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GUEST REVIEW ARTICLE

Thymoma and thymic carcinoma

Federico Venuta, MD · Erino A. Rendina, MD
Marco Anile, MD · Tiziano de Giacomo, MD
Domenico Vitolo, MD · Giorgio F. Coloni, MD

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Abstract Thymic tumors comprise a heterogeneous group of neoplasms with a wide spectrum of clinical presentations. The evolution of the disease is often unpredictable, ranging from an indolent attitude to the possibility of intra- and extrathoracic spread. From the histological point of view, thymoma and thymic carcinoma are the most frequent subtypes and arise only from thymic epithelial cells. Other histological types are even more rare and are usually considered separately. A number of prognostic factors have been validated as predictors of outcome: staging, World Health Organization histological classification, diameter of the tumor, associated paraneoplastic syndromes, completeness of resection, and early onset of recurrence. Complete surgical resection is the key factor for cure and should be considered the gold standard at any stage. Especially for more aggressive lesions, surgery should be considered with a multimodality approach, involving induction and adjuvant therapy according to the stage. Multimodality therapy protocols have been designed based on the integration of clinical staging and histology. Neoadjuvant therapy is now administered before surgical resection in patients with tumors considered inoperable as it improves resectability and survival and reduces the risk of recurrence. Adjuvant treatment has been extensively reported after both complete or partial resection. New targeted therapies are in the developmental stage, and in the future they will be part of the standard protocols. Integrated treatment modalities require strict cooperation between medical and radiation oncologists, thoracic surgeons, and pathologists.

Key words Thymoma · Thymic carcinoma · Mediastinal tumors · Myasthenia gravis

Introduction

Thymic tumors are considered rare neoplasms, although they are the most frequent mediastinal tumors in adults. This group of lesions shows an extremely heterogeneous morphological and clinical spectrum: from lesions with an indolent, almost benign behavior to locally infiltrative or metastasizing lesions. From the histological point of view, thymoma and thymic carcinoma are the most frequent subtypes. Other tumors (e.g., neuroendocrine, thymolipoma) are even more rare, and they are usually considered separately.

Epidemiology

The overall incidence is of 0.13 per 100 000 person-years according to SEER (Surveillance, Epidemiology and End Results) data.[1] The incidence has declined over time, but this trend could potentially reflect changes in the classification, provide a better understanding of the histological differences with other mediastinal tumors, encourage extensive use of immunochemistry, and indicate trends in reporting to SEER. Thymomas have been found to occur at all ages,[2] although they are extremely uncommon in children and young adults. If a paraneo-

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F. Venuta (✉) · E.A. Rendina · M. Anile · T. de Giacomo · D. Vitolo · G.F. Coloni
Cattedra di Chirurgia Toracica, Policlinico Umberto I, Università di Roma SAPIENZA, V. le del Policlinico 155, 00161 Rome, Italy
Tel. +39-06-446-1971; Fax +39-06-499-70735
e-mail: federico.venuta@uniroma1.it

plastic syndrome (usually myasthenia gravis, or MG) is present, the tumor occurs at a younger age. The incidence in the United States is higher among African Americans and Asians/Pacific Islanders than among Hispanics. In addition, thymomas appear in African Americans at a much younger age than among Caucasians.[1]

Etiology

The etiology and risk factors for the development of thymic tumors are unknown. A number of reports support the potential role of previous irradiation and Epstein-Barr virus (EBV) infections.[3,4] Some of these studies reported on the isolation of viral genomes in thymic carcinoma.[3,4] Disruption of EBV latency and reactivation with increased EBV levels may elicit malignant progression of infected cells. Two studies reported detection of the human foaming virus or other retroviruses in patients with thymoma or MG,[5,6] but subsequent larger studies did not confirm this observation.

The distribution of alleles at the HLA locus in chromosome 6 varies across racial groups.[7] Class I and II HLA proteins are highly expressed on thymic epithelial cells, but further studies are required to detect a possible genetic predisposition to develop thymoma. However, the absence of reports on family clustering argues against genetic risk factors. Conversely, the increased risk among Asians and Pacific Islanders suggests a genetic component, as does the association with malignant fibrous histiocytoma in the Japanese population.[1]

Clinical presentation

Approximately 30% of patients with thymic malignancies are asymptomatic; 40% present with local symptoms, and 30% show systemic symptoms. Local symptoms include pain, cough, hoarseness, and dyspnea. Superior vena cava (SVC) syndrome and weight loss occur in a small number of patients and are usually associated with more aggressive tumors. Other symptoms include fever and night sweats. Thymomas are associated with MG in approximately 45% of the patients.[8–10] Conversely, only approximately 10%–15% of patients with MG have a thymoma. Other parathymic syndromes are observed in approximately 2%–6% of patients; the most frequent are hypogammaglobulinemia and pure red blood cell aplasia (Table 1).

Metastases at presentation are uncommon; the pleura is the most frequent site.[11–13] Extrathoracic spread is observed in <10% of the cases (kidneys, lymph nodes, liver, brain, adrenals, thyroid, bone). Thymic carcinoma more frequently has distant metastases at presentation.

Thymic tumors may rarely occur as primary lesions outside the anterior mediastinum. Such localizations include the middle and posterior mediastinum, the pleura, and the neck. Intrathyroidal lesions with the histological characteristics of thymoma are called SETTLE (spindle cell epithelial tumors of thymic-like epithelium).[7]

Table 1 Parathymic syndromes in patients with thymoma

- *Neuromuscular syndromes*: myasthenia gravis, Eaton-Lambert syndrome, myotonic dystrophy, limbic encephalopathy, stiff-person syndrome, radiculopathy
- *Gastrointestinal disorders*: ulcerative colitis, regional enteritis
- *Collagen diseases and autoimmune disorders*: systemic lupus erythematosus, sarcoidosis, scleroderma, rheumatoid arthritis, polymyositis, dermatomyositis, acute pericarditis, myocarditis, cardiac disorders, Sjögren's syndrome, Raynaud's disease, thyroiditis
- *Immune deficiency syndromes*: hypogammaglobulinemia, T-cell deficiency syndrome
- *Dermatologic disorders*: pemphigus, alopecia, chronic mucocutaneous candidiasis
- *Endocrine disorders*: Cushing's syndrome, panhypopituitarism, Addison's disease, hypertrophic osteoarthropathy, macrogenitosomia praecox
- *Renal disorders*: nephrosis, minimal change nephropathy, nephrotic syndrome
- *Hematological syndromes*: red cell aplasia, red cell hypoplasia, pernicious anemia, erythrocytosis, agranulocytosis, multiple myeloma, hemolytic anemia, acute leukemia, T-cell lymphocytosis, pancytopenia

Diagnosis

The suspicion of thymoma is usually raised by symptoms (when present) and the radiographic appearance. Chest radiography identifies the presence of a soft tissue density mass in the anterior mediastinum. Computed tomography (CT) confirms it and helps define the density of the lesion, the presence of calcium, and the relations with the surrounding structures. Thymomas usually appear as a well-defined round or oval mass located anterior to the great vessels and the heart, just below the left innominate vein. Larger and more aggressive lesions may surround and even infiltrate the mediastinal vessels and extend caudally and laterally toward both pulmonary hila. Extension of the tumor into the mediastinal fat and surrounding structures is sometimes suggested by CT, but this finding carries false-positive and false-negative rates of 20% and 7%, respectively. Features suggesting malignancy include vascular invasion, encasement, and pleural dissemination; the latter may be associated with pleural effusions. Attempts to differentiate thymoma

from thymic carcinoma and well-differentiated thymic carcinoma on CT scans has been reported, but the false-negative and false-positive rates are excessively high.[14] Smooth contours and a round shape are suggestive of type A thymoma, whereas irregular margins and enlarged mediastinal lymph nodes suggest thymic carcinoma. Calcifications are more frequently associated with BI, B2, and B3 types; the combination of homogeneous enhancement and a high degree of enhancement is suggestive of type A or AB thymoma.[14]

Magnetic resonance imaging (MRI), although more cumbersome and expensive, may be helpful for evaluating vascular invasion. There are a few reports concerning the correlation between the MRI appearance and the various World Health Organization (WHO) subtypes,[14] but this technique does not add anything to the information derived from CT.

Several reports evaluated the role of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET).[14] Sung and colleagues[15] reported a higher maximum standard uptake value (SUVmax) for WHO types B2 and B3 when compared with types A, AB, and B1, but it was significantly lower than that for type C. One report assessed the role of dual-phase FDG-PET to differentiate various subtypes of thymic tumors based on the WHO classification.[16] An early SUVmax cutoff value of 6.2 is useful for differentiating thymoma from thymic carcinoma, and a value >7.1 could completely differentiate these two entities. The delayed SUVmax tends to be higher when compared to early values for all epithelial tumors types. Overall, the integration of CT, MRI, and FDG-PET may be important before considering pretreatment biopsy.[14]

If the diagnosis cannot be defined by clinical and radiological data or if patients require induction chemotherapy, tissue sampling is mandatory. CT-guided needle aspiration is often discouraged because cytology might be unable to distinguish the subgroups; the sensitivity of this examination does not exceed 60%. Core cutting may improve accuracy and refine the diagnosis; multiple samples should be obtained. Large samples can be obtained by incisional biopsy (anterior mediastinotomy or video-assisted thoracoscopy). The sensitivity of surgical biopsy exceeds 90%. These procedures can be performed on an ambulatory basis under local anesthesia in most patients.[17] Metastatic disease should always be cytologically or histologically confirmed.

Secondary malignancies

A number of studies and case reports have confirmed that between 17% and 28% of thymoma patients develop a second synchronous or metachronous malignancy.[18–20] This is perhaps related to a genetic predisposition or to immune disorders. Secondary malignancies include common cancers (lung, thyroid, gastrointestinal, prostate, lymphoma) but also more rare tumors (brain, sarcoma, leukemia). The overall risk to develop cancer was estimated to be three to four times higher in this population than in controls.[19]

The risk of developing a second cancer is not statistically different between patients receiving adjuvant therapy and those who do not receive it. Malignancies occur more frequently outside the radiation field.[21] In 2003, a study by Engels based on SEER data[1] offered more reliable information than other single center reports; they included 733 U.S. patients with thymoma. Secondary malignancies arose in 66 patients (9%), corresponding to an overall risk on only 1.5, which was clearly lower than the one observed in other hospital-based series. In that study, malignancies at elevated risk included cancer of the digestive system, non-Hodgkin's lymphoma (NHL), and soft tissue sarcoma. The study suggested a more limited spectrum of cancers associated with thymoma than previously reported. The most important association was for NHL. All NHLs were of B-cell origin. The risk of NHL was elevated for a prolonged period of time after the diagnosis of thymoma, reaching 7.1 during a 5- to 9-year period after the diagnosis. It is possible that abnormally functioning T cells arising in association with thymoma may either induce or fail to control B-cell proliferation, leading to the development of NHL.[1] This is similar to what occurs in patients with other T-cell dysfunctions, such as those with acquired immunodeficiency syndrome (AIDS) or after organ transplantation, and in patients with autoimmune disorders.[1] In the study by Engels, the unusual risk of soft tissue sarcoma was related to two cases only; one was a liposarcoma and the other a malignant fibrous histiocytoma in a Japanese patient. This is notable because a previous report described three cases of sarcoma among 102 Japanese patients with thymoma.[22]

Staging

Many staging systems have been proposed in the past; and attempts to develop a TNM classification (Tables 2, 3) were without success.[23] Yamakawa et al., in 1991, proposed a TNM scheme based on the observation of 207 patients. Involvement of intrathoracic lymph nodes (LNs) was referred to as N1 or N2 disease, and extrathoracic LN metastases were classified as N3.[23] The authors postulated that the lymphatic spread affects, in sequence, the anterior mediastinal, intrathoracic, and

Table 2 TNM staging of thymic tumors: criteria

T factor
T1: macroscopically completely capsulated and without microscopic capsular invasion
T2: macroscopic adhesion or invasion into surrounding fatty tissue or pleura or microscopic invasion into neighboring organs, such as great vessels, pericardium, lung
T3: invasion into neighboring organs, such as great vessels, pericardium, lung
T4: pleural or pericardial dissemination
N factor
N0: no lymph node metastases
N1: metastases to anterior mediastinal lymph nodes
N2: metastases to intrathoracic nodes other than anterior mediastinal stations
N3: metastases to extrathoracic lymph nodes
M factor
M0: no distant metastases
M1: hematogenous metastases

Table 3 TNM staging of thymic tumors: staging

Stage	T	N	M
I	T1	N0	M0
II	T3	N0	M0
III	T3	N0	M0
IVa	T4	N0	M0
IVb	Any	N1–3	M0
	Any	Any	M1

Table 4 Masaoka-Koga staging of thymic tumors

Stage	Criteria
I	Macroscopically and microscopically completely capsulated
IIA	Microscopic transcapsular invasion
IIB	Macroscopic invasion into the surrounding mediastinal fat tissue or grossly adherent to but not through the mediastinal pleura
III	Invasion into neighboring organs
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastases

eventually extrathoracic LNs. N- or M-positive tumors were grouped into stage IVB, and pleural or pericardial dissemination was classified as T4 and thus included in stage IVA.

The only classification that gained worldwide acceptance and stood the test of time is the one proposed by Masaoka et al. in 1981[24] and subsequently modified by Koga in 1994[25] (Table 4) The system is based on the presence of invasion into the capsula and surrounding mediastinal fat and structures; it also takes into account the presence of intra- and extrathoracic spread. The latter occurs less often than with other tumors, and it is predominantly in the chest (pericardium, pleura, lung).

Table 5 GETT (Groupe d'Etude des Tumeurs Thymique) staging of thymic tumors

Stage	Criteria
Stage I	
Ia	Capsulated tumor completely resected
Ib	Macroscopically capsulated tumor totally resected; presence of mediastinal adhesion/invasion or suspected microscopic capsular invasion
Stage II	Invasive tumor totally resected
Stage III	
IIIa	Invasive tumor subtotally resected
IIIb	Invasive tumor; simple biopsy
Stage IV	
IVa	Supraclavicular metastasis or distant pleural implant
IVb	Distant metastases

Extrathoracic or lymphatic dissemination may also occur.

The Masaoka-Koga staging system has been repeatedly validated, and it is strictly related to completeness of the resection. There are other classifications that have been adopted by selected groups. In France, the GETT (Groupe d'Etude des Tumeurs Thymique) system was proposed (Table 5),[26] which takes into account the relations with the surrounding structures and the extent and completeness of the resection. This system remained confined to that group.

Masaoka and Koga referred to the concept of "invasiveness," considering the capsula and mediastinal fat as a landmark (stage II) with progression of the tumor toward the surrounding tissues as stage III.[24,25] Other authors reported that recurrence was more frequent as soon as the tumor breached the capsula and involved the mediastinal fat.[27] Haniuda et al. in 1992[28] suggested that Masaoka stage II should be further divided into subgroups with a "p" designator to report on the status of the mediastinal pleura: IIp0 includes lesions with no pleural adhesions; IIp1 shows fibrous adhesions with the pleura without true invasion; IIp2 tumors clearly infiltrate the mediastinal pleura. In that study, an adverse break point was observed at stage IIp1, with a higher risk of recurrence. For that reason, at this stage they recommended additional treatment with chemotherapy, irradiation, or both.

Histology

Histological classification of thymic tumors has been historically one of the most controversial pathological issues. In fact, it has been difficult to establish a correla-

Table 6 World Health Organization histological classification of thymic tumors: synonyms for each subtype

WHO type	Synonyms
A	Spindle cell thymoma, medullary thymoma
AB	Mixed thymoma
B1	Lymphocyte-rich thymoma, lymphocytic thymoma, predominantly cortical thymoma
B2	Cortical thymoma
B3	Well-differentiated thymic carcinoma, epithelial thymoma, squamoid thymoma
C	Thymic carcinoma (heterogeneous)

tion between histology and clinical outcome. Despite the repeatedly stressed indolent behavior of thymomas, local recurrence and distant spreading have been reported also at stage I and for each histological subtype.[8,9,11,13,25,29–36] For this reason, attempts to integrate histology and staging have been made and reported.[11,31,36]

It is now agreed that thymoma and thymic carcinoma originate from thymic epithelial cells. The variable amount of lymphocytes present within the tumor is considered reactive. Historically, the most widely used classification has been the one proposed by Bernatz et al.,[37] which includes four histologic subtypes: lymphocytic, predominantly epithelial, mixed, and spindle cell. However, with the exception of spindle cell thymoma, which typically follows a benign course, the Bernatz classification did not offer any prognostic information.

The modern histogenetic classifications completely changed the impact of histology on clinical practice. The Marino and Muller-Hermelink classification[11,38] and more recently the WHO system (Table 6)[39] rapidly gained popularity, were repeatedly validated,[33,34,40–42] and well correlated with Masaoka staging, prognosis, and outcome. The new systems relate thymoma epithelial cells to the differentiation process in the medullary and cortical areas of the normal gland. The first histogenetic classification was proposed by Marino and Muller-Hermelink[43] and was subsequently confirmed by other authors.[11,31,38] It included six subtypes: medullary, mixed, predominantly cortical, cortical, well-differentiated thymic carcinoma (WDTC), and thymic carcinoma. This new concept progressively gained acceptance because it clearly correlated with the outcome[11]: Medullary and mixed tumors are usually indolent and do not recur; conversely, cortical thymoma, WDTC, and thymic carcinoma tend to be locally more aggressive and to produce metastatic spread.

In 1999, the WHO proposed a system based on the morphology of the epithelial cells and the lymphocytic/epithelial ratio[39]; it includes three categories: A, B, C. It has some similarities with the previous system with six subtypes (A, AB, B1, B2, B3, C); and it is now officially accepted, being considered an independent prognostic variable. From type A to C there is progressive deterioration of the prognosis: A, AB, B1, and B2 show a progressively worse outcome; B3 (WDTC of the previous classification) is more aggressive and shows intermediate outcome; and type C (<10% of thymic tumors) is clearly a malignant tumor, associated with a poor survival rate and a high recurrence rate. The peculiar histological and prognostic implications related to this group of lesions have recently encouraged us to consider them as a completely separate entity. Some cases of squamous cell carcinoma are thought to arise from a preexisting thymoma based on the observation of mixed tumors harboring both squamous cell carcinoma and conventional (usually B3) thymoma components[44]; these two entities may be well separated or mixed with a gradual transition within the same mass. This hypothesis is supported by the evidence of histological progression when recurrence is seen in the cortical histological differentiation.[45]

Experience has demonstrated that the WHO classification has a low intra- and interobserver level of agreement; furthermore, with the present WHO scheme, reproducibility can be poor, particularly among pathologists with limited exposure to these tumors. Most of the problems are related to type B, but discrepancies are also related to type AB and the ability to differentiate B3 from well-differentiated squamous cell carcinoma. This problem could be overcome if some subtypes are amalgamated. A meta-analysis demonstrated that only four WHO categories are associated with significant survival differences: A+AB+B1, B2, B3, and C; this allows a reduction in the number of classes with different prognostic values.[45]

Suster and Moran[46] tried to simplify the WHO classification with a new system. They proposed that *well-differentiated* tumors correspond to those conventionally designated as thymoma, *poorly differentiated* neoplasms correspond to thymic carcinoma, and those showing intermediate features are designed *atypical thymoma*. This classification simplifies histological characterization and also helps to predict outcome.

Prognostic factors

Staging and histology, with all the limitations previously reported, are certainly the most important prognostic factors. However, other variables have been assessed. Completeness of resection is considered extremely important. In fact, for stage III and IV tumors, survival and recurrence rate appear to be significantly worse after

incomplete resection.[47] The outcome after partial resection or debulking seems to be better than when simple biopsy is performed.[2,9,24,35] The diameter of the tumor is also considered a reliable prognostic factor.

Until a few years ago, the association with MG was believed to affect the prognosis adversely.[12] Advances in MG medical management made surgery less risky and contributed to an improved postoperative recovery and outcome. As a consequence, most of the recent reports have supported either a trend[8,29] or significantly better survival[7,9,30,49,50] in MG patients. This is probably related to the fact that the MG workup favors early diagnosis of thymoma; in fact, most of the MG patients included in these studies had predominantly stage I and II tumors.[7,13,29,34] Conversely, other syndromes, such as hypogammaglobulinemia and red blood cell aplasia cause significant morbidity and mortality.

An attempt to predict outcome on the basis of LN status has been reported. Although a positive LN is clearly a negative prognostic factor, the rarity of this presentation (<2%) indicates that the "N factor" would not be ideal to stratify survival in a staging system. LN mapping certainly contributes to improved staging in the Masaoka classification (stage IVB), and it helps assess prognosis and plan the most appropriate treatment.

Involvement of the great vessels has been found to be an independent negative prognostic variable[29] and favors the onset of recurrence.[51] For this reason, some authors have suggested a subdivision of stage III based on the presence of great vessel invasion.[30]

Finally, the onset of recurrence has been reported as a poor outcome indicator: Early recurrence should be considered an ominous prognostic sign.[42]

Surgical treatment

Complete resection is the gold standard at any stage. However, up to 40% of thymic tumors are invasive; in these cases complete resection may be hampered by direct invasion of the surrounding structures or by metastatic spread. Operative mortality usually does not exceed 2%, with a 20% morbidity rate. The 10-year survival rates are approximately 90%, 70%, 55%, and 35% at stages I, II, III, and IV, respectively. The 10-year disease-free survival rates are approximately 94%, 88%, 56%, and 33% at each stage.

Most authors recommend complete thymectomy even in the case of partial involvement of the gland.[50] However, there are few objective data substantiating this assumption. The occasional occurrence of multiple thymoma has been reported in other studies.[32,37] Better survival after complete thymectomy compared to tumor resection alone was suggested in one report (5-year survival 92% vs. 59%),[50] although another study on 126 patients suggested no difference.[34]

Surgery alone is effective at stage I, with a 10-year survival rate exceeding 80%.[9,33] Local recurrence has rarely been observed at this stage. Many reports have supported the feasibility and safety of thoracoscopic or robot-assisted resection.[52,53] Capsular integrity and avoidance of pleural seeding by gentle manipulation and extraction is crucial.

Stage II lesions can be easily completely removed. When the capsula and the surrounding mediastinal fat are extensively involved, local recurrence and metastatic spread have been reported in up to 11% of the cases. This may happen notwithstanding the administration of radiotherapy.[40] At this stage, B2, B3, and C tumors show a higher recurrence rate also outside the mediastinum and may require systemic chemotherapy.[54]

Stage III tumors require en bloc resection of the adjacent involved structures. At this stage, only 50% of the lesions can be completely resected, with a wide variability (0–89%).[55,56] This may be partially explained by the different philosophy, judgment, experience, and skills of each surgeon. Thymomas may invade the pericardium, lung, SVC, and left innominate vein. Rarely, the ascending aorta and main pulmonary artery are involved. All of these structures can be resected en bloc with the tumor. After SVC resection, reconstruction should be performed by a conduit of expanded polytetrafluoroethylene (PTFE) or bovine pericardium[57]; or when only the anterior wall is involved, it can be patched with autologous pericardium or other materials.[58] Extended resection of locally invasive tumors may raise problems with phrenic nerve injury, a risk that should be carefully considered in MG patients. The phrenic nerve can be unilaterally sacrificed to allow complete resection. In these patients, diaphragmatic plication might be simultaneously accomplished to prevent relaxation and preserve respiratory function. Long-term survival at this stage is often unsatisfactory even after complete resection: it ranges between 35% and 53% at 10 years, often after the administration of adjuvant radiotherapy.[42] There is recurrence in up to 50% of patients within 5 years.[41,42] It is usually on the pleura and more rarely outside the chest. Induction and adjuvant chemotherapy should always be considered at this stage to increase results.

For stage IV lesions, surgery alone is rarely considered; more often it is performed within a multimodality protocol. In the original report by Masaoka at al.,[24] patients at stage IVA/B showed 5- and 10-year survivals of 50% and 0%, respectively. For unknown reasons, the pleura is a favored host site, particularly in the paravertebral gutter and over the diaphragm. Treatment options

Table 7 Stage IV thymic tumors: review of the literature

Study	Year	No. of patients	5-Year survival (%)	10-year Survival
Masaoka et al.[24]	1981	11	50.0	0 %
Nakahara et al.[2]	1988	15	47.0	47 %
Maggi et al.[9]	1991	21	59.0	40 %
Regnard et al.[8]	1996	19	—	30 %
Wilkins et al.[30]	1999	5	40.0	40 %
Nakagawa et al.[34]	2003	11	47.0	47 %
Lucchi et al.[67]	2005	16	—	46 %
Wright[59]	2006	5	75.0	50 %
Huang et al.[60]	2007	18	78.0	65 %
Ishikawa et al.[63]	2009	11	81.0	70 %
Yano et al.[62]	2009	28	13.3	—

include pleurectomy and extrapleural pleuropneumonectomy (EPP), systemic or intrapleural chemotherapy, photodynamic therapy, and irradiation. Since the initial report by Masaoka et al., a wide range of survival rates have been reported at this stage (Table 7). Recently, more aggressive surgical interventions have been proposed with EPP.[59–63] This approach, within a multidisciplinary protocol, was able to significantly improve survival. A salvage approach with maximum debulking, hyperthermia, and perfusion with cisplatin has also been reported. It allows the tumor to be exposed to higher drug concentrations with fewer systemic toxic effects.

Recurrence

The pattern of recurrence after resection includes local relapse in the mediastinum, pleural or pericardial implants, and systemic spreading including LN metastases. The incidence, as mentioned before, ranges between 5% and 50% according to stage and histology. In fact, invasive tumors invading the pleural and adjacent structures tend to recur more frequently.[24] Histology plays a major role as WHO B2, B3, and C types show a higher relapse rate.[24] About 75% of the recurrences are pleural implants.[64] It is not clear whether they are related to the peculiar biology of these tumors or to direct seeding during surgery. For this reason, some authors recommend that one should avoid opening the mediastinal pleura and that minimally invasive procedures with a transpleural approach (VATS or robotic) be used.[8,9] Pleural recurrences are rarely single; more often they are multiple and diffusely involve the pleural surface and the diaphragm. In these cases, EPP could be considered.

Overall, in the case of recurrence, complete resection provides improved survival (up to 72% at 5 years).[32,65] There are reports on patients being disease-free more than 10 years after surgery for recurrence.[26] A second recurrence after complete resection of the first one has been observed in 16%–25% of patients.[65] In this setting, surgery should be performed with a multimodality approach.

Chemotherapy

Systemic chemotherapy is primarily administered to patients with an unresectable or recurrent thymoma. A number of drugs have been documented in the literature; however, given the low incidence of these tumors, prospective trials are rare. Early case reports and small retrospective series have clearly demonstrated that chemotherapy can help shrink the tumor and palliate symptoms, with a response rate approaching 70% in Phase II studies with combination regimens. Modern regimens consist of a combination of drugs almost always including a platinum compound; other drugs are cyclophosphamide, doxorubicin, vincristine, etoposide, and epirubicin. Chemotherapy can be administered before surgery, for palliation of advanced disease, and postoperatively.

Induction chemotherapy should be considered in a multimodality protocol to achieve complete resection and prevent recurrence. Most of the studies focus only on the neoadjuvant strategy; however, in this group chemotherapy is usually administered after surgery as well. Induction is used to decrease the size of the tumor and convert unresectable tumors to those that are respectable. Down-staging has also been reported.[41,42] The most appropriate indication for induction chemotherapy is still to be defined.

The background supporting the potential advantages of induction is based on increased patient's compliance before surgery, fewer drug-resistant mutations during the early course of the disease, and the potential increase of overall long-term survival. In fact, preoperative treatment has been well tolerated, and most patients are able to reach surgery in good health. In this setting, pretreatment histological confirmation is mandatory; in fact, after induction, there may be no viable tumor cells in the surgical specimen. This finding has been reported in approximately 20% of patients, with a complete radiological response as high as 43%.[66] Induction regimens are also well tolerated by MG patients; in fact, no functional deterioration was observed in our experience[41,42] or by other authors.[66–68] Partial MG remission may be observed; this should be considered additional evidence of the efficacy of chemotherapy and a marker to monitor response to chemotherapy. It may also contribute to improving the clinical status before surgery.

Macchiarini et al. first reported a prospective study on induction chemotherapy (cisplatin, epirubicin, and etoposide)[68] in seven patients with invasive thymomas. All patients showed at least 50% reduction in tumor size with two complete pathological responses (29%). Complete resection was feasible in four patients (57%). All patients received postoperative radiotherapy (45 Gy after complete resection and 60 Gy after debulking).

Rea et al.[66] reported similar results in 16 patients with stage III and IV thymomas (no thymic carcinoma). The overall response rate was 100%, with a complete radiological response of 43%. Complete resection was feasible in 61% of the patients, with a complete pathological response of 31%. The overall 3-year survival was 70%.

A study evaluating the impact of induction therapy has been reported by the M.D. Anderson group.[69] The enrolled stage III and IVA patients were administered cyclophosphamide, doxorubicin, cisplatin, and prednisone. Consolidation after surgery included chemoradiotherapy. The complete resection rate was 76%, but only two patients (9%) had complete tumor necrosis or a complete pathological response. The 5-year overall disease-free survivals for patients with stage III and IVA tumors were 95% and 77%, respectively; at 7 years they were 79% and 77%, respectively.

Venuta et al.[41] conducted a prospective study in 65 patients including 25 at stages III and IV. Neoadjuvant chemotherapy included cisplatin, epirubicin, and etoposide. One stage III patient had a complete response, and all of them showed a radiological response to therapy; two were down-staged to stage II. The complete resection rate was 83% at stage III and 77% at stage IV. A subsequent report from the same group updated the long-term follow-up in stage III patients.[42]

The Japan Clinical Oncology Group performed a Phase II trial before surgery and/or radiation therapy in 23 patients.[70] Chemotherapy included cisplatin, vincristine, doxorubicin, and etoposide. In all, 57% completed the planned protocol: 62% showed a partial response and underwent thoracotomy with a 39% complete resection rate. Overall survival was 85% at 5 years.

It has been reported that completeness of resection loses statistical significance in patients treated with a multimodality approach that includes induction, surgery, and adjuvant treatment.[67] However, this finding has not been observed by all groups.[41,69] It has been justified with the hypothesis that with a multimodality approach complete resection becomes not crucial because 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 chemotherapy.[67] This could help revitalize the concept of "debulking" in patients with advanced-stage thymic tumors when performed with a "salvage" multimodality approach.

Patients undergoing incomplete resection, those presenting with tumors that are at high risk for recurrence, or those with recurrence are candidates for systemic chemotherapy. Many chemotherapeutic drugs showed single-agent activity. In addition, a number of combinations have been evaluated.

The South-Western Cancer Study Group in 1983 performed one of the first prospective trials to evaluate the activity of cisplatin, doxorubicin, and cyclophosphamide (PAC) in patients with unresectable or advanced thymoma. In patients with limited disease, they were able to achieve a 70% response rate with 50% 5-year survival. In a literature review,[71] an overall response rate of 84% was obtained with cisplatin-containing regimens. Durable responses have been observed also with non-platinum-based regimens.[72–75] Overall, to date the best results in a Phase II study have been obtained with either a PAC or ADOC (cisplatin, doxorubicin, vincristine, cyclophosphamide) regimen,[76,77] with a higher response rate for ADOC. In particular, Fornasiero et al. included 37 patients at stages III and IV with an overall response rate of 92% and complete remission in 43%. The median duration of response was 12 months, and median survival was 15 months.[77] Other studies with different protocols confirmed these results.[70,78–83]

Thymic carcinoma is less responsive to systemic chemotherapy. Its inclusion in many series have contributed to decreased survival and to masking the real effectiveness of each regimen. Various therapeutic schemes have been attempted in a limited number of patients with an overall response rate ranging from 20% to 60%.[84] A small number of complete responses lasted approximately 1 year.

The role of steroids in the treatment of thymic malignancies have never been fully evaluated. Most prospective trials did not include them as an intent-to-treat drug; however, steroids are included as antiemetic prophylaxis in platinum-based regimens. Prednisone has demonstrated effects on the lymphatic component of the tumor with consequent shrinking of the lesion; however, activity on the epithelial part has not been confirmed.

The presence of somatostatin receptors has been documented in thymomas.[85,86] Octreotide, an octapeptide somatostatin analog, has been investigated and has been found to show uptake in these tumors.[87] Phase II trials in patients with advanced thymomas have demonstrated responses after somatostatin administration alone or in combination with prednisone.[85,88] Palmieri and colleagues[88] reported the use of daily somatostatin and prednisone in 16 patients with thymic tumors not responding to chemotherapy. Complete and partial

remission rates of 6% and 31%, respectively, were observed. Loehrer et al. administered 0.5 mg of octreotide three times daily to 38 patients.[89] Patients with at least stable disease received, in addition, daily prednisone (0.6 mg/kg). Initial octreotide therapy led to a partial remission rate of 10.8%, and subsequent addition of prednisone allowed partial and complete remission rates of 25.0% and 5.3%, respectively. An estimated 2-year survival rate of 75% was reported. These encouraging results will hopefully be confirmed by future studies.

Targeted therapies

Insights were made about the biology of thymic malignancies following anecdotal responses to targeted therapies.[90] The rarity of epidermal growth factor receptor (EGFR) mutations in thymic tumors explains why responses to EGFR inhibitors had been rarely observed.[91] One Phase II trial with gefitinib was conducted in chemorefractory tumors. A partial or stable response was observed in 1 and 14 patients, respectively, from a group of 19 patients.[91] Three observations of heavily pretreated recurrent thymomas showing a partial response to cetuximab alone have been reported.[90] The recent identification of *HRAS*/*KRAS* mutations predicting primary resistance to anti-EGFR drugs[92] has to be integrated in trials evaluating cetuximab to avoid false-negative results.

Another small subset of tumors are *kit*-mutant thymic carcinomas. The rarity of this finding may explain the absence of responses observed in two Phase II trials with imatinib, when patients were selected by histology (WHO types B3 and C) using KIT immunohistochemistry staining.[93] However, the use of imatinib should not be recommended given the higher efficacy of second-generation inhibitors and the results available in clinical trials.

Even if it is not a prognostic factor, insulin-like growth factor-1R (IGF-1R) expression may represent a powerful predictive marker of response to specific inhibitors. Figitumumab recently showed clinical activity in a patient with a refractory thymoma.[94] An ongoing Phase II trial is evaluating IMC-A12, an anti-IGF-1R antibody in advanced refractory epithelial thymic tumors (clinicaltrial.gov ID NCT00965250).

Few data are available on the use of angiogenesis inhibitors in thymic malignancies. A Phase II trial tested bevacizumab in combination with erlotinib in 18 patients[95]: No response was observed. In a Phase I study with docetaxel and aflibercept, one patient had a partial response.[96]

Multikinase inhibitors may also play a role in this setting. Beyond the inhibition of KIT, sunitinib and sorafenib also inhibit vascular endothelial growth factor receptor-1 (VEGFR-l), VEGFR-2, and VEGFR-3. The effect of these drugs on thymic tumors may be also related to their antiangiogenetic activity. Motesanib diphosphonate (a specific inhibitor of VEGFRs) produced 1 year of control of a thymic carcinoma refractory to standard chemotherapy.[97]

Radiotherapy

Thymic tumors are usually well responsive to radiotherapy. Although the role of irradiation has never been tested in randomized trials, many retrospective reports have shown improved local control and survival with adjuvant treatment after surgery.[24,56,98]

Stage I tumors clearly do not require additional treatment after surgery. Stage IIB tumors are at increased risk of recurrence, especially in cases of WHO B2, B3, and C histology. Haniuda et al. reported additional benefit with postoperative irradiation at this stage.[28,55] In that study, local recurrence was 0% versus 36.4% with and without irradiation. In another report by Monden et al., there was a 29% recurrence rate for stage II patients without adjuvant radiotherapy, whereas it was 8% with it.[35] However, in both studies the decrease in local recurrence was not echoed by a parallel reduction of pleural dissemination. In fact, 92% of the recurrences were on the pleural surface also in the irradiated group.

At stages III and IVA, there is more evidence supporting the need for postoperative irradiation, although this issue is still controversial, especially after complete resection. Urgesi et al. reported no local recurrence in a group of 33 patients with completely resected stage III thymoma after postoperative irradiation.[99] On the other hand, Curran et al. reported a 53% relapse rate without postoperative irradiation, compared to 0% for those receiving it after complete resection.[98] Monden et al.[35] reported similar results: In a group of stage III and IVA patients, the recurrence rates were 20% and 50%, respectively, with and without postoperative irradiation.

In the case of incomplete resection, a number of studies have suggested a benefit after adjuvant radiotherapy.[9,98] Curran et al. reported no mediastinal failure after irradiation among 26 stage III patients with postresection residual disease,[98] whereas patients who did not receive radiotherapy had a 79% recurrence rate at 5 years. These results have been confirmed and supported by other authors.[99]

Several postoperative doses and fraction schemes have been reported, but generally 45–55 Gy is recommended.[55,87,98] This is true even if there is no clear dose–response relation because of the relatively small number

of patients in each study and lack of prospective trials. In patients with bulky disease, doses >60 Gy have been administered; lower doses have shown a reduced impact on the prognosis.

To prevent intrathoracic extramediastinal relapse, entire hemithorax (or entire thorax) irradiation was proposed by Uematsu et al. in 1996[100] in addition to mediastinal irradiation. With this approach, the 5-year relapse-free and overall survival rates were 100% and 96%, respectively, with a significant difference when compared to those undergoing mediastinal irradiation alone (74% and 66%, respectively). However, in the former group, 13% had symptomatic irradiation pneumonitis.

Neoadjuvant radiotherapy has been rarely proposed, probably for the fear of postoperative sternal and respiratory complications. Several studies, including a small number of patients undergoing induction irradiation, showed a reduction of the diameter of the tumor that was confirmed at surgery. The response rate was as high as 80%, and potential reduction of tumor seeding during surgery was postulated.[9,98] Overall, 10-year survival has not been reported for these small series. The role of induction radiotherapy remains controversial, and it has currently fallen from interest.

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