

# Thymic Tumors

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**T**hyamic tumors include thymic carcinoma, which exhibit aggressive behavior, and thymomas, which manifest a more indolent course. Complete resection is the mainstay of treatment, and there appears to be little benefit to partial resection. Postoperative radiotherapy may be useful in incompletely resected patients. Preoperative che-

motherapy appears to increase the rate of complete resection and survival of patients with a stage III or IVa thymoma and should strongly be considered in such cases.

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**B**ecause of the indolent course and sporadic occurrence of tumors of the thymus, clinical management has been based largely on observations in only a few patients from single-institution experiences. A larger body of literature now provides further insight into the biologic behavior of thymomas, and suggests that many previously held beliefs are not substantiated by data. New concepts regarding the clinical approach to thymic tumors are emerging as a result of a more evidence-based approach. This article reviews existing data and trends in the management of thymic tumors.

## Material and Methods

Literature searches were conducted using Medline for articles containing the words thymoma, thymic tumor, or thymic carcinoma published in English through June 2003. We also reviewed the references from these articles as well as references from major oncology and thoracic surgery textbooks. We made every effort to be inclusive rather than exclusive of published literature, although limitations of journal space prevented us from actually citing all of the references. With topics for which we found it necessary to not include all available literature we used objective criteria, noted in the text, to select the most representative or useful articles (eg, series of >100 patients).

## Classification

### Staging Systems

The staging system that has gained the most widespread acceptance was proposed by Masaoka and colleagues [1] in 1981 (Table 1), and is based on the extent of either macroscopic or microscopic invasion into mediastinal structures. A TNM staging system has been proposed that closely parallels the Masaoka system, but no reported series have used it [2]. In France, multiple centers

have adopted the Gruppe d'Étude des Tumeurs Thymiques system [3], which is similar to the Masaoka system but also includes the completeness of resection. Although this may be of prognostic value, it does not lend itself to clinical staging of patients before treatment to select the optimal approach.

### Histologic Classification

One can distinguish three groups of thymic tumors: (1) those with no cytologic features of malignancy [4–6]; (2) an intermediate group, sometimes called well-differentiated thymic carcinoma (WDTC), that have the organotypic features of thymomas but also have areas of atypia and occasional mitoses (usually <2 per 10 high-power field) [7, 8]; and (3) thymic carcinomas (TC) that have abundant mitotic figures and other cytologic features of malignancy [9–11]. It has been suggested these be called typical thymoma, atypical thymoma, and TC [12].

Thymic carcinomas clearly represent a distinct, but small (<10%) group. These tumors occur in patients of all ages [9, 10, 13], are typically not associated with myasthenia gravis (MG) [7, 10, 13–15], are frequently symptomatic because of the extent of local invasion [7, 10, 13], and consistently exhibit much more aggressive behavior [9, 15]. Thymic carcinoma has been divided into subtypes, including squamous cell, mucoepidermoid, basaloid, lymphoepithelioma-like, small cell/neuroendocrine, sarcomatoid, clear cell, and undifferentiated/anaplastic [10]. Thymic carcinoid tumors are generally classified as a type of TC, although some authors place them in a separate category of neuroendocrine tumors of the thymus [11].

Whether WDTC should be recognized as a distinct group is controversial. The consistency of this classification among independent review by different pathologists is very high in one study [16], but was found to be problematic in another [17]. Variability in how such tumors are classified is reflected by wide variations in the reported survival rates of this group as well as in the incidence of TC, which is less than 10% in some series [5, 18–20] and about 30% (range, 18% to 41%) in others, apparently owing to the inclusion of WDTC [7, 8, 13, 14,

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**Table 1.** Masaoka Staging System<sup>a</sup>

Stage	Definition
I	Macroscopically encapsulated tumor, with no microscopic capsular invasion
IIa	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
b	Microscopic invasion into the capsule
III	Macroscopic invasion into neighboring organs
IVa	Pleural or pericardial metastases
b	Lymphogenous or hematogenous metastasis

<sup>a</sup> From Masaoka and colleagues [1].

21–23]. The demographic characteristics of patients with WDTC are similar to those of others with more typical thymomas [7, 8, 13, 15, 23, 24]. Myasthenia gravis is common in all series (range, 25% to 77%) [7, 13, 15, 23, 24], and other parathymic conditions are also seen [13], which is in stark contrast to patients with classically defined TC in which these conditions are distinctly absent.

The vast majority of thymomas are cytologically bland tumors that exhibit an indolent clinical course. Many histologic classification systems of these bland thymomas have been proposed, but their clinical utility is questionable at best. The categorization of a particular thymoma is often inconsistent, attempts to correlate prognosis with histologic classification have yielded conflicting results, and multivariate analyses have generally shown that the histologic type was not of independent prognostic value [6, 18, 23, 25, 26], with a few exceptions that found worse prognosis for WDTC ± TC compared with bland thymomas [22, 24, 27].

The most recent classification system was proposed in 1999 by an international committee assembled by the World Health Organization (WHO) [11]. This system bears some similarities to the Müller-Hermelink system [28] but recognizes six different types of thymic tumors (types A, AB, B1, B2, B3, and C). Type A tumors are composed of neoplastic spindle-shaped epithelial cells without atypia or neoplastic lymphocytes. Type AB tumors are similar to type A, but have foci of neoplastic lymphocytes. Type B tumors consist of plump epithelioid cells, and are subdivided into three subtypes as defined by an increasing proportion of epithelial cells and increasing atypia. Type B1 tumors resemble normal thymic cortex with areas similar to thymic medulla. Type B2 have scattered neoplastic epithelial cells with vesicular nuclei. Type B3 are composed predominantly of epithelial cells exhibiting mild atypia, thus resembling what others have described as WDTC. Thymic carcinoma is designated as type C.

Few studies have assessed the value of the WHO classification system as yet. One group found a correlation between the sequence of WHO histologic types and a progressively higher average tumor stage [29]. The same group subsequently reported a correlation with prognosis in a large cohort of 273 patients with long-term follow-up (significantly worse prognosis was seen for B3 types; TC were excluded) [24]. In fact, multivariate anal-

ysis in this study identified the WHO type as an independent prognostic factor along with Masaoka stage [24]. Another evaluation of the WHO system involving 90 patients found no prognostic differences among the A and B subtypes, but worse survival by univariate and multivariate analysis for type C (TC) [15]. However, the multivariate analysis is questionable because completeness of resection was excluded. Thus, the value of the WHO classification system over one separating thymoma, WDTC, and TC is unclear.

Some authors have applied the misleading term "benign thymoma" to bland thymomas that exhibit no gross evidence of invasion [3, 4, 20, 21]. However, recurrences and metastases after resection have been reported in all large series [5, 18, 19, 30]. This is true for stage I thymomas [1, 5, 6, 18, 19, 27, 30–35], and is true for each histologic subtype of thymoma [5, 6, 18, 23, 33] (although some authors have not yet observed recurrences among smaller cohorts of patients with medullary thymomas [8, 36]). Thus, even bland, noninvasive thymomas have the fundamental characteristics of a malignant tumor despite a relatively indolent course, and the term benign thymoma should be discarded.

### Clinical Presentation

The sex distribution of patients with a thymic tumor is roughly equal among series of more than 100 patients [5, 6, 18, 19, 22, 23, 25, 27, 31, 33, 37–39]. The age distribution is broad (<1 year to >90 years) [6, 33], with a peak around 30 to 40 years of age in patients with MG, and 60 to 70 years of age in those without MG (primarily women) among series of more than 50 patients [6, 18, 19, 23, 31, 33]. At presentation, approximately 40% of thymic tumors are stage I, 25% each are stage II or III, 10% stage IVa, and only 1% to 2% are stage IVb among series of more than 100 patients [5, 8, 18–23, 26, 27, 31, 33, 34, 37, 39, 40].

Approximately one third of patients with a thymic tumor are asymptomatic among series of more than 50 patients [6, 8, 20–22, 27, 41–43]. Of those with symptoms, approximately 40% present with local symptoms related to the intrathoracic mass, 30% have systemic symptoms, and the rest have symptoms of MG. Chest pain, cough, and dyspnea are the most common symptoms. Superior vena caval syndrome and weight loss occur occasionally, generally with more aggressive tumors, and a few patients present with fever and night sweats, which are more typically associated with lymphoma [6, 8, 20–22, 27, 41–43].

Thymomas are associated with several parathymic syndromes, which are generally autoimmune conditions [44, 45]. Myasthenia gravis is the most common, occurring in approximately 45% of patients with thymoma (range, 10% to 67%) among series of more than 100 patients [18, 19, 31, 33, 39]. Conversely, approximately 10% to 15% of patients with MG are found to have a thymoma [45, 46]. Pure red cell aplasia [6, 22, 23, 27, 45] and hypogammaglobulinemia [6, 22, 23, 44, 45] are the next most common, each occurring in 2% to 5% of

patients. Other conditions, including polymyositis, systemic lupus erythematosus, rheumatoid arthritis, thyroiditis, Sjögren syndrome, and ulcerative colitis, are less common in patients with thymoma and are frequently found in patients without thymoma, making the link between these conditions and thymoma less convincing. Many studies have also noted a higher than expected incidence of second primary malignancies in patients with a thymoma (average, 15%; range, 9% to 27%) [22, 27, 44, 47-49].

## Diagnosis

Thymic tumors account for approximately 50% of anterior mediastinal masses, whereas lymphomas (25%) and various other tumors comprise the remainder [50]. The latter group often has characteristic radiographic findings (eg, teratoma), but it can be difficult to distinguish between a thymic tumor and lymphoma unless there are symptoms typical of these tumors (ie, fever, night sweats, or parathyroid syndromes).

In many instances, a clinical diagnosis of a thymic tumor is sufficient—eg, a patient with a parathyroid syndrome or a small tumor that is confined to the thymus. A definitive diagnosis is needed primarily when a presumed thymic tumor is so extensive that it warrants a nonoperative approach or preoperative chemoradiotherapy, or in instances in which lymphoma is considered to be a strong possibility. Pathologic confirmation of the diagnosis of thymic tumor can be achieved by means of open surgical biopsy or fine-needle aspiration. The success rate in establishing the diagnosis of a thymic tumor is approximately 90% for surgical biopsy [22, 51] and 60% for fine-needle aspiration (frequently involving a core biopsy or multiple passes) [22, 42, 51, 52]. Recently, octreotide scanning has been shown to be 100% accurate in 17 patients [53].

A widespread dogma proscribes a biopsy of a presumed thymic tumor out of concern of seeding the pleural space or the biopsy site [41]. However, there are few data to substantiate this. No case of seeding of a needle tract or biopsy site has ever been reported. Three instances of recurrence in a thoracotomy scar have been mentioned [51, 54]. A large series of 136 patients found a trend to better survival in those patients who underwent a preresection biopsy by multivariate analysis ( $p = 0.056$ ) [27]. The concern over pleural dissemination presumably stems from the observation that resected thymomas frequently recur as nodules throughout the parietal pleura [55]. However, this pattern of spread appears to be characteristic of thymoma itself rather than related to an operative procedure, because pleural nodules are also commonly seen (68%) in patients who present with advanced tumors, never having undergone a biopsy [1, 2, 19, 22, 26, 33, 41]. Furthermore, many centers with extensive experience with thymic tumors routinely obtain a biopsy of larger tumors suspected to be a thymoma [19, 22, 26, 36, 42, 43, 51].

## Treatment

### Surgery

Surgical resection is the mainstay of treatment of thymomas, because the vast majority (90% to 95%) of these tumors are localized [2]. The reported operative mortality in series of more than 100 patients (spanning many decades) is an average of 2.5% (range, 0.7% to 4.9%) [6, 18, 19, 21, 22, 32, 33, 40]. The ability of carrying out a grossly and microscopically complete resection is uniformly high (100%) in patients with stage I thymomas in series of more than 50 patients. There is wide variation in the reported resectability rates between studies in patients with higher stage thymomas (43% to 100% [average, 85%] for stage II; 0% to 89% [average, 47%] for stage III; and 0% to 78% [average, 26%] for stage IV). This may reflect differences in the willingness of surgeons to undertake more extensive operations (eg, resection of the vena cava). Extended resections appear to be justified because complete resection is probably the most important prognostic factor (see subsequent section).

### Survival

The 5-year overall survival rates after resection are quite good, even for patients with stage III and IV disease (Table 2). Overall survival at 15 years for stage I, II, III, and IV disease is reported as 78%, 73%, 30%, and 8%, respectively [18]. Not all patients with stage III or IV thymomas underwent a complete resection, even though they were probably carefully selected. Among surgical series of more than 100 patients, an average of 38% of deaths are related to thymoma (range, 19% to 58%), 9% to postoperative causes (range, 2% to 19%), 22% to MG (range, 16% to 27%), 9% to other autoimmune diseases (range, 2% to 19%), and 29% (range, 8% to 47%) to unrelated causes (including other cancers) [5, 6, 8, 18, 19, 25, 27, 31-34].

Disease-free survival may be a better measure of the effectiveness of surgical treatment. Studies of more than 100 patients have found average disease-free survival rates at 10 years of 92%, 87%, 60%, and 35% for stages I, II, III, and IV, respectively [8, 18, 25, 31]. The best measure of outcome after resection may be the recurrence rate (Table 3). The recurrence rate for stage IV tumors shows wide variability, likely reflecting differences in selection and the small number of such patients in these reports. In general, recurrence rates are reported only for those patients in whom all gross tumor was removed.

The average time to recurrence is approximately 5 years (range, 3 to 7 years) [6, 18, 19, 22, 27, 30]. However, recurrences have been reported up to 32 years after resection [6, 56]. The mean time to recurrence is 10 years in patients with a stage I thymoma, compared with 3 years in patients with stage II, III, or IV thymomas [5]. Among series of more than 100 patients, an average of 81% of all recurrences were local, 9% were distant, and 11% involved both sites [5, 6, 18, 22, 30, 32]. In patients with recurrences, the pleural space or the lung was involved in 58% (most often as a nodule under the parietal pleura), the pericardium or medi-

**Table 2.** Overall Survival of Patients With Thymic Tumors<sup>a</sup>

Study	n	% R <sub>0</sub>	% 5-year Survival				% 10-year Survival			
			I	II	III	IVa	I	II	III	IVa
Kondo and Monden [39] <sup>b</sup>	924	92	100	98	89	71	100	98	78	47
Regnard et al. [18]	307	85	89	87	68	66	80	78	47	30
Maggi et al. [19]	241	88	89	71	72	59	87	60	64	40
Verley and Hollmann [5]	200	...	85	60	—33—		80	42	—23—	
Nakahara et al. [33] <sup>b</sup>	141	80	100	92	88	47 <sup>c</sup>	100	84	77	47 <sup>c</sup>
Wilkins et al. [27]	136	68	84	66	63	40	75	50	44	40
Blumberg et al. [22]	118	73	95	70	50	100	86	54	26 <sup>d</sup>	...
Quintanilla-Martinez et al. [8]	116	94	100	100	70	(70) <sup>e</sup>	100	100	60	(0) <sup>e</sup>
Pan et al. [23] <sup>b</sup>	112	80	94	85	63	41	87	69	58	22
Elert et al. [21]	102	...	83	90	46	...	...	...	...	...
Average <sup>f</sup>			92	82	68	61	88	70	57	38

<sup>a</sup> Inclusion criteria: results of ≥100 patients by Masaoka stage.  
<sup>b</sup> ≤5 patients. <sup>c</sup> Numbers in parentheses excluded.

<sup>b</sup> Thymic carcinoma excluded.

<sup>c</sup> Both stage IVa and IVb.

<sup>d</sup> 9-year survival.

R<sub>0</sub> = percent with complete resection.

astinum in 41%, bone in 10%, and liver in 8% [5, 6, 18, 22, 30, 32].

#### Subtotal Resection

Although it is clear that every effort should be made to achieve a complete resection, it is controversial whether there is a benefit to carrying out a subtotal resection (debulking) when a complete resection cannot be accomplished. Some authors argue that a partial resection provides better survival than a simple biopsy in unresectable cases [1, 19, 25, 33, 34, 39], and in general, this does appear to be the case (10-year survival approximately 39% versus 33%; Table 4). In most studies, the difference has been small, and only two studies have shown a substantial difference [19, 33]. Another large study [39] found a significant difference in 5-year survival among patients undergoing subtotal versus biopsy only (64% versus 36%), but little difference in 10-year survival,

suggesting that the benefit may be only in intermediate-term survival. Other authors argue that there is no additional benefit of incomplete resection over biopsy [3, 18, 20, 22, 26].

It is difficult to compare the results of patients undergoing partial resection or biopsy only because of the possible influence of other treatments, selection bias, differences in the stage of thymomas among these patients, and differences in the follow-up periods. In addition, it is unclear how recurrence is defined in incompletely resected patients, or how much tumor removal constitutes a partial resection in most of these studies. With regard to this latter issue, the recurrence rate appears to be lower (36% versus 71%) after a resection that is microscopically incomplete (R<sub>1</sub>) compared with a grossly incomplete resection (R<sub>2</sub>) in one study of 28 patients, all of whom received adjuvant radiotherapy (RT) [57].

**Table 3.** Recurrence Rates of Thymic Tumors<sup>a</sup>

Study	n	R <sub>0</sub>	% Receiving			% With Recurrence			
			Ch	RT	I	II	III	IVa	
Kondo and Monden [39] <sup>b</sup>	862	100	12 <sup>c</sup>	32 <sup>c</sup>	1	4	28	34 <sup>d</sup>	
Regnard et al. [18]	307	85	few	half	4	7	16	58	
Maggi et al. [19]	241	88	7	12	2	13	30	25	
Verley and Hollmann [5]	200	...	few	most	6	36	—38—		
Cowen et al. [25] <sup>be</sup>	149	42	100	50	(0) <sup>f</sup>	7	23	25	
Wilkins et al. [27]	136	68	7	37	8	10	24	(0) <sup>f</sup>	
Monden et al. [34] <sup>b</sup>	127	80	...	74	3	13	27	54	
Blumberg et al. [22]	118	73	32	58	4	21	47	80	
Ruffini et al. [30]	114	100	...	25	5	10	30	33	
Quintanilla-Martinez et al. [8]	105	100	0	24	0	13 <sup>g</sup>	13	(0) <sup>f</sup>	
Average <sup>h</sup>					4	14	26	46	

<sup>a</sup> Inclusion criteria: results of ≥100 patients, with results by Masaoka stage.  
<sup>b</sup> Thymic carcinoma excluded.  
<sup>c</sup> Estimated, not specifically reported.  
<sup>d</sup> IVa and IVb.  
<sup>e</sup> Recurrences only in the mediastinum excluded.  
<sup>f</sup> ≤5 patients.  
<sup>g</sup> 19% and 6% for IIa and IIb.  
<sup>h</sup> Numbers in parentheses excluded.

Ch = chemotherapy; R<sub>0</sub> = complete resection; RT = radiotherapy.

**Table 4.** Survival After Subtotal Resection of a Thymic Tumor<sup>a</sup>

Study	n			% 10-year Survival			<i>p</i> Value <sup>b</sup>
	R <sub>0</sub>	R <sub>1,2</sub>	Bx	R <sub>0</sub>	R <sub>1,2</sub>	Bx	
Kondo and Monden [39] <sup>cd</sup>	186	50	24	(93) <sup>e</sup>	(64) <sup>e</sup>	(36) <sup>e</sup>	<.003
Maggi et al. [19]	211	21	9	81	72 <sup>f</sup>	27 <sup>f</sup>	0.001
Nakahara et al. [33] <sup>d</sup>	113	16	12	(94) <sup>g</sup>	(68) <sup>g</sup>	(0) <sup>g</sup>	<.01
Blumberg et al. [22]	86	18	14	70	28	24	NS
Mornex et al. [71] <sup>d</sup>	4	31	55	...	43	31	<.02
Regnard et al. [18] <sup>h</sup>	43	28	12	75	29	35	NS
Gamondès et al. [3] <sup>d</sup>	45	15	5	91	32	53	...
Wang et al. [20]	34	9	18	48	20	20	NS
Kaiser and Martini [43]	39	13	7	82	48	44	...
Average <sup>i</sup>				75	39	33	

<sup>a</sup> Inclusion criteria: studies of >50 patients reporting outcomes after incomplete resection and biopsy. <sup>b</sup> *p* value for R<sub>1,2</sub> resection versus biopsy only. <sup>c</sup> Only stage III and IV thymoma. <sup>d</sup> Thymic carcinoma excluded. <sup>e</sup> 5-year survival. <sup>f</sup> 8-year survival. <sup>g</sup> Disease-free survival. <sup>h</sup> Stage III patients only. <sup>i</sup> Excluding values in parentheses.

Bx = patients undergoing biopsy only; NS = not significant; R<sub>0</sub> = patients undergoing complete resection; R<sub>1,2</sub> = patients undergoing microscopically or grossly incomplete resection.

In summary, the data are unclear as to whether a partial resection is of benefit. In general, the difference in survival appears to be small, and may be explained entirely by selection bias. However, it is possible that an incomplete resection that leaves only a minimal amount of residual disease may yield a survival benefit, especially in the context of adjuvant therapy.

### Prognostic Factors

By univariate analysis, stage has been widely found to correlate with prognosis (Table 2). Significantly better survival has been noted in patients who underwent complete resection by every large study examining this issue [6, 18, 19, 22, 27, 31-33, 37]. In one of the largest series, the 10-year survival of completely resected patients was 80%, 78%, 75%, and 42% for stages I, II, III, and IVa [18]. Other studies have also demonstrated good survival after complete resection in patients with a stage III or IV thymoma [33, 58]. It is remarkable that the long-term survival of patients with a stage III thymoma is similar to that of those with a stage I thymoma, provided a complete resection was carried out. The presence of MG was once thought to be a negative prognostic factor [55]. However, most studies suggest either a trend [18, 31, 42] or significantly better survival [19, 20, 27] in patients with MG.

Multivariate analysis of prognostic factors has been carried out in several large studies (>100 patients) [6, 18, 22-27, 31]. Consistent independent prognostic factors are the stage of the tumor and the completeness of the resection, with only rare exceptions [18, 24, 25]. In the largest series, completeness of resection was the only significant prognostic factor when all variables were included in the model (Masaoka stage was not of independent significance) [18]. In another large series, completeness of resection but not stage was of independent prognostic significance for overall survival, yet stage and not completeness of resection was significant for disease-

free survival [25]. There is some suggestion that patients with smaller tumors [22, 25] and that patients who are younger than 30 to 40 years of age have a better prognosis [6, 25, 26]. Histologic type was generally not of independent prognostic significance [6, 18, 23, 25, 26], with a few exceptions as noted previously [22, 24, 27]. Other factors have generally either been found not to be of value, or have not been studied.

### Adjuvant Radiotherapy

Whether adjuvant RT should be given after a resection remains controversial. Some authors recommend this for all patients [33, 34], others only for stage II and III thymoma [3, 18, 25, 41, 43], and others for incompletely resected patients [3, 25, 39]. Although most recurrences of a thymoma are local, these are primarily pleural or pericardial implants that are not necessarily within an RT port [37]. All series addressing postoperative RT involve retrospective reviews spanning many decades, rather than an experience with a consistent treatment plan and selection criteria. To minimize any selection bias, the analysis presented here is limited to studies that reported outcomes separately by stage and completeness of resection (the two most consistent prognostic factors).

Table 5 shows the results of retrospective series that have compared outcomes with and without adjuvant RT. In completely resected (R<sub>0</sub>) patients, the recurrence rates for stage I thymomas are so low, even without adjuvant RT, that the use of RT is probably not justified. The value of RT in completely resected stage II and stage III patients is unclear. Although some series suggest a trend to a lower incidence of recurrence with adjuvant RT for stage II thymomas, the largest series by far found no differences [39], and one of the larger series found the opposite result [30]. Among completely resected stage III thymomas, three series have reported no difference in recurrence rates [22, 39, 59], whereas another series noted a higher recurrence rate after adjuvant RT [30]. Studies

**Table 5.** Recurrence Rate After Resection and Adjuvant Radiotherapy<sup>a</sup>

Study	% R <sub>0</sub>	% of Patients with Recurrence						<i>p</i> Value	
		I		II		III			
		Obs	RT	Obs	RT	Obs	RT	II	III
Kondo and Monden [39] <sup>b</sup>	100	...	...	4	5	26	23	NS	NS
Ruffini et al. [30]	100	5	0	4	31	16	64	0.02	0.02
Regnard et al. [18]	100	...	...	(22) <sup>c</sup>	(13) <sup>c</sup>	...	...	—NS <sup>c</sup> —	—NS <sup>c</sup> —
Haniuda et al. [59] <sup>b</sup>	100	0	(0) <sup>d</sup>	24	19	25	25	...	...
Monden et al. [34] <sup>b</sup>	100	8	0	29	8	...	...	...	...
Curran et al. [38] <sup>b</sup>	100	0	(0) <sup>d</sup>	...	...	(42) <sup>c</sup>	(0) <sup>c</sup>	—NS <sup>c</sup> —	—NS <sup>c</sup> —
Blumberg et al. [22]	100	...	...	...	...	52	48	NS	NS
Average <sup>e</sup>		3	0	15	16	30	44		

<sup>a</sup>Inclusion criteria: studies of >50 patients by stage and completeness of resection.<sup>b</sup>Thymic carcinoma excluded. <sup>c</sup>Stage II, III combined.<sup>d</sup><5 patients in this category. <sup>e</sup>Excluding values in parentheses.NS = not significant; Obs = observation; R<sub>0</sub> = complete resection; RT = radiotherapy.

reporting data for completely resected stage II and III patients combined found a nonsignificant trend toward a decreased rate of recurrence with adjuvant RT [18, 38].

In incompletely resected patients, two studies have suggested a benefit to adjuvant RT, although neither study involved a large number of patients, and both are open to bias in terms of patient selection [19, 38]. A third study, involving both R<sub>0</sub> and R<sub>1,2</sub> resections of stage III thymomas, also found a lower recurrence rate with adjuvant RT (24% versus 40%; no *p* value given; 44 patients) [34]. Adjuvant RT was also found to result in a lower recurrence rate among patients with incompletely resected stage IV thymomas (44% versus 75%; 13 patients) [34]. Finally, mediastinal recurrences have been found to be lower with RT among 26 stage III patients undergoing subtotal resection (5-year actuarial rate 21% versus 100%; no *p* value given) [38]. The use of RT in incompletely resected patients is also supported by very low rates of mediastinal failure among incompletely resected patients with gross residual disease who were treated with adjuvant RT (16% to 21%) [38, 60, 61].

In summary, the role of adjuvant RT remains poorly defined. The benefit in stage I patients is marginal at best. Given the conflicting results and the potential selection bias in retrospective series, the role of adjuvant RT in completely resected stage II and stage III patients is unclear. It appears that RT does decrease the recurrence rate in incompletely resected patients.

## Chemotherapy

Thymomas are sensitive to chemotherapy, with an objective response seen in an average of two thirds of patients (range, 10% to 100%), and a complete response in one third (range, 0% to 43%) [49, 62–70]. The reason for the variability among studies is unclear. A variety of chemotherapy agents have been used. The small size of the series (11 to 37 patients) precludes any meaningful comparison between regimens, which have been primarily cisplatin-based. Only a few patients with TC were included in these studies. The median duration of response

varies dramatically among studies, ranging from 12 to 93 months. Again, it is not clear why this is the case.

The impact of chemotherapy on patient survival is difficult to assess. In a retrospective analysis, chemotherapy significantly reduced the rate of metastases to the lung, pleura, or distant sites (17% versus 38%; *p* < 0.05) among 90 patients with stage III or IV tumors who were treated with RT and either partial resection (34%) or no resection (61%) [25]. There was also a trend to better disease-free survival with chemotherapy among these patients (5-year survival 55% versus 32%, 10-year survival 41% versus 24%; not significant) [71]. In a much smaller study, no survival difference was seen whether or not chemotherapy was given in 19 patients with unresectable stage III thymomas (5-year survival 56% versus 58%) [22]. Treatment with somatostatin analogs (ie, octreotide) and prednisone has shown promise as a novel treatment approach in patients refractory to chemotherapy [72].

In summary, although it is clear that a variety of chemotherapy regimens are active in thymomas, no conclusions can be drawn about the optimal regimen or the impact of treatment.

## Preoperative Radiation

Preoperative RT has been used on a limited basis by some groups in patients thought to have thymomas invasive of other structures [37, 58, 73, 74]. The ability to carry out a complete resection in these patients has been reported to be 53%, 59%, and 75% [73, 74], which can perhaps be compared with an average resectability rate in stage III thymomas of 50% in studies involving resection alone [1, 3, 18, 22, 31, 33, 38, 43]. The survival is not obviously better than that of other patients with locally advanced thymomas, with 10-year survival rates of 44% to 48% reported in two series (19 and 12 patients) [73, 74]. A comparison of survival in only stage III patients with and without preoperative RT also does not suggest a survival benefit [58].

**Table 6.** Outcomes After Preoperative Chemotherapy and Resection<sup>a</sup>

Study	n	Preop Chemo	Adjuvant Therapy	% Obj Resp	% R <sub>0</sub>	% pCR	% 5-year Survival
Venuta et al. [26] <sup>b</sup>	25 <sup>c</sup>	PEEpi × 3	RT/Ch	...	80	4	80 <sup>d</sup>
Kim et al. [70] <sup>b</sup>	22	CAPPPr × 3	RT/Ch	77	82 <sup>e</sup>	18 <sup>e</sup>	95
Rea et al. [67] <sup>b</sup>	16	CAPV × 3	RT or Ch	100	69	31	57
Macchiarini et al. [90] <sup>b</sup>	7	PEEpi × 3	RT	100	57	29	...
Average				92	72	21	78

<sup>a</sup> Inclusion criteria: studies of >5 patients with preoperative chemotherapy. <sup>b</sup> Thymic carcinoma excluded. <sup>c</sup> Only 21 of 25 patients treated with preoperative chemotherapy. <sup>d</sup> 92% for stage III tumors, 68% for stage IVa tumors. <sup>e</sup> Data taken from Shin et al. [91].

Ch = chemotherapy; CAPPPr = cyclophosphamide, doxorubicin, cisplatin, prednisone; CAPV = cyclophosphamide, doxorubicin, cisplatin, vincristine; Obj Resp = objective response rate; pCR = pathologic complete response rate; PEEpi = cisplatin, etoposide, epirubicin; Preop Chemo = preoperative chemotherapy; R<sub>0</sub> = complete resection; RT = radiotherapy.

## Multimodality Therapy

Several series suggest that resectability and survival may be improved with multimodality treatment (preoperative chemotherapy, surgery, and postoperative chemotherapy or RT) in patients with stage III and IV thymomas (Table 6). Considerable chemosensitivity was observed in these studies with an objective response of 90%, a complete response of 23%, and a pathologic complete response of 20%. The ability to achieve a complete resection is high (72%) compared with rates of approximately 50% and 25% for stage III and stage IV thymomas, respectively, in studies involving resection alone [1, 3, 18, 22, 31, 33, 38, 43]. The 5-year survival (average, 78%) also appears to be slightly better than in patients with stage III or IV thymomas who underwent primary surgical resection (average, 65% and 62%; Table 2). Most of these studies were controlled prospective trials, and do not appear to have excluded many patients with appropriately staged tumors at these institutions.

There is no clear consensus on the best treatment approach for a thymoma that is deemed to be unresectable because the data are scant and uncontrolled. Overall, approximately one third of patients undergoing only a biopsy are alive 10 years later (Table 4).

## Special Treatment Issues

### Recurrence

An aggressive approach to recurrence of thymoma has been advocated by several authors [18, 19, 22, 30, 41, 54, 58, 75, 76]. Between half and two thirds of all recurrences were considered to be operable in series reporting these data [22, 30, 54, 76]. Of those patients in whom reoperation was undertaken, a complete resection was able to be accomplished in 62% (range, 45% to 71%) [30, 54, 75, 76]. Good 10-year survival has been reported among completely resected patients (53% to 72%) [30, 54] compared with incompletely resected patients (0% to 11%) [18, 30, 54]. Furthermore, a second recurrence was observed in only 16% to 25% of patients after a complete resection of a first recurrence in two series (mean follow-up of 4 and 5 years after the recurrence) [54, 75].

Other treatments for recurrent thymoma have in-

volved radiation or chemotherapy. Reasonable intermediate-term survival has been reported (5-year survival of 25% to 50%) in several studies using various treatment approaches, but long-term survival is poor [19, 22, 30, 76, 77].

### Well-Differentiated Thymic Carcinoma

The survival of patients with WDTC has been reported to be variable, with 5-year survival rates ranging from 60% to 80% (average, 75%) and 10-year survival rates ranging from 30% to 78% (average, 61%) [8, 13, 23, 24, 36]. The majority (73%, range, 58% to 83%) of these patients have stage III or IV tumors at presentation [7, 8, 13, 23, 24, 36]. Surgery has been the mainstay of treatment, with approximately two thirds of patients able to undergo a complete resection [13, 15, 36]. There are no data that specifically address the effectiveness of RT or chemotherapy in this group of patients.

### Thymic Carcinoma

The majority (50% to 95%) of patients with TC present with advanced disease (stage III or IV) [10, 14, 24, 39, 78–81]. The majority of TC is either squamous carcinoma (42%) or lymphoepithelioma-like (32%) [10]. Some authors have grouped TC into low-grade tumors (squamous cell, basaloid, and mucoepidermoid carcinomas) and high-grade tumors (lymphoepithelioma-like, undifferentiated/anaplastic, small cell, sarcomatoid, and clear cell carcinomas) [10, 80].

The prognosis of patients with TC is generally poor, with a median survival of approximately 2 years [9, 10, 15, 78, 81] and 5- and 10-year survival rates averaging 40% and 33%, respectively [9, 10, 13, 15, 39, 80]. Surgery has been the mainstay of treatment, although a complete resection is possible in only about one third of all patients [14, 15, 39, 79–81]. Two reviews have found that the survival was markedly better in patients with low-grade tumors compared with high-grade tumors (5-year survival of 57% and 13% for squamous and lymphoepithelioma-like carcinomas, respectively) [9, 10]. Recurrences are seen in approximately three fourths of patients overall, and distant recurrences in about 50% [9, 10, 14, 15, 39, 78, 81].

Median survival among unresected or partially resected patients with TC is approximately 12 to 36 months [9, 14, 39, 80]. Chemotherapy (various regimens) has been used in a limited number of patients, with an overall response rate of 20% to 60% [63, 79]. Radiation has produced partial response rates of 86%, with local tumor control in 83% of the responders during follow-up periods of 1 to 10 years in one study [79].

### Thymic Carcinoid

Thymic carcinoid tumors are rare, with only approximately 150 to 200 cases having been reported [82]. They occur in all age groups, with at least a 3:1 male predominance [39, 82–87]. About 25% of patients present with Cushing's syndrome [39, 80, 82–85, 88]. An association with tumors seen in multiple endocrine neoplasia 1 syndrome is seen in approximately 15% [39, 82–84, 86, 88, 89]. Myasthenia gravis or any of the parathyroid conditions associated with thymomas have not been reported in patients with thymic carcinoid tumors although other paraneoplastic syndromes are seen occasionally. Only 2 reported patients have exhibited carcinoid syndrome [80]. The majority of tumors (72%) were of intermediate grade, similar to atypical carcinoid tumors in the lung [82, 84–86]. The rest are either high-grade tumors, similar to small cell lung cancer, or, less commonly, low-grade tumors similar to typical carcinoid tumors [82].

About half of patients have nodal metastases [85, 88], but this does not appear to predict survival [85]. However, even in the face of a complete resection, distant metastases have developed in the majority of patients [39, 82–86, 88]. Local recurrence is also frequent, and the disease-free interval is generally short (1 to 2 years) [82–86, 88]. Nevertheless, intermediate-term survival is fairly good. In a collected series of 81 cases, the 5-year and 10-year survival rates were 77% and 30%, respectively, among completely resected patients ( $n = 53$ ), 65% and 19%, respectively, after partial resection ( $n = 11$ ), and 28% and 0%, respectively, in unresectable patients ( $n = 16$ ) [82]. This is corroborated by a collected series of 50 patients, in which the 5-year and 10-year survival rates were 28% and 10%, respectively [87]. Dramatically better survival was reported in another series of 41 patients (10-year survival of approximately 75%, with no perceptible differences between stages) [39]. Multivariate analysis has found only unresectability and advanced stage to be associated with poorer survival, whereas sex, age, Cushing's syndrome, chemotherapy, RT, and recurrence had no impact [82]. Among smaller series survival appears to be better the lower the histologic grade (median survival, 9 to 11 years for low-grade tumors, 5 to 7 years for intermediate-grade tumors, and 1.5 to 3 years for high-grade tumors) [82, 87].

### Conclusion

Despite what is often an indolent course and a cytologically bland appearance, all thymic tumors can manifest malignant behavior. Classification schemes focusing on subtypes of bland tumors have questionable prognostic

value, whereas distinguishing TC and perhaps also WDTC from bland thymomas is more useful. The frequent presence of associated parathyroid conditions has engendered much interest, but does not affect the treatment of the thymoma itself. Biopsy of a mass suspected to be a thymoma is not detrimental, and should be done in cases in which the ability to achieve a complete resection with surgery alone or the diagnosis is unclear.

Surgery continues to be the mainstay of treatment, and the ability to accomplish a complete resection appears to be the most important prognostic factor. Therefore, every effort must be made at the time of resection to achieve this. There appears to be little, if any, benefit of partial resection (debulking). Thymomas also have a high response rate to chemotherapy or RT. The value of post-operative (adjuvant) RT in completely resected stage II or III tumors appears to be unclear at best, whereas the data suggest a benefit in patients who are incompletely resected. Multimodality therapy involving preoperative chemoradiotherapy appears to increase the rate of complete resection of stage III and IVa thymomas. Because the ability to achieve a complete resection results in excellent long-term survival of even advanced stage tumors, a multimodality approach should strongly be considered in such cases. A recurrence should be completely resected whenever possible, because this approach is associated with good long-term survival.

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