REVIEW

Optimal therapy for thymoma

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Abstract : Thymoma is the most common tumor of the anterior mediastinum. This tumor is associated with unique paraneoplastic syndromes (myasthenia gravis, pure red cell aplasia, hypogammaglobulinemia, and other autoimmune diseases). The rarity of this tumor has somewhat obscured the optimal treatment. Although the histologic classification of thymoma has remained a subject of controversy for many years, the WHO classification system, published in 1999, appeared to be an advance in our understanding of thymoma. The optimal treatment for thymoma depends on its clinical stage. Surgery remains the mainstay of treatment for thymic epithelial tumors. Thymomas also have a high response rate to chemotherapy or radiotherapy. Only surgical resection is performed for patients with stage I (non-invasive) thymoma. The value of postoperative radiotherapy in completely resected stage II or III tumors is questionable. Multimodality therapy involving surgery, chemotherapy and radiotherapy appears to increase the rate of complete resection and survival in advanced (stage III and IV) thymomas. J. Med. Invest. 55 : 17-28, February, 2008

Keywords **:** *thymoma, WHO histologic classification, Masaoka's clinical staging system, postoperative radiotherapy, multimodality therapy*

INTRODUCTION

Thymoma is an uncommon neoplasm derived from epithelial cells of the thymus. It is well known for several interesting features : association with myasthenia gravis (MG) or other autoimmune disease, histologic variability, and heterogeneity of malignant behavior (1, 2). Surgery remains the mainstay of treatment, and radiation and chemotherapy also have been applied widely as adjuvant and palliative procedures (3-5) ; however, the optimal treatment for invasive thymoma has long been debated. Recently, new concepts regarding the clinical approach to thymoma have emerged as a result of a more evidence-based approach (6, 7). This article reviews the therapeutic strategy for thymoma.

Received for publication December 27, 2007 ; accepted January 10, 2008.

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HISTOLOGICAL CLASSIFICATION

The histologic classification of thymoma has remained a subject of controversy for many years (8). In 1976, Rosai and Levine (1) proposed that thymoma is restricted to neoplasms of thymic epithelial cells and is divided into benign encapsulated (noninvasive) and malignant invasive thymoma. Two years later, they divided malignant thymoma into invasive but cytologically bland thymoma (malignant thymoma, category I) and cytologically malignant epithelial tumors, which correspond to thymic carcinoma (malignant thymoma, category II) (9). In 1989, Muller-Hermelink and associates (10) divided thymic epithelial tumors into medullary, mixed medullary and cortical, predominantly cortical, cortical thymoma, well-differentiated thymic carcinoma and high-grade carcinoma. This classification was

reported to be useful for predicting the outcomes of patients with these tumors (11, 12).

In 1999, the World Health Organization (WHO) Consensus Committee published a histologic typing system of tumors of the thymus (13). Thymomas are stratified into six entities (types A, AB, B1, B2, B3, and C) on the basis of the morphology of epithelial cells and the lymphocyte-to epithelial cell ratio (Table 1). The WHO Consensus Committee (2004) recently proposed that thymic epithelial tumors consist of thymoma (type A, AB, B1, B2 and B3) and thymic carcinoma, including neuroendocrine epithelial tumors of the thymus (well-differentiated neuroendocrine carcinoma ; typical carcinoid and atypical carcinoid, poorly differentiated neuroendocrine carcinoma ; large cell neuroendocrine carcinoma and small cell carcinoma) (14).

Recently many reports have discussed the impact of the WHO system on clinical management decisions (whether the classification is reproducible, whether it defines clinically distinct patient groups, whether it has independent prognostic value) (15-25). The WHO classification system does appear to be an advance in our understanding of thymoma. Detterbeck summarized that the WHO classification is reasonably reproducible, and general trends toward different clinical characteristics of patients of a particular subtype are suggested. In general, the WHO classification has independent prognostic value in addition to stage ; however, the value of histologic classification is primarily in distinguishing thymic carcinoma and, less clearly perhaps, type B3 from other types of thymoma (26).

CLINICAL STAGE

The clinical staging system for thymoma was first introduced by Bergh and associates in 1978 (27), later modified by Wilkins and Castleman (28), and confirmed by Masaoka and associates in 1981 (Table 2) (29). A TNM staging system has been proposed that closely parallels the Masaoka system (Table 3) (30). In France, multiple centers have adopted the Groupe d'Etudes des Tumeurs Thymiques (GETT) staging system (Table 4), as described by the French Study Group on Thymic Tumours (31). In this system, the predominant feature is the extent of surgical resection. The clinical staging of patients should be determined before treatment to select the optimal approach.

The Masaoka classification is now the most widely accepted and is an excellent predictor of the prognosis of thymoma (2, 3, 6, 7, 32) ; however, several

Table 1. World Health Organization Histologic Classification

A	A tumor composed of a population of neoplastic thymic epithelial cells having a spindle/oval shape, lacking nuclear atypia, and accompanied by few or no non-neoplastic lymphocytes.
AB	A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes.
B1	A tumor that resembles the normal functional thymus in that it combines large expanses practically indistinguishable from normal thymic cortex with areas resembling thymic medulla.
B2	A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes. Perivascular spaces are common and sometimes very prominent. A perivascular arrangement of tumor cells resulting in a palisading effect may be seen.
B3	A type of thymoma predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia. They are admixed with a minor component of lymphocytes, resulting in sheetlike growth of neoplastic epithelial cells.
C	A thymic tumor exhibiting clear-cut cytologic stypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. Type C thymomas lack immature lymphocytes. The lymphocytes present are mature and usually admixed with plasma cells.

Table 2. Masaoka Staging System

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

Table 3. TNM Classification of Thymic Epithelial Tumors

T factor	
T1 :	Macroscopically completely encapsulated and microscopically no capsular invasion
T2 :	Macroscopically showing adhesion or invasion into surrounding fatty tissue or mediastinal pleura, or microscopic invasion into capsule
T3 :	Invasion into neighboring organs, such as pericardium, great vessels, and lung
T4 :	Pleural or pericardial dissemination
N factor	
N0 :	No lymph node metastasis
N1 :	Metastasis to anterior mediastinal lymph nodes
N2 :	Metastasis to intrathoracic lymph nodes except anterior mediastinal lymph nodes
N3 :	Metastasis to extrathoracic lymph nodes
M factor	
M0 :	No hematogenous metastasis
M1 :	Hematogenous metastasis

Table 4. GETT Staging System of Thymomas

Stage I	
Ia	Encapsulated tumor, totally resected
Ib	Macroscopically encapsulated tumor, totally resected, but the surgeon suspects mediastinal adhesion and potential capsular invasion
Stage II	
	Invasive tumor, totally resected
Stage III	
IIIa	Invasive tumor, subtotally resected
IIIb	Invasive tumor, biopsy
Stage IV	
IVa	Supraclavicular metastasis or distant pleural implant
IVb	Distant metastases

articles have pointed out problems and have suggested that an update of the system is desirable (33, 34). 1) The classification system does not provide appreciable prognostic separation between stages I and II (2, 35, 36). 2) Some definitions are not clinically applicable because surgical or pathological assessment is required. In particular, the definition of stage II is unclear. Some pathologists propose that microscopic invasion into the capsule in stage II should be replaced by microscopic transcapsular invasion (2, 8). The most recent World Health Organization classification of thymic epithelial tumors in 2004 defined T2 thymoma as "tumor invades pericapsular connective tissue" (14). 3) As stage III thymoma is highly heterogenous in terms of the involved organs, the classification should divide the subgroups according to prognosis. Okumura and associates (37) reported that involvement of the great vessels is an independent prognostic factor in patients with stage III thymoma. 4) The system is not well suited to staging thymic carcinomas (38, 39). The TNM system classification of thymic epithelial tumors has not been established. Yamakawa and Masaoka (30) presented a tentative TNM system classification of thymoma in 1991, which some reports subsequently supported. In Masaoka's system, the presence of local invasion (T factor) is strongly emphasized in comparison with lymphogenous and hematogenous metastasis (N and M factors) because of the rarity of lymphogenous and hematogenous metastasis in thymoma. However, it is necessary to determine how N or M factors influence prognosis to establish a TNM system classification of thymic epithelial tumors, including thymic cancer and carcinoid. The WHO histologic classification of 2004 (14), which can distinguish thymic carcinoma and carcinoid from thymoma, has been widely adopted, and large-scale clinicopathologic studies of thymic carcinoma and carcinoid may provide sufficient prognostic information to include N or M factors in a TNM system of thymic epithelial tumor.

THERAPY

Surgery remains the mainstay of treatment for thymic epithelial tumors, and radiation and chemotherapy also have been applied widely as adjuvant and palliative procedures (2, 3, 6, 7). The treatment of thymoma depends upon its clinical stage. Kondo and Monden presented the therapeutic modality of 1,093 patients with thymoma in Japan (32). Most patients with stage I thymoma underwent only surgery. About half of the patients with stage II thymoma and three-fourths of the patients with stage III thymoma underwent surgery with adjuvant therapy. Most of the adjuvant therapy in stages I, II, and III thymomas consisted of radiotherapy. Seventy percent of patients with stage IV thymoma underwent surgery with adjuvant therapy. In more than half, adjuvant therapy included chemotherapy.

1) SURGERY

Surgical resection is the mainstay of thymoma treatment, because most of these tumors are localized (7, 30). The reported operative mortality is an average of 2.5% (0.7%-4.9%) (6, 7). Surgery for thymic epithelial tumors was classified into three groups : total resection (no tumor remained macroscopically), subtotal resection (almost all of the tumor was resected macroscopically), and inoperable (including partial resection, exploratory thoracotomy and simple biopsy) groups. The resectability rates of stage I, II, III, and IV thymomas were 100%, 100%, 85%, and 42%, respectively (32). Detterbeck surmmarized from 8 series of more than 100 patients with thymoma that the average resectability rates of stage I, II, III, and IV thymomas were 100%, 80% (43-100%), 47% (0-89%), and 26% (0-78%), respectively. Several large studies (>100 patients) demonstrated that completeness of resection is an independent prognostic factor using multivariate analysis (7).

2) RADIOTHERAPY

A) Postoperative radiotherapy

Most authors do not recommend radiotherapy after totally resected stage I (noninvasive) thymoma (3, 5) ; however, recommendations for the appropriate use of adjuvant radiation therapy for stage II or III thymoma are controversial. We reviewed 11 papers in which patients with stage II or III thymoma both received and did not receive adjuvant radiation therapy after complete resection, thus enabling a comparison between the two groups (Table 5) (40-49). Monden and associates reported that 8% and 24% of patients with postoperative radiotherapy and 29% and 40% of patients without postoperative radiotherapy relapsed in stage II and III thymoma, respectively (40). Another nine papers (12, 42-49) were unable to demonstrate an advantage over radiation therapy in terms of recurrence including local, pleural dissemination and distant metastasis. In patients with stage II thymoma, recurrence rates ranged from 0% to 31% after radiation, and from 0% to 29% without radiation. In patients with stage III thymoma, recurrence rates ranged from 13% to 64% after radiation, and from 13% to 52% without radiation. These differences did not reach statistical significance, except in a paper by Ruffini and associates (45), who demonstrated a significant advantage to not receiving adjuvant radiation (p=0.02). We do not recommend adjuvant radiation therapy as a means to prevent recurrence, including local, pleural dissemination and distant metastasis, for patients with completely resected stage II and III thymoma. Haniuda and associates reported that 19% of patients with postoperative radiotherapy and 12% of patients without postoperative radiotherapy had pleural dissemination in stage II and III thymoma, and recommended that mediastinal irradiation may have been effective in preventing local recurrence, although it did not control pleural dissemination (44).

On the other hand, two reports demonstrated an advantage to radiation therapy in terms of mediastinal recurrence. Curran, *et al.* reported that no patient with postoperative radiotherapy and 33% and 67% of patients without postoperative radiotherapy relapsed in stage II and III thymoma, respectively (41). Haniuda, *et al.* reported that 3.6% of patients with postoperative radiotherapy and 17.2% of patients without postoperative radiotherapy relapsed in stage II and III thymoma (44). Another five papers (12, 32, 47-49) were unable to demonstrate an advantage to radiation therapy in terms of local recurrence. Although the utility of postoperative mediastinal radiotherapy in preventing local recurrence in patients with completely resected stage II and III thymoma is controversial, the frequency of cases with only local recurrence is low.

Moreover, there are some late complications of radiation therapy to the chest (hematopoietic malignancies, esophageal malignancies, dysmotility and strictures, or radiation pneumonitis and chronic pulmonary fibrosis) and the heart (cardiac valve fibrosis, pericardial effusions, or accelerated coronary artery disease) (46, 49).

Table 5. Postoperative radiotherapy for patients with completely resected stage II and III thymoma

Author	period	total cases	stage	number of patients with radiation	number of patients without radiation	recurrence rate* with radiation	recurrence rate* without radiation		mediastinal recurrence rate with radiation		mediastinal recurrence rate without radiation	
Monden *et al.* 40)		127	II	25	7	8.0%	29.0%		-		-	
			III	34	10	29.0%	40.0%		-		-	
Curran *et al.* 41)$	1960-1985	117	II	1	18	-	-		0%		33.0%	6
			III	4	3	-	-		0%		66.7%	2
Quintanilla-Martinez *et al.* 12)#	1970-1990	116	II	7	24	23.0%	8.0%		14.3%	1	0%	
			III	15	8	13.0%	13.0%		0%		0%	
Blumberg *et al.* 42)	1949-1993	118	II	9	17	similar rate			-		-	
			III	17	5	48.0%	52.0%		-		-	
Regnard *et al.* 43)	1955-1993	307	II and III	90	24	30.0%	45.0%	(10-year)	-		-	
						41.0%	45.0%	(15-year)	-		-	
Haniuda *et al.* 44)	1973-1992	89	II	16	21	18.8%	23.8%		3.6%	1	17.2%	5
			III	12	8	25.0%	25.0%					
Ruffini *et al.* 45) &	1974-1993	310	II	13	45	31.0%	4.0%		-		-	
			III	14	36	64%	16%		-		-	
Mangi *et al.* 47)46)#	1972-1999	155	II	14	35	0%	2.9%		0%		0%	
			III	38	7	32%	29%		0%		0%	
Kondo and Monden 32)	1990-1994	1093	II	86	122	4.7%	4.1%		0.0%		1.6%	2
			III	78	31	23.0%	26.0%		5.1%	4	3.1%	1
Singhal *et al.* 48)$	1992-2002	167	II	20	20	5.0%	0.0%		0.0%		0.0%	
Rena *et al.* 49)&	1988-2000	197	II	26	32	11.5%	6.3%		3.8%	1	3.1%	1

* including preural dissemination and distant metastasis
#, $, & same institute

We recommend that patients with completely resected stage II and III thymoma should be followed with long-term serial physical and radiological examination, as this disease has an indolent natural history. If these patients develop recurrence, they should be treated by radiotherapy or surgery.

B) Radiotherapy for unresectable or locally advanced disease

Thymomas are moderately radiosensitive. Radical postoperative radiotherapy may control residual disease and provide long-term, disease-free survival in a subset of patients after incomplete resection. Loehrer summarized selected clinical experiences for which approximate 5-year data are available and noted that approximately two thirds of patients with locally advanced disease were locally controlled, with 5-year survival rates of approximately 40% to 50% (6, 50-55).

Stage III and stage IV thymomas with significant macroscopic infiltration to neighboring structures are rarely completely resectable. In incompletely resected invasive thymoma, whether tumor debulking following radiotherapy influences prognosis and local control is unclear. Mornex and associates reviewed the cases of 90 patients (biopsy only in 55 patients and partial resection in 31 patients) with incompletely resected invasive thymoma. There was a great impact of the extent of surgery on survival : 5- and 10-year survival rates were 64% and 43%, respectively, after partial resection, compared to 39% and 31% after biopsy, $p < 0.02$). There is a significant

relationship between the extent of surgery and local failure (16% of relapse after partial resection vs. 45% after biopsy, $p < 0.05$) (56). Pollack and associates also reported that the disease-free survival rate by the extent of surgery was 60% for subtotal resection and 20% for biopsy only (54). Other studies have described better clinical outcomes with tumor debulking comparing with biopsy only in patients with incompletely resectable thymomas (29, 51, 52, 54).

On the other hand, Ciernik and associates reviewed the cases of 31 patients (biopsy only in 16 patients and subtotal in 15 patients) with incompletely resected stage III and IV thymomas following postoperative irradiation. They demonstrated that both groups yielded similar results in respect to survival and local tumor control. Local recurrence or local tumor progression was not influenced by the amount of surgery (tumor debulking vs biopsy) or by the stage of the thymoma (56). Other studies have not shown any consistent significant benefit of postoperative radiotherapy after incomplete or subtotal resection (57-59).

3) CHEMOTHERAPY

Hejina, *et al.* summarized the efficacy of single agent cisplatin for thymoma and that 3 (14.3%) and 6 (28.6%) patients achieved complete remission (CR), resulting in an overall response rate of 43% (5). Park and associates reported a high response rate to cisplatin with or without predonisone (6 CR (35%), 5 partial remission (PR) (29%), for an overall response rate of 64%). Patients with response to therapy had a significantly longer median survival time than nonresponders (67 months vs 17 months) (61). Hejina and associates also summarized 2 CR (15%) and 9 PR (69%) with the application of steroid therapy as a single treatment modality (5).

The Southeastern Cancer Study Group initiated one of the first prospective trials evaluating combination chemotherapy in 1983 (62, 63). This trial was designed to identify the activity of cisplatin, doxorubicin, and cyclophosphamide (PAC) in patients with unresectable or advanced thymoma. In patients with advanced disease, patients received up to six cycles of PAC chemotherapy. A 50% response rate (three complete and 12 partial responses) was noted in 30 assessable patients treated with PAC chemotherapy. The median survival time was 38 months and the 5-year survival rate was 32% (62). In patients with limited disease (defined as encompassable in a single radiotherapy portal), the trial design was to administer two to four cycles of PAC followed by radiotherapy. PAC produced a 70% response rate before radiation therapy in 23 assessable patients, with an approximate 50% 5-year survival rate (63). Forniasiero, *et al.*, who treated 37 patients with stage III and IV invasive thymomas using combination chemotherapy with doxorubicin, cisplatin, vincristine, and cyclophosphamide (ADOC) at monthly intervals. A median of five courses of the described ADOC regimen (3-7 courses) was administered. A 47% complete and 90% overall response rate was observed. The median survival time (MST) was only 15 months. The MST of 16 patients with complete remission was 27 months, and 18 patients with a partial response was 9.5 months (64).

Giaccone, *et al.* reported the results of a trial conducted by the European Organization for Research and Treatment of Cancer using cisplatin and etoposide. Among 16 patients with recurrent or metastatic thymoma, 33% complete and 60% overall response rate was observed, with a median progression-free survival time of 2.2 years and a median survival time of 4.3 years (65). An intergroup trial coordinated by the Eastern Cooperative Oncology Group evaluated ifosfamide, etoposide, and cisplatin in 28 patients with recurrent and metastatic thymoma, including 8 thymic carcinoma. Among 28 evaluable patients, there were no complete responses and 9 partial responses (32%). The median duration of response was 11.9 months, and median overall survival was 31.6 months. Among 20 patients with thymoma, 0% complete and 35% overall response rate was observed. The 1-year and 2-year survival estimates for thymoma patients were 95% and 79%, respectively (66).

We reviewed 9 papers in which patients with stage III or IV thymoma received multimodality treatment (preoperative chemotherapy, surgery, and postoperative chemotherapy or radiotherapy) (Table 6) (67-75). The results of induction chemotherapy in these studies demonstrated that thymomas are sensitive to chemotherapy. The regimen in most studies was cisplatin/doxorubicin-based combination chemotherapy (ADOC ; 3 studies, cisplatin + epirubicin + etoposide : 3 studies, PAC + steroid ; cisplatin + doxorubicin + cyclophosphamide + steroid : 2 studies, PAC : 1 study, cisplatin + etoposide : 1 study, and doxorubicin + cisplatin + steroid : 1 study), and the regimen cycles were 3-4 times. Considerable chemosensitivity was observed in these studies with an objective response of 67%-100%, a complete re-

Table 6. Multimodality Therapy for patients with advanced (stage III and IV) thymoma

Author	number of Pts#	stage	Regimens of preoperative chemotherapy	cycle	CR rate$	pCR&	response rate
Macchiarini *et al.* 67)	7*	III	cisplatin, epirubicin, etoposide	3	57%	29%	100%
Berruti A *et al.* 68)	6	III and IVA	ADOC	4	-	-	83%
Rea *et al.* 69)	16	III and IVA	ADOC	3 or 4	43%	31%	100%
Shin *et al.* 70)	13	III and IVA	cisplatin, doxorubicin, cyclophosphamide, prednisone		25%	17%	92%
Venuta *et al.* 71)	15*	III	cisplatin, epirubicin, etoposide (early 8 patients)		13%	7%	67%
			cisplatin, adriblastin, cyclophosphamide				
Bretti *et al.* 72)	25*	III and IVA	ADOC (18 cases)	4	8%	8%	72%
			cisplatin, etoposide (7 cases)				
Kim *et al.* 73)	22	III and IV	cisplatin, doxorubicin, cyclophosphamide, prednisone	3	14%	9%	77%
Lucchi *et al.* 74)	30	III and IVA	cisplatin, epidoxorubicin, etoposide	3	7%	-	73%
Yokoi *et al.* 75)	14	III and IVA	cisplatin, doxorubicin, methylpredonisolone	4	7%	-	93%

Pts = patients
$ CR rate =complete remission rate
& pCR = pathological complete remission
!DFS = disease-free survival
* including thymic carcinoma
ADOC ; doxorubicin, cisplatin, vincristine, cyclophosphamide

surgery	complete resection rate	radiotherapy	postoperative chemotherapy	cycle	DFS!	overall survival
+	57%	45Gy-com	-	-	-	-
		60Gy-incom				
+	83%	-	-		-	-
+	69%	11 cases-Rad+	ADOC (5 cases)	3	-	70 (3y)
+	92%	50 Gy-com	cisplatin, doxorubicin, cyclophosphamide, prednisone	-	73% (7 y)	100% (7y)
		60Gy-incom,<80%				
+	91% in only thymoma	40Gy-com	cisplatin, epirubicin, etoposide (8 patients)	2 or 3	-	-
		50-60Gy-incom	cisplatin, adriblastin, cyclophosphamide			
+	44%	45Gy-com	-	-	-	-
	III-57%, IVA-27%	55Gy-incom				
+	76%	50Gy-com,	cisplatin, doxorubicin, cyclophosphamide, prednisone	3	77% (5y)	95% (5y)
		60Gy-incom, <80%			77% (7y)	79% (7y)
+	77%	45Gy-com	cisplatin, epidoxorubicin, etoposide	-	-	82% (10y)
		60Gy-incom	8 cases			III-86%
		21 cases				IVA-76%
+	22%	50Gy	-	-	-	81% (5y, 10y)
9 cases		8 cases				III-100% (10y)
						IVA-89% (10y)

sponse of 7-57%, and a pathologic complete response of 7-31%, although the response rate was slight low in studies including thymic carcinoma (67%-72%).

In summary, thymomas are sensitive to chemotherapy, with an objective response seen in an average of two thirds of patients (67%-100%), and com-

plete response in one third (7%-57%). Cisplatin/doxorubicin-based combination chemotherapy seems to produce the best overall response rate and survival.

4) MULTIMODALITY THERAPY

Macchiarini, *et al.* were among the first to evaluate preoperative chemoradiotherapy in patients with stage III thymoma (67). Seven patients received three cycles of cisplatin, epirubicin, and etoposide before surgery. Four patients, including 2 pathological CR cases, experienced complete remission (objective response >70%) and the response rate was 100%. A similar disease trial was also developed in 8 studies (Table 6) (68-75), most of which were controlled prospective trials. The probability to achieve complete resection after induction chemotherapy was 69-92%, except in the worst 2 studies (22%-44%), although differences in the resectability rate may reflect the willingness of surgeons to undertake more extensive operations and the extent of invasiveness before chemotherapy. Postoperative radiotherapy was performed at doses of 40-50 Gy for patients with complete resection or 50-60 Gy for patients with incomplete resection. In 5 studies, postoperative chemotherapy was performed using the same regimen as for preoperative chemotherapy. The 7-year disease-free survival and overall survival was 73-77% and 79-100%, respectively.

In summary, these series suggest that resectability and survival may be improved with multimodality treatment (preoperative chemotherapy, surgery, and postoperative chemotherapy or/and radiotherapy) in patients with stage III and IV thymomas. There is a need for prospective, large intergroup-driven trials to help identify the optimal multimodality therapy for this disease.

CONCLUSION

Despite an indolent course and a cytologically bland appearance, all thymic tumors can manifest malignant behavior. The WHO classification is reasonably reproducible, and can be divided into different clinical characteristics of thymic epithelial tumor. It is necessary to perform a large intergroup-driven study because of the rarity of thymic epithelial tumor ; however, the value of histologic classification remains primarily in distinguishing thymic carcinoma, and type B3 from other types of thymoma. The Masaoka classification is the most widely accepted and is an excellent predictor of the prognosis of thymoma, although an update of this system is desirable. Optimal treatment for thymoma should be performed according to its clinical stage. Surgery continues to be the mainstay of treatment, and the ability to achieve complete resection appears to be the most important prognostic factor ; therefore, every effort must be made at the time of resection to achieve this. Thymomas also have a high response rate to chemotherapy or radiotherapy. Only surgical resection should be performed for patients with stage I (non-invasive) thymoma. The value of postoperative radiotherapy in completely resected stage II or III tumors is questionable, but there is a benefit of postoperative radiotherapy in patients who are incompletely resected. Multimodality therapy involving preoperative chemotherapy and postoperative radiotherapy or/and chemotherapy appears to increase the rate of complete resection and improve survival in advanced (stage III and IV) thymomas.

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