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Treatment of Thymoma: A Comparative Study Between Thailand and the United States and A Review of the Literature

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Abstract: This article provides a unique perspective on thymoma by describing the clinical scenarios from 2 diverse patient populations followed by an update. A comparative chart review was conducted on patients diagnosed at 2 university-based hospitals, 1 in the United States and 1 in Thailand. A comprehensive review of the literature was then performed through MEDLINE for articles between 1980 and 2002. During the last 23 years, charts from 16 patients at each institution were available for review. The most common presenting symptoms were myasthenia gravis (47%), dyspnea (25%), and chest discomfort (19%) and are similar to those reported in the literature. The primary treatment of stages I–III disease included surgery with or without radiation. Trimodality therapy with surgery, radiotherapy, and chemotherapy was pursued in 43% of patients with stage IV disease in the United States, whereas no patients from Thailand underwent this regimen. Median overall survivals were 124 and 76 months in the Thai and the US groups, respectively ($P = 0.76$). No major differences in the clinical features were observed between the 2 institutions, although a trend toward more advanced disease was seen in the United States. Surgery and radiation remain the backbone of treatment, but the role for chemotherapy is increasing.

Key Words: thymoma, treatment, surgery, radiotherapy, chemotherapy

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Thymoma is an infrequent tumor but represents the most common tumor of the mediastinum in adults. The age-standardized incidence rates of thymoma are 0.2 in males and 0.1 in females in Thailand, and 0.5 in males and 0.3 in females in the United States per 100,000 populations.[1] This article will provide a unique perspective and update on the status of thymoma. Clinical data on patients with thymoma from 2 university-based hospitals, 1 in the United States and 1 in Thailand, will compare the clinical features, treatment, and outcome of their respective patients. A comprehensive review of the literature and future directions for patients with thymoma is provided.

MATERIALS AND METHODS

Medical records of adult patients from Prince of Songkla University Hospital (PSUH) and University of Colorado Hospital (UCH) with pathologically proven thymoma during the years 1984 to 2000 and 1977 to 1999, respectively, were reviewed. The data from both hospitals were compared in terms of clinical characteristics, treatment, and outcome. The criteria derived by Masaoka's were used to categorize patients into stages. Stage I is a tumor that is macroscopically completely encapsulated and that microscopically has no capsular invasion. Stage II is a tumor that has either macroscopic invasion into surrounding fatty tissue or mediastinal pleura, or microscopic invasion into capsule. Stage III is defined as macroscopic invasion into neighboring organs such as the pericardium, great vessels, or lung. Stage IVa requires pleural or pericardium disseminated, whereas stage IVb has lymphatic involvement or hematogenous spread.[2] A Kaplan-Meier analysis using a log rank statistical model was applied to obtain survival outcome of patients from both institutions. AQ: 1

A literature review by MEDLINE search of published articles between the years 1980 and 2002 on thymoma treatment was conducted. The findings are summarized and compared with our patient population.

RESULTS

Nineteen patients from PSUH were diagnosed with thymoma. Three patients were excluded because of lack of pathologic documentation in 2 and misdiagnosis in 1. Eighteen patients were diagnosed at UCH, but 2 patients were excluded because of misdiagnoses of thymic carcinoma.

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Consequently, clinical data from 16 patients at each institution were available for review. Patient characteristics are shown in Table 1. Interestingly, differences in gender were apparent. At PSUH 69% of the patients were male, whereas at UCH 38% of cases were males. The mean ages were similar between the 2 groups (54 and 57 years, respectively). Approximately half of the patients at both institutions had myasthenia gravis: 44% in UCH, and 50% in PSUH. Common presenting symptoms among patients who did not have myasthenia gravis were dyspnea (25%) and chest discomfort/pain (19%). Most patients from PSUH had stage I disease (31%), whereas patients from UCH were stage II (50%). Patients with stage III or IVa were rare at both institutions. In patients with stage IVb disease, the sites of metastases were lung, pleura, liver, spleen, and lymph node. Four patients were unable to be staged because of missing data.

Table 2 shows treatment and outcome by stage of disease. The primary treatment modality for stages I, II, and III was surgery with or without radiation at PSUH. For the 5 patients with stage I, 1 patient received radiation therapy after surgery because of the progression of myasthenic symptoms. One patient was alive 14 years from presentation. Two patients have died, 1 from myasthenic-related respiratory failure at 14 months, and the other from sepsis at 124 months. Survival data on the remaining 2 patients were not available. Of the 4 patients with stage II, 2 patients were alive at 13 and 17 months, and 2 patients were dead. There were 2 patients with stage III at PSUH. One patient had an incomplete surgical resection and died 1 month later of respiratory failure. The other patient had surgery followed by radiation therapy. No follow-up information is available. Two patients with stage IV disease received chemotherapy, 1 plus surgery and the other plus radiation and were alive at 17 and 52 months, respectively. The other stage IV patient had an incomplete surgical resection followed by radiation but refused chemotherapy and died of unknown causes at 29 months. Two patients at PSUH could not have their stage verified. One patient received best supportive care because of advanced age and asymptomatic disease. This patient died of unknown causes at 26 months. No treatment or survival data were available for the second patient. The patients who had chemotherapy received cisplatin/adriamycin/cyclophosphamide (PAC). The patients given radiotherapy were treated with doses ranging from 28 to 50 Gy. No patient at PSUH with advanced thymoma (stage III and IV) underwent trimodality treatment.

At UCH, 9 patients with stages II-III disease were treated with surgery plus radiation. Six of the 8 patients with

TABLE 1. Clinical characteristics of patients with thymoma

	PSUH (N = 16)	UCH (N = 16)	Total (N = 32)
Sex			
Male	11 (69%)	6 (37.5%)	17 (53%)
Female	5 (31%)	10 (62.5%)	15 (47%)
Mean age	54 (25–74)	57 (28–73)	56 (25–74)
Presenting features			
Myasthenia gravis–related	8 (50%)	7 (44%)	15 (47%)
Dyspnea	4 (25%)	4 (25%)	8 (25%)
Chest discomfort/pain	4 (25%)	2 (13%)	6 (19%)
Weight loss, anorexia, fatigue	3 (19%)	2 (13%)	5 (16%)
Pericardial effusion	3 (19%)	2 (13%)	5 (16%)
Pleural effusion	2 (13%)	2 (13%)	4 (13%)
Chronic cough	2 (13%)	1 (6%)	3 (10%)
Asymptomatic	0	2 (13%)	2 (7%)
SVC syndrome	1 (6%)	0	1 (3%)
Hoarseness	0	1 (6%)	1 (3%)
Stage (Masaoka)			
I	5 (31%)	0	5 (16%)
II	4 (25%)	8 (50%)	12 (38%)
III	2 (12.5%)	1 (6%)	3 (9%)
IVa	0	1 (6%)	1 (3%)
IVb	3 (19%)	4 (25%)	7 (22%)
Unknown	2 (12.5%)	2 (13%)	4 (13%)

PSUH, Prince of Songkla University Hospital; SVC, ; UCH, University of Colorado Hospital.

TABLE 2. Treatment and outcome of thymoma patients

	PSUH	UCH	Total	Median survival
Stage I	5	0	5	Not reached
Complete surgery	4 (80%)	0	4 (80%)	
Complete surgery + RT	1 (20%)	0	1 (20%)	
Stage II	4	8	12	112 mo
Complete surgery	1 (25%)	0	1 (8%)	
Complete surgery + RT	3 (75%)	6 (75%)	9 (75%)	
Incomplete surgery + RT	0	2 (25%)	2 (17%)	
Stage III	2	1	3	114 mo
Incomplete surgery	1 (50%)	0	1 (33%)	
Incomplete surgery + RT	1 (50%)	1 (100%)	2 (67%)	
Stage IV	3	5	8	46 mo
Complete surgery + chemo	1 (33%)	0	1 (12.5%)	
Incomplete surgery + RT	1 (33%)	1 (20%)	2 (25%)	
Incomplete surgery + chemo	0	1 (20%)	1 (12.5%)	
Incomplete surgery + RT + chemo	0	2 (40%)	2 (25%)	
Radiation + chemotherapy	1 (33%)	0	1 (12.5%)	
Chemotherapy	0	1 (20%)	1 (12.5%)	
Unknown stage	2	2	4	26 mo
Complete surgery + RT + chemo	0	1 (50%)	1 (25%)	
Radiation + chemotherapy	0	1 (50%)	1 (25%)	
Best supportive care	1 (50%)	0	1 (25%)	
Unknown treatment	1 (50%)	0	1 (25%)	

chemo, chemotherapy; PSUH, Prince of Songkla University Hospital; RT, radiation therapy; UCH, University of Colorado Hospital.

stage II thymoma had complete resections. Four patients were alive at 146, 182, 185, and 235 months. The remaining 4 patients died of unrelated causes as well as the 1 stage III patient. Among the 7 patients with advanced diseases (including 2 patients with unknown stages, presumably advanced), 6 patients received chemotherapy, alone (1) or in combination with surgery and/or radiation (5). Three patients (43%) received trimodality therapy. Two patients were alive at 39 and 58 months. Five patients died: 3 from the disease, 1 from unrelated cause, and the other from unknown cause. Chemotherapy regimens used were PAC (2 patients), bleomycin, paclitaxel/carboplatin, and cisplatin/etoposide (PE) in 1 patient each. The most frequent dose of radiation administered was 50 Gy.

Median overall survival time of PSUH patients was 124 months, whereas that of UCH was 76 months ($P = 0.76$). Median survival times by disease stage were analyzed and are shown in Table 2. There was no statistical difference obtained between each tumor stage ($P = 0.66$).

DISCUSSION

Thymoma is not a common tumor, but is the most frequent primary tumor of the mediastinum in adults, accounting for two thirds of all tumors in this area. Reports from the literature state that the incidence is similar between male and female and occur in patients 40 to 50 years of age.[3] Interestingly, the ratio of male:female in patients from PSUH was close to 2:1, which was reversed in UCH patients with a ratio of 1:1.7. The mean ages were also slightly higher than reported at 54 and 57 years from both institutions. Thymoma is associated with paraneoplastic disorders, especially myasthenia gravis. Approximately 10 to 25% of myasthenic patients have thymoma and in those patients, thymoma was not a negative determinant for the long-term clinical outcome.[4] Myasthenia gravis was the primary presenting symptom in patients at both institutions and in the literature (21 to 47%). Almost half of all patients with thymoma are asymptomatic at the time of diagnosis, although only 7% were asymptomatic in our series. Patients complained of dyspnea, nonspecific chest pain, weight loss, anorexia, and fatigue, which were typically reported in other studies.

The most well-recognized clinical staging system to classify thymoma is Masaoka's.[2] The recently adopted histologic classification system of thymic tumors by the World Health Organization (WHO), the Muller-Hermelink, is based on the morphologic resemblance of the tumor epithelial cells

to subtype of normal epithelial cells in the thymus, distinguishing medullary, mixed medullary and cortical, predominantly cortical, and cortical thymomas, plus well-differentiated thymic carcinoma as subtypes with organotypic (thymus-like) features.[5] Reports from different institutions found the Muller-Hermelink and WHO classification systems reproducible and related to the tumor grades and prognosis.[6] The predominantly cortical and cortical tumors tend to have more aggressive behavior compared with the medullary subtype. In this study, most patients (54%) were stages I and II, which is similar to previous reports. However, some institutions observed higher incidence of advanced disease. Factors that influence good prognosis and long-term survival from large series include early stage, complete resection status, and the medullary variant in Muller-Hermelink classification.[7]

The median survival time of patients with thymoma varied from 15 months to 12 years in different series with various stages and heterogeneous patterns of treatment.[8,9] The overall 5-year survival rate ranged between 30 and 95%. By stage, the 5-year survival rates were 70 to 93%, 50 to 100%, 23 to 72%, and 23 to 50%, respectively, for stage I, II, III, and IV disease. Overall 10-year survival rates varied from 0 to 81%.[2,10–13] In this study, median overall survival was 124 months in PSUH and UCH patients had a median survival of 76 months. The poor survival in UCH patients can be attributed to more advanced stage of disease at diagnosis. Although most thymomas follow an indolent course, they have the potential for invasiveness and a predisposition for late locoregional recurrence. No data clearly address the issue of timing and duration of follow-up. Nevertheless, because of the possibility of late recurrence occurring up to 10 years or more, follow-up is recommended for a minimum of 10 years or even for a lifetime.[14]

SURGERY

Surgery is the treatment of choice for patients with stage I-III thymoma.[15] Reports of effectiveness of surgery, including incomplete resections, are promising and may have advantages over biopsy alone because of the localized and slow-growing nature of this tumor. A group from France conducted a study in 90 patients with stage III-IV thymomas and revealed the 5- and 10-year overall survival rates of 64 and 43% in 31 patients undergoing a partial resection versus 39 and 31%, respectively, in 55 patients having a biopsy, $P < 0.02$.[16] All patients received postoperative radiation and 59 patients (66%) received chemotherapy. These authors subsequently reported on a larger series of 149 patients with all stages of tumors. With a median follow-up time of 7.7 years, the extent of surgery had a substantial impact on local control, with 78.5% of patients without evidence of progressive disease and 5-year survival rates of 74%, 60%, and 38% in patients who underwent complete resection, partial resection, and biopsy alone, respectively.[17] Other authors reported on the role of radical resection of the tumor and the adjacent tissue, giving an overall 5-year survival rate of 46 to 69% in all tumor stages.[18,19] Reconstructive surgical techniques to treat tumors invading vascular structures positively influenced outcome.[20]

For recurrent thymoma, secondary surgery may be performed with the aim of curative intent.[21] An aggressive surgical approach with resection of new tumor masses and pleural metastases revealed a high successive rate, either in combination with radiotherapy/chemotherapy or alone. Regnard et al reported on 28 patients with recurrent thymoma who underwent reresection. Nineteen patients had a complete resection, whereas 9 patients had an incomplete resection. Five- and 10-year survival rates were 51% and 43%. There was a trend toward improved survival with complete resection but it was not statistically significant. Three of the 19 patients (16%) who underwent complete resection had a subsequent recurrence. One patient underwent a repeat operation and remains disease free. Seven of the 9 patients with incomplete resections died of disease.[22] Other series supporting the role of reoperation for recurrent thymoma were mentioned in the literature.[14,23] AQ: 2

Video-assisting thoracoscopic surgery (VATS) or VATS-assisted techniques have been reported to be an option for managing small thymoma. Yim et al reported their experience on the management of anterior mediastinal masses using VATS, either for diagnosis or treatment. Eleven biopsies and 13 resections were successfully performed.[24] Longer follow-up and more experience with the VATS technique is needed but appears promising.

RADIATION

Thymoma is characterized as a radiosensitive tumor. Radiotherapy alone has provided significant survival in some series. Survival of 58% (7/12 patients) and estimated 5-year survival of 87% were obtained in unresectable diseases and in a small group of stage IVA patients, respectively, receiving only primary radiation according to a review.[25] Moreover, postoperatively adjuvant radiotherapy improved local control and survival, however this benefit was not apparent in patients with stage I.[26] Zhang et al conducted a prospective randomized trial to determine the effect of postoperative radiation given to stage I thymoma. Twenty-nine patients were randomly assigned to a treatment of surgery alone ($n = 13$) or surgery followed by radiotherapy ($n = 16$). The dose of radiation given was 50 to 60 Gy. Results showed the 10-year survival of 92% in the group treated by surgery alone compared with that of 88% in the group received postoperative radiation.[27] Wilkins et al reported on 136 patients with thymoma with all stages treated at a single institution, and a better survival rate was seen in patients with Masaoka stage I with no radiation compared with those received adjuvant radiation; however, no statistical significance was reached.[9]

Adjuvant radiotherapy after surgery has been recommended for tumors beyond stage I. Currently, most authors recommend postoperative radiation for all patients undergoing resection if the tumor capsules were invaded or penetrated, or in tumors with invasion of surrounding tissues, despite a radical resection. In a recent multi-institutional review addressing the effectiveness of postoperative mediastinal radiotherapy in preventing local recurrence of thymoma, 103 patients with stages I-III whose tumors were completely resected were reported.[28] Postoperatively, 52 patients received involved field (IF) irradiation covering the primary tumor bed with 1- to 2-cm margins, while 51 were irradiated to the whole mediastinal field (WM) including the primary tumor bed, with the upper margin at the thoracic inlet and the lower margin at the diaphragmatic crura, with or without boost. The median dose was 40 Gy. No recurrence was found in patients with stage I, whereas those of stage II and III were 10% and 44%, respectively. The most frequent site of first recurrence was pleura. Mediastinal recurrences were observed in 11% of patients who were treated with IF irradiation, but none of the WM irradiation group had recurrence. The authors emphasized the effectiveness of WM irradiation and suggested an additional treatment such as prophylactic pleural and pulmonary irradiation or chemotherapy for preventing pleural-based recurrence in patients with pathologic pleural invasion.

The impact of locoregional control from radiation therapy in advanced stage thymoma was addressed by Mornex et al. Ninety patients with stage III-IVA underwent surgery and radiation, with or without chemotherapy. The median radiation dose was 50 Gy. The rate of local recurrence of 14% after complete surgery compared with that of 34% in incompletely resected patients suggested that a higher dose of radiation beyond 50 Gy should be given to incompletely resected patients.[16] The doses of radiotherapy used have been variably reported in the literature. A recent review recommended a total dose in excess of 50.4 Gy for totally or partially resected stage III tumors.[26] Computed tomography scan–based treatment planning providing 3-dimensional radiotherapeutic images allows conformal therapy to be performed more efficiently. The role of low-dose entire hemithorax irradiation (EH) in addition to mediastinal irradiation (MRT) after surgery for stage II-III invasive thymoma has also been addressed. Uematsu et al used a radiotherapy dose of 15 Gy to the entire hemithorax additionally to a median of 40 Gy to the mediastinum in 23 patients, postoperatively.[29] Outcome of the EH-MRT was compared with that obtained from 20 patients who received only MRT. The 5-year relapse-free rate was 100% for those receiving EH-MRT and 66% for those with MRT ($P = 0.03$). The major complication was radiation pneumonitis requiring treatment that occurred in 3 patients receiving EH-MRT and 1 with MRT.

The use of preoperative radiation is unclear. Neoadjuvant radiation has had some success in unresectable or locally advanced disease to shrink tumors down and render them resectable in small series. A report from Japan giving a mean dose of 18.3 Gy radiotherapy to 12 patients with advanced thymomas with invasion to the great vessels followed by surgical resection made 9 patients (75%) able to undergo complete resections.[30] Ten patients also received postoperative radiotherapy with a mean dose of 42.3 Gy. Bretti et al recently reported on 33 inoperable stages III-IVa patients undergoing neoadjuvant radiotherapy (8 patients) or neoadjuvant cisplatin-based chemotherapy (25 patients). Complete surgical resection was performed in only 1 patient (13%) submitted to radiotherapy compared with 11 patients (44%) from the chemotherapy group.[31]

The role of radiotherapy for recurrent disease was reported by Urgesi et al.[32] Radiotherapy with radical intent (range, 38 to 44 Gy) was given to 21 patients with recurrent mediastinal lesions and/or pleural nodules. Surgery was attempted when considered feasible and was performed in 11 patients (6 partially and 5 totally) before irradiation. The other 10 patients received only radiotherapy. No significant difference in survivals was observed between the 2 groups. The 7-year survival of the group receiving upfront surgery was 74% versus 65% of the group receiving radiotherapy alone.

CHEMOTHERAPY

Thymomas are considered to be chemosensitive despite their indolent nature; therefore, systemic chemotherapy has been used primarily to treat patients with locally advanced or metastatic disease. Chemotherapeutic regimens administered in clinical trials are summarized in Table 3. Among numerous T3
single agents evaluated, cisplatin is the most extensively studied one. Its promising antitumor activity that was consistently demonstrated in several case reports led the Eastern Cooperative Oncology Group (ECOG) to conduct a phase II trial (Table 3). Twenty evaluable patients with advanced thymoma received cisplatin 50 mg/m^2 every 3 weeks. Two patients (10%) achieved a partial remission (PR). The median survival was 19 months and the 2-year survival was 39%. There were no treatment-related deaths and no life-threatening toxicity.[33] Eight smaller series from a review using single-agent cisplatin demonstrated an overall response rate of 8 to 100% with the median response duration of 4 to 24 months.[3] More recently ifosfamide 1.5 g/m^2 on days 1 to 5 was given to 13 evaluable patients with advanced thymoma (Table 3). Five patients achieved a complete response (CR) and 1 patient had a PR for an objective response rate of 46%. The most frequent but well-controlled toxicities were nausea, vomiting, and leukopenia.[34] Steroids have also shown to be effective. In a review of 30 patients, the overall response rate was 60%, primarily with prednisone at 10 to 100 mg per day.[35]

TABLE 3. Chemotherapy trials of advanced thymomas

Regimen	# Pts	Overall response rate	Complete response rate	Partial response rate	Median response duration (mo)	Median survival (mo)
Cisplatin (33)	20	10%	0%	10%	NR	19
Ifosfamide (34)	13	46%	38%	8%	66+ **a**	2-y OS = 39% 51+
ADOC (8)	37	92%	43%	49%	12	5-y OS = 57% 15
PAC (41)	29	51%	10%	41%	12	38
PACE (43)	14 **b**	43%	0	43%	NR	5-y OS = 32% 14.7
VLCPP (44)	9	22%	11%	11%	NR	NR
PE (45)	16	56%	31%	25%	3.4 years	4.3 y
VIP (46)	28 **b**	32%	0%	32%	12	5-y OS = 50% 32

ADOC, adriamycin, cisplatin, vincristine, cyclophosphamide; NR, not reported; OS, overall survival; PAC, cisplatin, adriamycin, cyclophosphamide; PACE, cisplatin, doxorubicin, cyclophosphamide, etoposide + G-CSF; PE, cisplatin, etoposide; VIP, etoposide, ifosfamide, cisplatin; VLCPP, vincristine, lomustine, cyclophosphamide, cisplatin, prednisone.

a in complete responders; **b** thymic carcinoma included.

The limited efficacy of single agents led investigators to evaluate combination chemotherapy regimens in the advanced setting. Cyclophosphamide 800 mg/m^2, adriamycin 50 mg/m^2, and vincristine 1.4 mg/m^2 (CAV), given every 3 weeks was used in a limited number of 11 patients with malignant thymoma in 3 reports.[36–38] They demonstrated impressive responses, with a 40 to 100% CR rate. However, the duration of response was short at 7.5 to 9 months. Overall, CAV produced high responses but in shorter durations as compared with other regimens producing response duration more than 12 months.

A retrospective review on other combination regimens for thymoma described complete remissions in 5 of 13 patients receiving CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP/bleomycin and in 3 of 6 patients receiving COP (cyclophosphamide, vincristine, and prednisone) or COP plus procarbazine (COPP).[39] Another series reported an overall response rate, all for partial, of 80% in 5 patients receiving COPP.[40]

In a formal study, Fornasiero et al administered ADOC: adriamycin 40 mg/m^2 and cisplatin 50 mg/m^2 on day 1, vincristine 0.6 mg/m^2 on day 3, and cyclophosphamide 700 mg/m^2 on day 4, every 3 weeks to 37 assessable patients with stage III and IV thymoma (Table 3).[8] The overall response rate was 92% (34 patients) with a 43% (16 patients) CR rate. The median duration of response was 12 months and the median survival was 15 months. Ten of the 16 patients who achieved a radiographic CR underwent surgery. Seven patients (19%) had a pathologic remission. A United States Intergroup study evaluated PAC: cisplatin 50 mg/m^2, doxorubicin 50 mg /m^2, and cyclophosphamide 500 mg/m^2 on day 1 every 3 weeks (Table 3). Twenty-nine untreated patients with advanced disease were evaluable for response. Three CRs and 12 PRs were documented for an overall response rate of 51%. The median survival was 38 months and the 5-year survival rate was 32%.[41] A single institution reported an overall response rate of 64% (35% CR and 29% PR) among 17 patients receiving PAC with or without prednisone.[42]

A Japanese group reported on an intensive combined chemotherapy regimen, PACE, which consisted of cisplatin (80 mg/m^2), doxorubicin (45 mg/m^2), cyclophosphamide (800 mg/m^2) on day1, and etoposide (80 mg/m^2) on days 1 to 3 (Table 3). Granulocyte colony-stimulating factor (90 ig/m^2) was also administered on days 5 to 18 to every patient. There were 14 patients with invasive, metastatic, or recurrent thymoma or thymic carcinoma enrolled. A partial response rate of 43% in 3 thymomas and thymic carcinomas each was reported, but no CRs were observed. The major side effect was myelosuppression and infection in 6 patients (43%) despite growth factor support.[43] A group from Denmark conducted a study using a 5-drug regimen (VLCPP), consisting of vincristine 1.3 mg/m^2, lomustine 70 mg/m^2, cyclophosphamide 1 g/m^2 on day 1, cisplatin 75 mg/m^2 on day 2, and prednisone 40 mg/m^2 on days 1 to 7 (Table 3). All 9 patients participating were stages III and IV and chemotherapy-naïve. Unfortunately, the results obtained were not promising, with an overall response rate of 22% in 2 patients, 1 partial and 1 complete.[44]

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Meanwhile, the European Organization for Research and Treatment of Cancer (EORTC) evaluated the commonly used lung cancer regimen of cisplatin plus etoposide (PE) (Table 3). Sixteen patients were treated with cisplatin 60 mg/m^2 on day 1 plus etoposide 120 mg/m^2 on days 1 to 3. Five patients achieved a CR and 4 patients had a PR, for an objective response rate of 56%. The median duration of response was 3.4 years and the median survival was 4.3 years.[45] Encouraged by these results, the Intergroup conducted a trial adding ifosfamide to PE (VIP) (Table 3).[46] Twenty-eight evaluable patients, including 8 with thymic carcinoma, were given ifosfamide 1.2 g/m^2, cisplatin 20 mg/m^2, and etoposide 75 mg/m^2, days 1 to 4 every 3 weeks. No patient achieved a CR and 9 patients had a PR (32%). The median survival was 32 months. The authors concluded that this regimen was inferior to other regimens. At the present, ECOG has a phase II study of carboplatin and paclitaxel for patients with invasive, recurrent, or metastatic thymoma not amenable to primary surgery or radiotherapy. Patient accrual is still going on.[47] Currently, ADOC, PAC, and PE remain the standard treatment regimens.

Data on salvage chemotherapy for relapsed patients is limited. Fornasiero and colleagues reported moderate success with the use of mitoxantrone in 2 patients, and VIP in 3 patients who failed ADOC chemotherapy. Two patients who received VIP demonstrated stable disease, whereas mitoxantrone provided PRs to both patients. The time to disease progression ranged from 2 to 6 months.[8] However, in 2 patients who had recurrence of disease 12 months after their first chemotherapy, both achieved a benefit when retreated with the same initial PAC regimen.[48] Dramatic responses of recurrent or metastatic thymoma to steroid therapy in 10 patients after failure with conventional treatment have also been reported. Thus, a trial of steroid in relapsed thymoma is reasonable.[49,50]

NEOADJUVANT CHEMOTHERAPY

The encouraging response with combination chemotherapy in advanced disease has led to the evaluation of chemotherapy in earlier settings with the hope of impacting local control and eradicating micrometastases. A summary of neoadjuvant chemotherapy from larger series is shown in Table 4. The benefit of chemotherapy followed by definitive radiotherapy was evaluated by Lochrer et al in patients with limited-stage unresectable thymoma, defined as all disease encompassed within a single radiotherapy portal.[51] Twenty-three assessable patients received PAC chemotherapy for 2 to 4 cycles. Twenty-two nonprogressing patients got 54 Gy of radiation to their primary tumor and regional lymph nodes. The overall response rate to chemotherapy was 70% (48% PR and 22% CR). The median time to treatment failure and the median survival time were 93 months with a 5-year survival

TABLE 4. Summary of neoadjuvant chemotherapy in thymoma

Chemotherapy → radiation

Authors (ref.)	# Pts	Chemotherapy	ORR (CR)	Surgery	Radiation	Median survival (mo)
Lochrer[51]	23	PAC	70% (22%)	—	54 Gy	93 5-y OS = 53%

Chemotherapy → surgery → radiation

Authors	# Pts	Chemotherapy	ORR (CR)	Surgery	Radiation	Median survival (mo)
Macchiarini[52]	7	CEE	100% (0)	4 complete 3 partial	45–60 Gy	8 − 24+, NED 2-y OS = 80%
Rea[53]	16	ADOC	100% (43%)	11 complete 5 partial	NR	66 3-y OS = 70%
Venuta[54]	21	CEE	NR	16 complete 5 partial	30–50 Gy	8-y OS = 76%
Berruti[55]	16 a	ADOC	81% (8%)	NR	45 Gy	48
Kim[11]	22 b	PAC + P	77% (13%)	NR	50–60 Gy	5-y OS = 95% 7-y OS = 79%

ADOC, adriamycin, cisplatin, vincristine, cyclophosphamide; CEE, cisplatin, epirubicin, etoposide; CR, complete response; NED, no evidence of disease; NR, not reported; ORR, overall response rate; OS, overall survival; PAC, cisplatin, adriamycin, cyclophosphamide; PAC + P, PAC + prednisone.

a3 recurrent patients; b 1 recurrent patient.

rate of 53%. It is difficult to determine survival with radiotherapy alone, but in 1 review by Koh et al, the 5-year survival was 45% in 109 incompletely resected patients receiving radiation.[51] Thus, the authors showed that sequential treatment was safe and tolerable and may improve survival over radiotherapy alone in patients with unresectable thymoma.

Neoadjuvant chemotherapy in trimultimodality treatment has been studied by several groups. A prospective, single treatment arm study from Macchiarini et al was conducted in 7 patients with untreated clinical stage IIIa thymoma. All patients received neoadjuvant chemotherapy with cisplatin 75 mg/m^2, epirubicin 100 mg/m^2 on day 1, and etoposide 120 mg/m^2 (CEE) on days 1, 3, and 5, repeated every 3 weeks for 3 cycles. Patients who achieved an objective response underwent surgery followed by postoperative radiation at doses of 45 Gy (complete resection) or 60 Gy (incomplete resection). All patients showed a partial response to chemotherapy. Four patients had a complete surgical resection, with 1 patient having a pathologic CR while 3 patients had incomplete resection. Their survivals range from 8 to 24+ months with a projected 2-year survival of 80%. No recurrences have been reported.[52] Rea et al conducted a multimodality trial in 16 patients with stage III and IVa, unresectable thymoma.[53] All patients received neoadjuvant ADOC. Courses were repeated every 3 weeks for a minimum of 3 cycles. Complete responses were achieved in 43% (7 of 16 patients) and 57% (9 of 16 patient) had a PR, for an overall response rate of 100%. All patients underwent surgery, 11 patients had radical resections, and 5 patients had partial resection. Eleven patients with pathologic evidence of tumor received postoperative radiotherapy, and 5 patients with pathologic CRs received 3 additional cycles of ADOC. The median overall survival was 66 months, with a 3-year survival of 70%.

Venuta and colleagues evaluated a multimodality approach in 21 initially unresectable patients with stage III or IVA. All patients received neoadjuvant CEE chemotherapy followed by surgical resection plus postoperative chemotherapy and radiotherapy. The response rate to chemotherapy was not reported, but all patients had some degree of tumor shrinkage. Sixteen patients were able to undergo complete operations after chemotherapy. The 8-year survival rate was 76%, which was markedly improved as compared with 43% for historical controls ($P = 0.049$).[54] Another Italian group conducted a prospective study using primary chemotherapy of ADOC regimen, followed by surgery and radiotherapy of 45 Gy in 16 patients with stages III-IVa. Objective responses were achieved in 13 patients (81%), 1 with complete and 12 with partial. Nine partial responders underwent surgical resections, and 8 had evidence of residual tumors. Thirteen patients received radiotherapy, including the 8 patients with residual disease after resection and 5 inoperable patients who achieved a PR or stable disease to chemotherapy. Median disease-free interval and overall survival were 33 and 48 months, respectively.[55] Investigators from M.D. Anderson Cancer Center reported a phase II study of a multidisciplinary treatment with induction chemotherapy, followed by surgery, radiotherapy, and consolidation chemotherapy for patients with stage III-IV thymoma.[11] PAC + P (plus prednisone) was used for both induction and consolidation. After surgical resection, patients with no residual tumor received 50 Gy of radiation and 60 Gy was administered to patients with residual tumors or an incomplete resection. After induction chemotherapy, 77% of patients (17 of 22) had major responses (64% PR, 13% CR). The overall survival rates were 95% at 5 years and 79% at 7 years.

POSTOPERATIVE CHEMOTHERAPY

The use of adjuvant chemotherapy is a popular concept that is very attractive in this disease, where surgical resection is the cornerstone of treatment. It is difficult to gather and extract data on chemotherapy effects in advanced thymomas when given postoperatively because of the limitation of clinical trials and the overlapping results from other treatment modalities provided from most reports. A summary of larger series using chemotherapy in the adjuvant setting is shown in Table 5. Chahinian et al reported on 11 cases of invasive or metastatic thymoma undergoing surgery with an attempt at complete resection as the first step, followed by radiotherapy in 10 and systemic chemotherapy in 8. Five patients received a combination of bleomycin 12 mg/m^2, adriamycin 50 mg/m^2, cisplatin 50 mg/m^2 on day 1, and prednisone 40 mg/m^2 on days 1 to 5 (BAPP) every 4 weeks and 2 patients (40%) achieved a partial remission. Five-year survival rate was 45% (5 of 11 patients).[56] An updated report including 4 additional patients with thymoma given BAPP chemotherapy revealed an overall response rate of 67%, and survivals of responders ranged from 6 to 37+ months. However, the details about whether these additional patients also received radiotherapy postoperatively were not provided.[57] T5

A group from Denmark reported a series of 9 patients with invasive thymoma receiving a 4-drug regimen (VLCP) consisting of vincristine 1.3 mg/m^2, lomustine 70 mg/m^2, cyclophosphamide 1 g/m^2 on day 1, and prednisone 40 mg/m^2 on days 1 to 7.[58] Seven patients underwent prior treatment with surgery and/or radiation. An overall response rate was achieved in 5 patients (56%), 4 CR and 1 PR. Mornex et al reported a multicenter retrospective review of 90 patients with stage III–IVa thymomas treated with combined therapy. Four patients had complete resections, 31 patients underwent partial resection, and 55 patients had a biopsy only. All patients received radiation with a median dose of 50 Gy. Fifty-nine patients (66%) subsequently received combination platinum-based chemotherapy. The 5- and 10-year overall survival rates for all patients were 51%

TABLE 5. Summary of postoperative chemotherapy in thymoma

Authors	# Pts	Chemotherapy # Pts; regimen	ORR (CR)	Radiation # Pts; dose	Median survival (mo)
Surgery → radiation → chemotherapy					
Chahinian[56]	11	8; BAPP in 5 patients	40% (0) a	10; 36–60 Gy	NR 5-y OS = 45%
Daugaard[58]	9 b	VLCP	56% (45%)	5; 38–60 Gy	NR
Mornex[16]	90 c	59; platinum-based	NR	30–70 Gy	5-y OS = 51% 10-y OS = 39%
Surgery → chemotherapy → radiation					
Goldel[39]	10 d	CHOP-based	60% (40%)	4; 30–50 Gy	3-y OS = 34% 8-y OS = 100%
Venuta[54]	26 e	CEE	NR	30 Gy	f
Milstein[3]	15 g	PAC	62% (62%)	46 Gy	17+
Surgery → chemotherapy and/or radiation					
Froudarakis[59]	23 h	16; cisplatin-based	65% (48%)	13; 40–65 Gy	20 5-y OS = 44%

BAPP, bleomycin, adriamycin, cisplatin, and prednisone; CR, complete response; CEE, cisplatin, epirubicin, etoposide; CHOP-based, BAPP, CHOP; cyclophosphamide, doxorubicin, vincristine, prednisolone, CHOP/bleomycin; COP, cyclophosphamide, vincristine, prednisolone; COPP, COP+ procarbazine; NR, not reported; ORR, overall response rate; OS, overall survival; PAC, cisplatin, adriamycin, cyclophosphamide; VLCP, vincristine, lomustine, cyclophosphamide, prednisone.

a in patients who received BAPP chemotherapy; **b** 5 patients had biopsies only; **c** 55 patients had biopsies only. Chemotherapy was delivered after surgery, either before or after radiation; **d** 5 patients had biopsies only; **e** group II = 22 patients, resectable group III = 4 patients; **f** in group II patients; **g** including 7 thymic carcinoma patients; **h** 12 patients had biopsies only.

and 39%, respectively.[16] Goldel et al reported on 10 patients who received chemotherapy as primary treatment of incompletely resected thymoma. Four patients (40%) achieved a CR. One patient with a PR and 3 patients with a CR received adjuvant radiotherapy (30 to 50 Gy). The 3-year survival rate for all 10 patients was 34%.[39] Venuta et al gave CEE chemotherapy to 26 completely resected patients with thymoma. Twenty-two patients were in group II, identified as stages I and II invasive cortical or stage II mixed thymomas, and 4 patients were in resectable group III, identified as resectable stage III disease. Radiotherapy was also administered to all patients postoperatively. It is unclear whether radiotherapy was given concurrently or sequentially to chemotherapy. The overall responses in these patient subgroups were not reported, but the 8-year overall survival was 100% in group II patients, which was better than that of 81% from historical control.[54]

Another study was conducted by Milstein et al.[3] Eight patients with thymoma and 7 of thymic carcinoma were treated with postoperative PAC chemotherapy, and all patients received postchemotherapy radiation. Eight of 13 patients (62%) who underwent partial surgery before chemotherapy achieved a CR (83% in thymoma and 43% in thymic carcinoma), and the median survival in the thymoma group was beyond 17 months. The French retrospectively studied 23 patients with invasive thymoma and 87% had stage III and IV. Forty-eight percent (11 patients) underwent tumor resection followed by cisplatin-based chemotherapy and/or radiation, whereas the remaining 12 patients had palliative treatment including radiation and/or chemotherapy. Of the 11 patients whose tumors were resected, 5 patients received chemotherapy plus radiation whereas 4 patients had radiation only, and 2 patients had chemotherapy only. After initial treatment, 15 patients (65%) responded with 48% CRs and 17% PRs. It is hard to identify the effects of chemotherapy and radiotherapy separately in those who received both treatments. The median overall survival was 20 months, and the 5-year survival rate was 44%. A statistically significant survival benefit ($P < 0.0001$) was observed in the patients who had surgery.[59]

Overall, the role for chemotherapy in the multimodality approach to the treatment of locally advanced thymoma is ill defined because of the lack of prospective studies. One schema with neoadjuvant chemotherapy, followed by surgery and postoperative radiation, has been used by several investigators and has shown an impressive outcome. However, long-term follow-up is required to detect the possibilities of late recurrence.

FUTURE DIRECTIONS

The data above suggest that systemic therapy plays a valuable role in the treatment of thymoma. Currently, a

variety of cytotoxic and cytostatic agents are being investigated. Some trials with somatostatin analogs have been conducted. Palmieri et al reported on 17 patients with extensively advanced thymoma refractory to prior multimodality treatment.[60] All patients had positive octreotide scans and were subsequently treated with octreotide 1.5 mg/d subcutaneously, or a long-acting somatostatin analog, lanreotide 30 mg every 2 weeks intramuscularly until progression. Among 13 patients evaluable, 7 (53%) had an objective response rate (2 CR, 5 PR, and 6 stable diseases). Overall the treatment was well tolerated with mild toxicity. Based on laboratory data showing some effects of interleukin-2 (IL-2) on T-cell precursors differentiation and antitumor activity, Gordon et al conducted a phase II trial giving IL-2 to 14 patients with thymoma who failed standard treatment.[61] IL-2 was administered subcutaneously at 12 mIU/m^2/d for 5 days for 4 weeks, followed by a 2-week rest period. Each cycle was repeated for a maximum of 4 cycles. No objective responses were observed, and 36% of patients required a dose reduction for grade 3 toxicity.

A unique strategy combined cytoreductive surgery with hyperthermic intrathoracic chemotherapy for pleural metastases.[62] Three patients who had failed systemic chemotherapy underwent this therapy. After cytoreductive surgery, doxorubicin (25 mg/m^2) and cisplatin (80 mg/m^2) at 40 to 42°C were perfused into the pleural cavity during 90 minutes. No systemic toxicities were observed. With a median follow-up time of 8.6 months, all 3 patients were alive without evidence of disease. High-dose chemotherapy with peripheral blood stem cell transplantation in advanced stage thymoma has been attempted. A phase II trial of high-dose carboplatin and etoposide with tandem stem cells transplantation was performed in 5 patients with recurrent metastatic disease.[63] Progression-free survival after the transplantation ranged from 3.5 to 16.5 months. The authors concluded that this procedure was feasible with acceptable toxicity, but did not appear to be superior to standard-dose salvage therapy. Molecular-targeted therapy is a cutting edge treatment modality and has been investigated in several types of cancers. A recent report investigating the epidermal growth factor receptor (EGFR) expression in invasive thymoma found 84% of tumors positive for EGFR using immunohistochemistry. The additional studies addressing the benefits of anti-EGFR in the treatment have been investigated.[64]

CONCLUSIONS

We reviewed medical records of patients with thymoma from 2 university-based hospitals in Thailand and the United States. The data showed lower ratio of Thai patients who had advanced diseases undergoing multimodality treatment, especially for chemotherapy. Because of the favorable outcome of patients with thymoma receiving multidisciplinary approach for their advanced-stage tumors, this strategy should be considered and offered to patients to achieve the best response and outcome.

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