tumours are invasive [79] and, in these cases, complete resection may be hampered either by extended local infiltration or by dissemination outside the mediastinum [80—82]. The ability to achieve complete resection is clearly the key factor for cure [6,17] and must be regarded as the gold standard for treatment at any stage; incomplete resection and debulking should be interpreted as a failure, since they offer no advantage over simple biopsy, as mentioned before [6,9,10,17]. The ability to perform a grossly and microscopically complete resection is obviously related to stage; however, also the willingness and ability of each surgeon to perform an extended resection incorporating the surrounding structures play an important role in this process.

Surgery alone is an effective way of curing patients with stage I thymoma with a nearly 80% 10-year survival [6,18,37,42,53], although local recurrence has been occasionally reported. Incomplete resections do not occur at this stage and the administration of adjuvant radiotherapy does not increase survival [83]. With the advent of minimally invasive thoracic surgical techniques, many reports have recently been published, showing the feasibility of exciting early-stage thymomas by this technology [84,85]. In addition, robotic has been applied to surgical resection of thymic tumours [86,87]. Since capsular integrity and avoidance of pleural seeding are of utmost importance, careful long-term follow-up is required to demonstrate whether these minimally invasive techniques will result in survival rates comparable to those obtained with standard open surgical approaches.
Surgery plays a major role also for locally invasive disease. Complete resection clearly helps to improve survival even if extracapsular invasion is present [88—91]. Locally invasive thymomas include stages II and III; they can often be completely resected; however, notwithstanding complete resection, the tumour can subsequently recur and metastasise. Stage II lesions are easily removed (Fig. 2), even when the capsule and adjacent mediastinal tissue may be macroscopically involved; however, also at this stage, local recurrence and distant metastases are observed, notwithstanding the administration of adjuvant radiotherapy [53]; in particular, also at this stage B2, B3 and C tumours show a higher incidence of recurrence. Stage III lesions require more extended procedures with en bloc resection of the primary tumour and involved structures. In this group of patients, only 50% of the lesions can be completely resected on average; however, there is a wide variability (0—89%) [79] that may be explained by the different philosophy, judgement and skills of each surgeon. Based on the topographic relationships of the gland, thymomas often invade the pericardium, mediastinal pleura, lung parenchyma and great vessels; in particular, the SVC (Fig. 3) and left innominate vein can be infiltrated. These structures can be resected en bloc with the tumour. After SVC resection, the vessel can be reconstructed either by a conduit of expanded polytetrafluoroethylene (PTFE) [92] or of bovine pericardium [93] or, when the resection is limited to the anterior wall, by autologous or heterologous patch. Resection of invasive tumours may pose problems with phrenic nerve injury; this condition should be seriously considered, especially in patients with MG. The phrenic nerve can be unilaterally sacrificed to allow complete resection. In this case, when resection of the nerve is consciously performed, diaphragmatic placation might be accomplished during the same operation to prevent relaxation and preserve respiratory mechanics. The reported long-term survival for patients with advanced disease is unsatisfactory even after complete resection: only between 35% and 53% at 10 years, often with administration of adjuvant radiotherapy [54]. At this stage, up to 50% of patients undergoing surgery will show recurrence within 5 years [12,94,95], even if adjuvant therapy is administered (mainly radiotherapy) [12,53,54,66,94]; recurrence is usually on the pleural surface or in the lung [12], more rarely outside the chest.

Stage IVA lesions (Fig. 4), although disseminated only within the chest, pose additional problems, and surgery alone should not be considered the most effective approach any more. In the original report by Masaoka and colleagues [28], patients with stages IVA and IVB showed a 5- and 10-year survival of 50% and 0%, respectively. Since then, a wide range of survival rates has been reported at this stage (from 40% to 78% at 5 years) [18,28,94,96,97]. Recently, aggressive surgical interventions have been proposed as well, such as pleuropneumonectomy [96,97]; this approach was able to significantly improve survival when performed within a multidisciplinary protocol.
Surgical resection plays an important role in the treatment of recurrences as well [98]. These data are not reported in all the studies; however, between 50% and 75% of all recurrences are considered to be operable [11,36,75,76,90,99] and complete resection is feasible in 62% of the cases (range: 45–71%) [36,76,90,99,100]. Complete resection of the recurrence allows to achieve improved survival (up to 72% at 5 years) as opposed to patients with incomplete resection (0–25%) [36,79,81,99,100]. A second recurrence after complete resection of the first one has been reported in 16–25% of patients in two series (4 and 5 years of mean follow-up, respectively) [99,100].

4. Chemotherapy

The efficacy of chemotherapy has been initially validated in patients with inoperable thymic tumours. Although single agents have demonstrated activity in recurrent, metastatic and locally advanced disease, combination regimens have generally shown higher response rates and certainly contribute to create the basis for the current multimodality regimens.

Early case reports and small retrospective series showed that thymomas are relatively sensitive to a number of antineoplastic drugs; they clearly demonstrated that chemotherapy can shrink the tumour and palliate symptoms [101] with a response rate that approaches an average of 70% in phase II studies with combination regimens [102]. The Southwestern Cancer Study Group coordinated one of the first prospective trials evaluating combination chemotherapy in 1983 [103,104]; this trial was designed to identify the activity of cisplatin, doxorubicin and cyclophosphamide (PAC) in patients with either unresectable or advanced thymoma: in the former group, they administered two to four cycles of chemotherapy followed by radiotherapy; in patients with advanced disease or those previously treated by radiotherapy, six cycles were administered; the latter group showed a 50% response rate (three complete and 12 partial responses); the median survival time was 38 months and survival was 32% at 5 year. In patients with limited disease, they were able to obtain a 70% response rate with a 50% 5-year survival. Anthracycline and cisplatin are the basis of most of the protocols. In a literature review [105], an overall response rate of 84% was obtained with regimens containing this drug; however, durable (lasting several months up to 10 years) and substantial (up to 58%) responses have been observed also in patients receiving non-platinum-containing regimens [80,106–109]. To date, the best results in phase II studies have been obtained with the PAC and ADOC regimen (cisplatin, doxorubicin, vincristine and cyclophosphamide) [110], with a higher response rate for the latter association (92% vs 50%) and a comparable median duration of response [110,111]. Furthermore, the association of cisplatin and etoposide [112] showed encouraging results at advanced stages. Isofosfamide showed impressive single-agent activity [104], but the incorporation of this drug into a cisplatin-based combination chemotherapy regimen did not improve results: there were no complete responses with a response rate of 32%. Fornasiero and colleagues [113] treated 32 patients with stages III and IV disease with a 90% overall response rate; 47% of the patients showed complete response. However, median survival was only 15 months. The Eastern Cooperative Oncology Group (ECOG) evaluated also octreotide alone or with prednisone in patients with advanced thymic tumours; they concluded that octreotide alone has only modest activity in patients with octreotide scan-positive tumours; prednisone improves the overall response rate but is associated with increased toxicity [114].

Thymic carcinoma is less responsive to cytotoxic chemotherapy, and its inclusion in many series certainly contributes to decrease overall survival. Chemotherapy with various regimens has been administered in a limited number of patients with an overall response rate between 20% and 60%; [115,116] some complete responses lasted approximately 1 year [116]. At least one patient survived 5 years after treatment with chemotherapy alone [117]. There are no data available addressing specifically the effectiveness of chemotherapy in the group of patients with well-differentiated carcinomas.

5. Radiotherapy

The role of radiation therapy has never been tested in prospective randomised studies; however, this treatment modality has always been considered effective as adjuvant therapy for invasive lesions since these tumours are usually well radio-responsive [118]. Many retrospective studies have shown improvement in local control and survival with adjuvant irradiation after surgery for invasive thymoma [6,13,28,90,119,120].

Stage I tumours are completely capsulated and clearly do not require additional treatment after complete resection. Stage II thymoma with macroscopic invasion of the capsule and surrounding mediastinal fat, or gross adhesions to the mediastinal pleura present different implications with an increased risk of recurrence, especially for types B2, B3 and C. Haniuda and colleagues reported that at this stage, although there is no microscopic invasion of the pleura, there may be additional benefit with postoperative radiotherapy [88,121]: they showed that in this group the recurrence rate within the mediastinum was 0% versus 36.4%, respectively, with and without radiotherapy. In another study by Monden and associates, there was a 29% recurrence rate for patients with resected stage II thymoma who did not receive adjuvant radiation therapy, compared with an 8% for those undergoing postoperative irradiation [40]. However, the lower local recurrence rate did not parallel with a significant decrease of subsequent pleural dissemination: in fact, in Haniuda’s study 92% of the 13 recurrences (12 patients) were on the pleural surface.

At stages III and IV, there is more evidence supporting the need of postoperative radiation therapy. Urgesi and colleagues reported no local recurrence in 33 patients with completely resected stage III thymoma undergoing postoperative irradiation [122]. However, Curran reported a 53% mediastinal relapse rate in stages II and III tumours without postoperative irradiation, compared to 0% for those receiving radiotherapy after complete resection. In that study [13], postoperative radiotherapy offered only little additional help in those patients undergoing only partial resection or biopsy.
with a 21% relapse rate. In addition, Monden and colleagues [40] observed similar results: in a group of patients with stages III and IV thymoma, the recurrence rate after adjuvant radiotherapy was 20% while it was 50% in those not receiving irradiation, and most of the recurrences were outside the irradiated field.

There are various postoperative dose and fraction schemes reported in the literature [123], but generally 45–55 Gy are recommended [8,11,13,88,124–127], even if there is no clear dose—response relationship because of the relatively small number of patients enrolled in the different studies and lack of prospective randomised trials. In patients with bulky disease, doses higher than 60 Gy have been proposed [127,128] since lower doses have been found to adversely affect prognosis [129]. However, postoperative mediastinal irradiation may still be insufficient because relapses in the pleural cavity sometimes develop remote from the initial tumour site. To reduce this pattern of failure, prophylactic entire hemithorax (or entire thorax) irradiation has been proposed by Uematsu and colleagues [130] in addition to mediastinal irradiation. The radiation doses ranged from 10 Gy per 10 fractions to 16 Gy per 16 fractions using anterior—posterior opposite fields. With this approach, the 5-year relapse-free and overall survival rates were 100% and 96%, with a statistically significant difference when compared with patients receiving only postoperative irradiation of the mediastinum (74% and 66%; \( p = 0.03 \)). However, in this study, 13% of the patients had symptomatic radiation pneumonitis.

Primary radiation therapy alone as a definitive treatment has repeatedly been advocated up to the early 1990s in non-surgical candidates or in patients with unresectable or advanced disease (stages III and IV). Results were acceptable but not comparable, with a 5-year survival that was even higher than 85% in a small group of patients with IVA disease treated with radiotherapy alone [131].

Preoperative radiotherapy has rarely been employed [14,94], probably for the fear of the onset of sternal and respiratory complications after surgery. Several studies with a small number of patients receiving preoperative radiotherapy for the presence of extensive disease showed a reduction of the diameter of the tumour confirmed at the time of surgery; the response rate was as high as 80% and a potential reduction of tumour seeding during surgery was also postulated [13,18,132–134]. Currently, the role of preoperative and primary radiation therapy has generally fallen out of interest.

In general, the improved response rates to chemo- and radiotherapy has encouraged integrating them with surgery and treating patients with a combined modality approach, with a strategy planning treatment from the time of diagnosis to management after surgery.

6. Multimodality approach

Based on the assumption that invasive thymoma shows a relatively high recurrence rate when complete resection is not feasible and it responds favourably to radiation and chemo- and radiotherapy, many authors have proposed a combined modality approach with the association of these three treatment modalities (surgery, chemo- and radiotherapy). Most of the studies focus only on the induction strategy with chemotherapy protocols; however, a combined modality approach should also consider postoperative consolidation with radio/chemotherapy.

The appropriate indication to neo-adjuvant chemotherapy is still debated: it should be reserved to histologically proven invasive thymoma or thymic carcinoma; patients should show a good performance status, normal renal and hepatic function, normal haematology and left ventricular function; and the diameter of the tumour should be measurable at CT. The administration of induction chemotherapy should allow improvement in the complete resection rate; postoperative treatment should improve control of the disease even in case of partial resection; in case of invasive tumours, the latter should be administered not only to those patients receiving induction, but also to those preoperatively deemed completely resectable, and thus not receiving induction chemotherapy. Adjuvant treatment should be administered both in case of complete and incomplete resection and should include chemo- and radiotherapy, if the clinical status of the patient allows it. The combined modality treatment should allow prevention of local and distant recurrence and, besides this, long-term survival and cure. In addition, a small subset of stage II tumours might take advantage of the administration of postoperative treatment.

Since the true novelty of the combined approach is induction therapy, some general considerations should be made. The background supporting the potential advantages of induction chemotherapy over adjuvant therapy might be a supposed increased compliance before surgery, fewer drug-resistant mutations earlier in the disease course and an increased likelihood of receiving complete resection. Preoperative chemotherapy regimens have been well tolerated and the vast majority of patients arrive to surgery in good health; this is because patients with thymoma show different clinical features when compared with those with other thoracic malignancies: they are younger, fitter, show less comorbidities and, in general, they can certainly tolerate much better aggressive regimens. The decision to administer neo-adjuvant therapy is obviously made preoperatively. In this setting, a correct histological diagnosis before starting chemotherapy is extremely important; in fact, after induction in the resected specimen, there may be no viable tumour; this finding has been observed in approximately 20% of the patients [2] with a maximum of 43% (radiological) [135]. Furthermore, the possibility to diagnose thymoma only on the basis of the radiological appearance, although feasible [2,24], may present some difficulties with reasonable chances to misdiagnose lymphoma or germ cell tumours.

A second point concerns the administration of induction chemotherapy in patients with paraneoplastic syndromes, and in particular MG. Chemotherapy is usually well tolerated by these patients: in fact, no deterioration was observed either in our experience [53,54] or by others [76,125,135–137]; partial remission may be observed [135], and this should be considered an additional evidence of the efficacy of chemotherapy on the tumour and an adjunctive marker to monitor response [107] to treatment, in an attempt to improve patient’s clinical status before surgery.
Preoperative radiotherapy has rarely been used in stage III patients [14,89,94,138,139]. The ability to carry out complete resection after this type of induction does not differ from the average resectability rate in patients not receiving induction [2] and also survival does not show any benefit. However, concerning radiotherapy, the modern three-dimensional conformal planning and intensity modulated radiation therapy certainly allows higher dosages with less toxicity. This technical improvement should be taken into account when evaluating the actual potential of radiotherapy compared to historical controls.

Macchiarini and colleagues were probably the first to report induction chemotherapy prospectively [137]. They enrolled seven patients with advanced-stage thymoma (three with thymic carcinoma). Chemotherapy consisted of three cycles of cycloplatin, epirubicin and etoposide every 3 weeks and allowed a reduction of tumour size of at least 50% in all patients. There were two complete pathologic responses. Complete resection was feasible in four patients; incomplete resection was due to extended invasion of the SVC and left brachiocephalic vein. All patients received postoperative radiotherapy (45 Gy after complete resection and 60 Gy in case of incomplete resection).

In addition, Rea and colleagues [135] reported similar results in a group of 16 patients with non-resectable stages III and IV thymoma (no thymic carcinoma) undergoing induction chemotherapy. They administered at least three cycles of chemotherapy with an overall response rate of 100%; 43% of patients experienced complete radiological response; 61% were able to receive complete surgical resection and 31% had complete pathological response. The 3-year survival was 70%.

Another study evaluating the role of induction therapy was reported by the group of the MD Anderson [125,140]. This group enrolled 22 patients with stages III and IVA thymoma in an induction protocol with three courses of cyclophosphamide, doxorubicin, cisplatin and prednisone; treatment was consolidated with adjuvant chem/o-radiotherapy after surgery. The complete resection rate was 76%, but only two patients (9%) had complete tumour necrosis or complete pathological response. In this group of patients, the 5-year overall and disease-free survival rates were 95% and 77%, while at 7 years it was 79% and 77%, respectively. These results were subsequently confirmed by our group [53,54] in a larger cohort of patients treated prospectively and compared with historical control.

Stage III tumours are certainly the group of thymic lesions approached more often with a combined modality treatment. Induction chemotherapy has proven to be effective in patients with potentially unresectable lesions; it clearly allows a higher incidence of complete resections and reduces the recurrence rate improving survival [53,54,76,135–137]. All the induction regimens are cisplatium based; the associated drugs vary from study to study, including more frequently cyclophosphamide, doxorubicin, vincristine, eto-poside or epirubicin. Three cycles are usually administered preoperatively.

This approach has not yet been validated as an independent prognostic factor, even if some benefit in terms of long-term survival has been reported [54,76,135–137]. Our policy is to deliver induction therapy only to patients with bulky aggressive tumours deemed unresectable or not completely resectable at preoperative work-up. Preoperative judgement of resectability greatly depends on the experience and technical skills of each surgeon: tumours considered resectable by someone could be judged unresectable by others. For this reason, invasive staging, with all the limitations of this approach, should be considered to facilitate decision making [53]; pre-induction invasive staging (anteri mediastinotomy or thoracoscopy) should be recommended, and in our experience it has never favoured seeding within the pleural space or through the thoracoscopic port [53,54]. Limited invasion of the SVC or the lung should not be considered an indication to induction therapy per se; vascular resection and reconstruction should be performed without induction if complete resection is feasible. The indication to this approach should be reserved to tumours with a more extended involvement of the mediastinum and no evident cleavage plans, to bulky lesions abutting and invading both mediastinal sides, with extended invasion of the great vessels, the lung and the chest wall. In this subset of patients, many groups [53,76,125,135,136,140] reported reliable complete response rates (radiological response up to 43%, pathological 31%), and also down-staging was observed in some cases [53,136,140].

In this group of patients, treatment should be completed with postoperative consolidation chemotherapy (two to three cycles) and 50–60 Gy of radiotherapy over the site of the primary lesion (both in case of complete and incomplete resection) [53,54,76,135,136,140]. Consolidation therapy is obviously mandatory in case of positive lymph nodes; for this reason, lymph nodes should always be at least sampled during the operation, especially if they are detected preoperatively. It has been reported that completeness of resection loses statistical significance in the cohort of patients receiving the combined approach (pre- and post-operative) [136]. This finding has not been observed by all groups [53,140], and it could be related to the small number of patients in each series. It has been justified with the hypothesis that, with a combined modality approach, complete resection does not become crucial since the goal of complete tumoral clearance is achieved by the whole treatment; postoperative radiotherapy on a small residual mass may be more effective after induction and in concurrence with adjuvant chemotherapy, allowing a complete clearance of the bed of the tumour. The loss of statistical significance of incomplete resection in a multi-modality treatment protocol could contribute to revitalise the concept of ‘deliberately incomplete surgery’ (debulking) in patients with stages III and IVA thymoma, when performed within a ‘salvage’ multimodality approach.

Masaoka stage IVA encloses patients with metastatic disease with pleural or pericardial dissemination without distant haematogenous and lymphatic spreading and offers a particularly difficult challenge. Although from the oncological point of view this stage represents a disseminated disease, the potential for complete resection should always be considered. There are only a few studies reporting management of thymoma at this stage; they are often difficult to interpret since they span many decades and, in many series, both stages IVA and IVB are included. Recently, extended operations such as pleurectomy and extrapleural
pneumonectomy have been reported with good results [96,97]. Most of the recent cases have been enrolled in a multimodality protocol with induction chemotherapy with a platinum-based regimen and consolidation therapy after surgery (chemotherapy, radiotherapy, brachytherapy). This combined approach allowed to increase survival up to 78% at 5 years and 65% at 10 years [97]. At this stage, there is only one study reporting induction therapy with both chemotherapy and radiation [141]; however, the latter tends to be avoided due to the possibility of increasing the rate of postoperative cardiac complications.

Stage II thymoma is an heterogeneous category and poses different problems; it includes lesions with microscopic invasion of the capsule or neoplasms with macroscopic involvement of the capsule and surrounding mediastinal fat, and even adhesions (‘fibrous’) to the mediastinal pleura. This category does not provide any difference on the basis of the diameter of the tumour and histology. Apparently this is the reason why the current therapeutic indications for stage II lesions are still controversial. Surgery is certainly the ‘gold standard’ and usually allows complete resection in all patients, even if partial resections have been reported [11,26,137]. The current indications for postoperative treatment range from radiation therapy in all patients [6,78] to radiation only in patients with large tumours (>5 cm in diameter) or with radiographic evidence of invasiveness [11] or patients with cortical thymoma, well-differentiated thymic carcinoma and thymic carcinoma (the WHO type B and C) [45], to no radiation at all in any patient [83]. This debate is based on the assumption and retrospective evidence that, at this stage, adjuvant radiotherapy does not offer a clear advantage over surgery alone, especially in terms of the risk of onset of distant metastases. In fact, a careful evaluation of the results shows that recurrence, whenever it happens, is more frequent on the pleura, outside the irradiated field [11,130]. This probably justifies the lack of effectiveness of postoperative mediastinal radiotherapy. We have observed an approximately 20% rate of recurrence with no standar-dised postoperative therapy in stage IIb and IIC tumours; since 1989 our policy included postoperative chemoradiotherapy for stage IIb lesions, in case of type B and C histology and a diameter larger than 5 cm. This policy dramatically reduced the incidence of recurrence, with no recurrence in B WHO type in the following period of time and a reduction of the rate in type C (1989—2008; data not published). The lack of recurrence also within the mediastinum could be justified by the enhancement of local effect of radiotherapy due to concomitant administration of chemotherapy.

7. The future

Combined modality therapy is rapidly gaining acceptance in the treatment of stages III and IVA thymic tumours; single-centre experiences demonstrate that there are certainly some advantages in selected groups of patients. However, the overall relatively low cure rate and the presence of recurrence and failures, notwithstanding the administration of multimodality therapy, impose the search of a better systemic therapy to find the ideal drug and optimise results. The expanding knowledge of tumour biology has thus resulted in a search for novel therapies as in many other tumour types that should be tested in large-scale multicentre prospective trials.

Since the thymus is derived from the endoderm of the third and fourth pharyngeal pouch, there might be organo-genic and therapeutic relationships between pharyngeal and thymic tumours [142]. Squamous cell carcinoma of the head and neck as well as thymoma and thymic carcinoma express tyrosine kinases as EGFR and c-KIT. Experimental studies have demonstrated a significant reduction of tumour growth in vivo and in vitro using combined treatment with COX-2 and EGFR inhibitors in a hypopharyngeal tumour cell line [143]. In patients with epithelial thymic tumours, the administration of EGFR inhibitors have shown some clinical response, since EGFR is over-expressed in thymoma [143—145] as well as c-KIT [146—148] in thymic carcinoma. Although in a recent study a clinical response to imatinib has been reported, results of a prospective study in patients with thymic carcinoma are still pending [149]. Clinical responses have been reported also to other tyrosine kinase inhibitors such as dasatinib [149]. Other authors have stressed the presence of an up-regulation of COX-2 with a potential separate therapeutic pathway [150,151]. Other markers, such as the expression of thymidine synthase and dihydropyrimidine dehydrogenase, which predict sensitivity to 5-fluorouracil-based chemotherapy, were not correlated with the clinicopathological characteristics in a series of thymomas [152].

These new therapies should be incorporated in a standardised approach that progresses from a careful assessment of histology, staging and lymph node status, and a constructive and non-empirical co-operation between the oncologist, radiotherapist, pathologist and thoracic surgeon.

References


