Thymoma: Update for the New Millenium

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ABSTRACT

Thymomas are relatively common tumors of the anterior superior mediastinum. They are usually relatively slowly growing tumors and their prognosis depends on the macroscopic and microscopic invasion of surrounding tissues. Surgery is the mainstay treatment of thymomas, and complete resection represents one of the most important prognostic factors in this disease. Other important prognostic indicators include the tumor stage and size and the presence of symptoms. Postoperative radiotherapy is indicated in tumors with invasion of surrounding tissues, even if resection was radical, since it improves local control and survival. Cytotoxic chemotherapy has been employed in several relatively small phase II studies and in advanced disease has been demonstrated to produce a 50%-80% objective response rate. Neoadjuvant cytotoxic chemotherapy and/or external beam radiotherapy has been used with some success in patients with tumors which are not readily resectable. Novel antiproliferative systemic agents, with both cytotoxic and cytostatic mechanisms of action, are being tested in ongoing prospective clinical trials. *The Oncologist* 2001;6:239-246

INTRODUCTION

Thymic tumors are common among anterior mediastinal tumors in adults. The vast majority of thymic lesions are thymoma [1]. Thymoma is relatively unique among tumors in that the prognosis appears to be more closely related to the invasive characteristics seen at operation rather than histological appearance. Indeed, the degree of encapsulation and invasion of adjacent tissues define malignancy for these tumors rather than the histologic appearance of the tumor cells [2]. Current treatment of thymoma is often multidisciplinary in nature, and has evolved based upon a growing number of studies to date. These studies have looked at various outcomes based upon associated patient syndromes, tumor histology, and tumor staging, as well as various surgical, radiotherapeutic, chemotherapeutic, and multimodality trials. These studies form the basis of this review.

CLINICAL PRESENTATION

Anatomically, the mediastinum is divided into three compartments: anterior, visceral (or middle), and paravertebral (or posterior) [3]. The anterior compartment is bounded by the undersurface of the sternum anteriorly and the pericardium/great vessels posteriorly. Space occupying lesions occurring in this compartment include thymoma, lymphoma, germ cell neoplasms, and others. Although lymphomas are the most common tumors in the mediastinum overall, for primary tumors, thymomas are more common in the anterior mediastinum [3, 4]. Clinical symptoms presenting in patients with thymoma are varied. Most patients are asymptomatic; however, when symptoms are present they most often consist of cough, dyspnea, and other upper respiratory complaints [4].

Approximately 15% of patients with myasthenia gravis (MG) have thymoma, either benign or malignant, while approximately 35% of patients with thymoma have MG [5]. In patients with MG, presenting symptoms typically involve neurologic findings consisting of both systemic and ocular abnormalities. Patients with thymoma and MG may have an increased operative mortality since most surgical deaths can be attributed to MG crisis [6]. For this reason the surgeon should carefully search for signs and symptoms of MG preoperatively in patients with thymoma that offer no previous history of MG. Interestingly, recurrence of thymoma may be higher in those without than in those with

MG [7]. In one study, death in patients with thymoma and MG was most commonly due to complications of MG, whereas in patients without MG, death was most frequently due to local progression of tumor [6]. While MG may influence the operative mortality of patients with thymoma and MG, the overall long-term prognosis does not appear to be adversely affected by the presence of MG [6, 8].

Other systemic syndromes may occur in 5%-10% of patients with thymoma [1, 4, 9]. These syndromes include erythroid and neutrophil hypoplasia, pancytopenia, Cushing's syndrome, DiGeorge syndrome, carcinoid syndrome, Lambert-Eaton syndrome, nephrotic syndrome, syndrome of inappropriate secretion of antidiuretic hormone, Whipple's disease, lupus erythematosus, pemphigus, scleroderma, polymyositis, polyneuritis, polyarthropathy, myotonic dystrophy, Sjogren's syndrome, Addison's disease, hypogammaglobulinemia, and thyroid carcinoma [2, 5, 9].

Diagnostic work-up of a patient with an anterior mediastinal mass begins with a thorough history and physical exam. Particular focus should be given to detect subtle physical findings that may suggest the presence of MG. Routine blood work and serum chemistries should be obtained as they may give clues to the presence of associated syndromes. Serum alpha-feto-protein and beta-human chorionic gonadotropin levels should be obtained in young adult males, as these are most certainly elevated in the presence of nonseminomatous germ cell tumors [10]. Imaging studies such as computerized tomography (CT) are helpful in clinically staging mediastinal tumors and defining their local extent. Although a preoperative biopsy of an anterior mediastinal mass may aid in its diagnosis, a planned resection of an anterior mediastinal mass may be appropriate without a preoperative biopsy in some cases when a thorough clinical and radiographical evaluation of peripheral lymph nodes is negative [4].

PATHOLOGY

Although there have been various attempts to classify the various histological subtypes of thymoma [11-13], it is generally agreed that tumors with true malignant cytologic characteristics are considered thymic carcinomas rather than thymoma. Malignant thymoma, on the other hand, refers to invasive thymoma (as defined either macroscopically or microscopically) that continues to retain typically "bland" cytologic characteristics [12]. Although the various histological subtypes of thymoma may be associated with different degrees of metastatic and invasive potential and, even in some cases, with various systemic syndromes, it is generally agreed that the cell of origin is epithelial and not lymphocytic [12, 14]. In addition, overall prognosis of patients with thymoma has more to do with the degree of

Table 1. Masaoka staging system [51]	
Stage I	Macroscopically encapsulated with no microscopically detectable capsular invasion
Stage II	Macroscopic invasion of mediastinal fatty tissue or mediastinal pleura, or microscopic invasion into the capsule
Stage III	Macroscopic invasion into surrounding structures (pericardium, great vessels, lung)
Stage IV	A) Pleural or pericardial dissemination B) Lymphogenous or hematogenous metastases

tumor invasiveness than the tumor's cytologic or histologic classification [13, 15, 16].

The most widely accepted histologic classification is that proposed by *Marino* and *Muller-Hermelink* that classifies thymoma into cortical, mixed (common versus predominately cortical versus predominately medullary), and medullary types [13]. Using this classification, tumors of the cortical type tend to be more aggressive and are associated with a less favorable prognosis than the medullary type, which, in most cases, tend to be less aggressive. Likewise, those tumors that are mixed tend to show an intermediate behavior and have an intermediate prognosis [17]. Although degree of tumor invasiveness is directly related to stage and prognosis of thymoma, histologic classification of thymoma may be an independent predictor of overall recurrence. In one study, none of the medullary or mixed-type tumors recurred, even though 30% were invasive [18].

STAGING

The most widely accepted staging system in use today is that which was proposed by *Masaoka* and colleagues (Table 1). In this staging system, stage I tumors are completely encapsulated, both macroscopically and microscopically. Stage II tumors violate the capsule, either grossly or histologically. Stage III tumors have obvious invasion into contiguous structures, oftentimes necessitating resection of additional tissue to obtain negative surgical margins. Stage IV tumors have either pleural or pericardial implants, which oftentimes can only be confirmed at the time of surgical exploration. It is for this reason that both pleural cavities should be widely opened and explored at the time of operation. Stage IV also includes patients with distant metastases. Although tumor histology may influence overall prognosis, tumor stage is a more important overall survival indicator, as confirmed by a number of published studies (Table 2).

SURGERY

Successful treatment of thymoma (both invasive and non-invasive) largely depends on complete surgical resection [19], if possible. Operation for thymoma carries a low morbidity

Table 2. Survival according to Masaoka stage

Study	Stage	% 5-yr survival	% 10-yr survival
Elert [59]	I	83	NS
	II	90	NS
	III	46	NS
	IV	—	—
Quintanilla-Martinez [18]	I	100	100
	II	100	100
	III	70	60
	IV	75	0
Schneider [60]	I	100	91
	II	95	88
	III	56	47
	IV	11	11

and mortality, and should be considered the mainstay of treatment in patients with resectable disease [20]. Although operative mortality is low, most surgical deaths can be attributed to MG crisis [6]. If MG is suspected, a preoperative consultation with a neurologist should be obtained. Patients with MG and resectable thymoma should be in as good physiologic condition as possible prior to elective surgery.

Principles of resection include: A) performance of a complete median sternotomy with wide opening of both pleural cavities no matter how small or limited the thymoma, and B) as complete a thymectomy as possible (versus enucleation of an encapsulated thymoma). Simple enucleation of a thymoma may result in recurrence as unresected thymic tissue can be a potential site for the later development of additional thymoma, or it can harbor multiple small tumors or lobules of tumors not detected grossly at the initial operation [21, 22]. For these reasons, cervical incisions and unilateral thoracotomies should generally be avoided. Furthermore, median sternotomy is well-tolerated. Once a median sternotomy is performed, the tumor can be, and should be, carefully evaluated since the full invasiveness and extent of tumor can only be accurately assessed intraoperatively. Successful surgical treatment of locally invasive thymoma is dependent on completeness of resection [19]. Resection of an involved phrenic nerve is controversial. Some surgeons would leave the involved nerve intact to avoid paralyzing the hemidiaphragm, and treat the residual disease with adjuvant postoperative radiotherapy. However, if both nerves are involved, most surgeons would agree that both be left intact. In those cases in which a complete resection is not possible, a "debulking" operation should be considered since good long-term results can still be achieved when surgery is followed by the addition of postoperative radiation therapy [6]. Clips to assist the radiation oncologist in treatment planning should be placed close to areas of questionable margin or residual disease. If the thymoma is invasive into local structures,

the surgeon must decide intraoperatively whether to attempt en bloc resections of adjacent tissue involved with tumor. Extensive en bloc resection of the aortic arch and anterior wall of the main pulmonary artery followed by vascular reconstruction has been reported with good results [23]. In addition, completely resected stage III disease requiring en bloc resection of superior vena cava and/or innominate vein have achieved 5- and 10-year survival rates of 94% [19]. Furthermore, successful resections of thymoma invading the right atrium and thymoma invading the right ventricular outflow tract have been reported [24, 25]. Although video-assisted resections of completely encapsulated thymoma have been reported with acceptable morbidity, mortality and short- and long-term results are not yet known [26]. In one study, overall five-year prognosis of surgically resected invasive versus noninvasive thymoma was 67% versus 85%, emphasizing that even in cases of complete resection, tumor stage remains an important predictor of long-term survival [8].

Recurrent thymoma is often limited to the thorax, thus facilitating reoperation. Patients undergoing surgery for local recurrence have similar 5-year survivals when compared with patients with no recurrence [27]. Reoperation for recurrent thymoma has acceptable short- and long-term results [21]. Of 28 patients undergoing re-resection for recurrent thymoma, *Regnard* and colleagues reported that 19 of them were able to undergo complete re-resection [28]. Actuarial survival curves after re-resection showed 5- and 10-year survival rates of 51% and 43% respectively, and 64% and 53% for those with complete resection. As a result, even patients who develop locally recurrent thymoma should be considered for re-resection since good results can be achieved.

RADIOTHERAPY

Recurrence of completely encapsulated stage I thymoma is rare (approximately 1.5%) and does not depend on whether postoperative radiotherapy is given [6]. For this reason it is generally accepted that for completely resected stage I disease, no further adjuvant therapy beyond surgical excision is necessary. On the other hand, recurrence of completely resected invasive thymoma may approach 30%, with median time for local recurrence to be around 3.8 years [27]. For patients with invasive disease, the risk of recurrence is proportional to the clinicopathologic stage. Patients with gross fibrous adhesions of the tumor to the pleura at the time of surgery, or who have microscopic invasion of the pleura on histology (Masaoka stage II), are at increased risk for recurrence, and for this reason should be strongly considered for postoperative adjuvant radiotherapy. In a study by *Monden* and colleagues, there was a 29% recurrence rate for patients with resected stage II thymoma who did not undergo adjuvant radiotherapy,

compared with an 8% recurrence rate in those patients that received postoperative radiotherapy [7]. In a subsequent study by *Haniuda* and colleagues, patients with fibrous adhesions to the mediastinal pleura without microscopic invasion benefited the most from postoperative radiotherapy (recurrence rate 0% versus 36.4%) [29]. Although postoperative radiotherapy has been shown to be effective at decreasing local recurrence in completely resected stage II disease, it does not appear to decrease the incidence of subsequent pleural dissemination that may occur in these patients whose pleurae were not treated. This possibly is a reflection of the normal pattern of spread of this disease before or at the time of surgery. Unfortunately, it has also been shown that extended radiation fields that include the entire thorax (in addition to the mediastinum) may significantly increase the normal tissue complication rate [29, 30]. As a result, most authors do not recommend the use of extended radiation fields routinely in cases of completely resected stage II disease. However, it is clear that total radiation dose is a significant prognostic factor in preventing local recurrence [31]. It has been suggested that patients with certain histological variants may have an increased risk of developing local recurrence in cases of completely resected thymoma. In one study, patients with medullary and mixed thymoma (less aggressive histologic variants) and stage II disease treated with excision alone developed no recurrence [18]. Even though other studies suggest that it may have a limited role in some stage II disease, postoperative radiotherapy should be strongly considered in patients with completely resected thymoma when tumor extension beyond the capsule is documented clinicopathologically [32-34].

The evidence supporting the use of postoperative radiotherapy is less debatable in resected stage III disease. In a study by *Urgesi* and colleagues, 33 patients with completely resected stage III disease given postoperative radiotherapy showed no infield recurrences (although three of the patients did develop out-of-field recurrences) [35]. Similarly, *Arakawa* and colleagues reported that in 15 patients with invasive thymoma (stage III and IV) who received postoperative radiotherapy (30-58.7 Gy in 1.8-2.0 Gy fractions) there were only two tumor recurrences and all of the patients were alive at the time of last follow-up [36]. In addition, *Nakahara* and colleagues reported a 95% 15-year survival rate in 35 patients who were given postoperative radiotherapy for completely resected stage III thymoma [37]. Pleural invasion appears to be a particularly strong risk factor for the subsequent development of pleural dissemination. In a study reported by *Ogawa* and colleagues, five of nine (56%) patients with initial pleural invasion developed subsequent pleural dissemination whereas 0 of 12 (0%) patients without initial pleural invasion relapsed [38]. However, in no case did

recurrence occur in the irradiated field. There is some evidence to even suggest that preoperative radiotherapy may be more effective at preventing pleural tumor recurrence in patients undergoing resection for stage III thymoma. In a retrospective study recently reported by *Myojin* and colleagues, all patients who developed subsequent pleural recurrence had received postoperative radiotherapy, whereas in those patients who had received preoperative radiotherapy, there were no patients who developed pleural recurrence [39]. Although there are a few studies that suggest there is no survival benefit in giving postoperative radiotherapy routinely to patients with completely resected stage III disease, most studies suggest that postoperative radiotherapy improves survival and decreases local recurrence [27, 40].

For unresectable or locally advanced disease, which consists primarily of patients with Masaoka stages III and IVA thymomas, primary radiation therapy may be used to shrink an unresectable thymoma to render it resectable. Several studies on limited numbers of patients who received preoperative radiotherapy for extensive tumors noted a decrease in tumor burden at the time of surgery and described a theoretic decrease in the potential for tumor seeding during surgery [6, 41, 42]. However, the value of preoperative radiation therapy remains inconclusive without larger studies. Definitive radiation therapy alone as the primary treatment has been advocated in non-surgical candidates or patients with unresectable advanced (stages III and IV) disease. *Arakawa* and associates reported 7 out of the 12 patients who presented with unresectable tumors and were treated with primary radiotherapy only were alive for observation periods from 1 year 8 months to 5 years and 1 month [36]. *Ciernik* and associates reported similar prognoses when comparing radiation alone to tumor debulking and radiation therapy in 31 stage III and IV patients [43]. *Ichinose* and associates reported an estimated 5-year survival of 87% in a small group of stage IVA patients treated with radiotherapy alone [44]. *Urgesi* and others reported the use of radiation therapy in 21 patients with intrathoracic recurrences of thymoma [45]. The 7-year survival of 70% was similar for those treated with radiation therapy alone and for those treated with surgery and radiation therapy. The retrospective nature of these studies, along with a small number of patients, different amount of clinical disease, variations in EBRT doses and techniques are likely confounding variables that relate to the results in the literature. The controversies surrounding the optimal treatment of unresectable thymomas remain to be resolved.

Reported radiotherapy doses have ranged from 30 to 60 Gy in 1.8 or 2.0 cGy fractions over three to six weeks. It is difficult to verify a consistent improvement in local control with higher doses, in part, due to the paucity of prospective clinical trials. Treatment fields and dose fractions should be arranged to minimize complications, of which pulmonary

fibrosis, pericarditis, and myelitis are most common. Treatment portals may include single anterior field, unequally weighted (2:1 or 3:2) opposed anterior-posterior fields, wedge-pair, and multifield arrangements. Three-dimensional treatment planning allows for conformal therapy to be delivered more readily. The gross tumor volume is defined by visible tumor and/or surgical clips seen on a treatment planning CT scan. Areas of possible microscopic disease and a small border to account for daily variability and respiratory motion are added to define the clinical and planning target volumes, respectively. Gating techniques to minimize the effect of respiratory variation and refinements in altering the fluence of the radiation beam, commonly referred to as intensity modulated radiation therapy, comprise some of the new technical adjuncts available in the clinical radiation oncologist's armamentarium, in order to minimize dose heterogeneity and normal tissue toxicity.

CHEMOTHERAPY

Most chemotherapeutic trials involving thymoma are case reports or phase II trials of advanced disease. Response rates are largely heterogeneous but range between 24% and 100% [46]. To the authors' knowledge, no prospective randomized trials have been done comparing different chemotherapeutic agents treating patients with advanced thymoma. However, a number of studies report reasonable results with various agents, either alone or in combination. In a study by *Forniasiero* and colleagues, 37 patients with stage III or IV thymoma were treated with cisplatin, doxorubicin, vincristine, and cyclophosphamide [47]. There was a 91.8% response rate, 43% of which were complete. More recently, in a study by *Highley* and colleagues, single-agent ifosfamide was given to patients with stage III and IV disease [48]. Out of 13 patients assessable for response, there were five (38.5%) complete responders and one (7.7%) partial responder. The most frequent toxicities seen were nausea, vomiting, and leukopenia, but all were well-tolerated. The most commonly employed drug in combination chemotherapy is cisplatin and several studies reported responses in excess of 50% with these combinations.

MULTIMODALITY THERAPY

In the absence of randomized trials, most chemotherapy studies involve multidisciplinary treatment of patients with advanced thymoma. Combined modality therapy consisting of radiotherapy, chemotherapy, and/or surgery can be used effectively with acceptable results even in cases of locally advanced or metastatic thymoma [49]. It has been shown that certain chemotherapy regimens can sterilize thymoma. In a study reported by *Macchiarini* and

colleagues, seven patients with clinically stage III invasive thymoma were given neoadjuvant cisplatin, epirubicin, and etoposide [50]. All seven patients subsequently underwent surgical resection—four complete and three incomplete. Two of the complete resections showed no tumor on subsequent histologic exam. It has also been shown that multimodality treatment of patients with neoadjuvant chemotherapy, and surgery, followed by additional adjuvant chemotherapy plus radiotherapy, may improve the survival of patients with locally advanced thymoma [51]. In a case report by *Yokoi* and colleagues, a locally advanced thymoma invading the heart and great vessels was successfully treated with preoperative/postoperative cisplatin and doxorubicin, in addition to postoperative radiotherapy, with good results [52]. Furthermore, induction chemotherapy may be effective at downstaging thymoma, allowing patients initially thought not to be surgical candidates to undergo resection. In a study reported by *Shin* and colleagues, induction chemotherapy consisting of cyclophosphamide, doxorubicin, and cisplatin was given to patients with unresectable stage III and IV thymoma [53]. Out of 11 patients initially thought to be unresectable, nine were able to undergo resection. All nine patients were given additional postoperative adjuvant chemotherapy and radiotherapy. Out of these patients, seven were disease-free at a median follow-up period of 43 months. Although multimodality treatment appears effective and may cure locally advanced unresectable malignant thymoma, this form of treatment is not without risk, however, as severe postoperative bleeding requiring reoperation has been reported following neoadjuvant chemotherapy for stage III invasive thymoma [41, 53].

PROGNOSIS

Recurrence of thymoma has been reported as late as 32 years after initial surgery [54]. As a result, patients with thymoma need to be followed life-long. The long-term prognosis of patients with thymoma is variable but most would agree that one of the most important independent predictors of tumor recurrence and long-term survival is the tumor stage [27, 55]. Five-year survival rates can be estimated based on the patient's tumor stage and are generally considered to be approximately 93% for stage I, 86% for stage II, 70% for stage III, and 50% for stage IV [56]. Other studies have suggested that completeness of resection, tumor size, and the presence of symptoms may also be important prognostic indicators [12, 27, 32]. Some studies suggest that histologic type (medullary versus cortical versus mixed) is an important prognostic indicator [57-59] whereas other studies do not [32, 60, 61]. Patients with autoimmune diseases such as red cell aplasia, hypogammaglobulinemia, and lupus erythematosus

appear to have a poorer prognosis [6]. Despite this, it is generally well accepted that the presence of MG does not negatively influence survival of patients with thymoma [32, 57, 58, 62]. The most important indicator of long-term prognosis is perhaps completeness of resection [27, 55, 59, 62-66]. Since the ability to resect thymoma is closely associated to its stage, improving long-term prognoses of patients with advanced thymoma may ultimately depend upon developing effective multidisciplinary neoadjuvant treatment protocols that can downstage unresectable disease, to allow most patients to undergo complete resection [67-69].

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