Concurrent Chemoradiotherapy for Unresectable Thymic Carcinoma

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Background: Thymic carcinoma is a rare anterior mediastinal neoplasm. It is more invasive and has a poorer prognosis than ordinary thymoma. Complete curative resection is frequently impossible to achieve because of extensive invasion or metastasis at diagnosis. The role of systemic chemotherapy and the optimal regimen in thymic carcinoma remain uncertain. We report our experience with 16 patients with unresectable thymic carcinoma who underwent concurrent chemoradiotherapy.

Methods: Between July 1989 and July 2003, 29 patients were diagnosed with unresectable thymic carcinoma at our hospital. Sixteen of the 29 patients were treated with concurrent chemoradiotherapy. There were 10 men and 6 women whose ages ranged from 45 to 66 years old. Chemotherapy regimens consisted of either (A) cisplatin plus 5-fluorouracil or (B) doxorubicin, cisplatin, vincristine and cyclophosphamide every 4 weeks for at least 2 cycles. Radiotherapy was given concurrently and ranged from 34.2 to 70 Gy.

Results: There were 4 (25.0%) patients with complete responses, 4 (25.0%) with partial responses, 6 (37.5%) with stable disease and 2 (12.5%) with progressive disease. The overall response rate was 50%. The median follow-up was 64 months, and the median survival was 82 months. The overall cumulative survival rates at 1, 2, 3, and 5 years were 93.8%, 81.3%, 74.5%, and 67.7%, respectively. The most common side effects were Grade I/II toxicity, including vomiting, fatigue, and esophagitis. All patients experienced radiation pneumonitis. No life-threatening side effects were noted.

Conclusions: Concurrent chemoradiotherapy seems effective for unresectable thymic carcinoma. Our experience, although preliminary, is encouraging and merits conducting a randomized trial to determine the impact of concurrent chemoradiotherapy on unresectable thymic carcinoma.

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Key words: thymuic, carcinoma, chemotherapy, radiotherapy, concurrent chemoradiotherapy.

Before the early 1970s, all neoplasms in the thymus were considered thymomas. In 1982, Snover, Levine and Rosai first postulated the presence of primary thymic carcinomas.[1] Thymic carcinomas are very rare in western countries, and constitute only 0.06% of thymic neoplasms.[2] Approximately, 150 cases have been reported in the literature.[3-8] Only 20 cases were diagnosed at Mayo

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Clinic within 75 years.[3] There is slight male preponderance. The peak incidence is around the fifth to sixth decade.[9]

Thymic carcinomas are believed by many to represent one end of the pathologic spectrum of thymomas in which the epithelial component proliferates without the typical lymphocytic admixture.[5] Unlike thymomas, thymic carcinomas have a more aggressive histologic appearance and clinical course. The clinical manifestations usually reflect tumor invasion, local compression of neighboring organs, and distant metastasis. The paraneoplastic syndromes, such as myasthenia gravis, red cell aplasia, autoimmune diseases, and opportunistic infections, are uncommon in thymic carcinomas. Myasthenia gravis is seen only in the well-differentiated form.[10]

Surgery is the major treatment modality for localized disease and provides the best outcome. Unfortunately, thymic carcinomas are mostly invasive or metastatic at diagnosis and complete curative resection is not possible to achieve. The prognosis of unresectable disease is dismal. Because of the rarity of theses tumors, there is scanty information about the role of chemotherapy in the treatment of advanced thymic carcinoma.[6,11] The dismal prognosis of unresectable thymic carcinoma has determined the necessity to seek new treatment modalities. To the best of our knowledge, few reports have addressed the efficacy of concurrent chemoradiotherapy (CCRT) for unresectable thymic carcinomas. We report here sixteen patients with unresectable thymic carcinoma who were treated with CCRT and followed long-term, and discuss the prognostic factors and the overall management of advanced thymic carcinoma.

METHODS

Between July 1989 and July 2003, 29 patients were diagnosed with unresectable thymic carcinoma at Chang Gung Memorial Hospital, Kaohsiung, Taiwan. The criteria for diagnosis of thymic carcinomas were those stated by Rosai and the WHO as follows:[12] a thymic tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features not specific to the thymus, with absence of a primary tumor at sites other than the anterior mediastinum, either at the time of presentation or at follow-up. Pathology based on Rosai's and Müller-Hermelink's classification revealed 2 patients with small cell carcinoma, 2 with carcinoid, 2 with poorly differentiated carcinoma, 3 with undifferentiated carcinoma, 1 with small-squamous cell carcinoma and 19 with squamous cell carcinoma. Classification of these patients' stages was based on the modified Masaoka staging system (Table 1).[13] The collection of data and follow-up were performed by reviewing medical charts and telephoning or visiting patients.

Table 1. Modified Masaoka Staging System for Thymoma and Thymic Carcinoma

Stage	Definition
I	Macroscopically completely encapsulated and microscopically no capsular invasion
II	
a	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
b	Microscopic invasion into capsule
III	Macroscopic invasion into neighboring organ (i.e., pericardium, great vessels, or lung)
IV	
a	Pleural or pericardial dissemination
b	Lymphatic or hematogenous spreading

We excluded 2 patients with small cell carcinoma, 2 patients with carcinoid, 3 patients who were lost to follow-up (one with poorly differentiated carcinoma, two with squamous cell carcinoma) and 6 patients who received radiotherapy alone. The remaining 16 patients were treated with CCRT. There were 10 men and 6 women whose ages ranged from 45 to 66 years old (median: 53 years old). Fourteen (88%) of the 16 patients presented with symptoms directly attributable to the primary tumors, i.e. chest pain, dyspnea, and cough. The other two patients (patients 5 and 10) had no symptoms and were found to have mediastinal tumors on routine examination. None of the patients exhibited any paraneoplastic syndromes. Eleven (69%) of the patients received surgical intervention. Seven patients had debulking surgery, 2 had post CCRT debulking surgery (patients 5 and 12) and 2 had incision biopsies (patients 13 and 14). According to the modified Masaoka staging system, 12 (75%) patients had stage III and 4 (25%) had stage IVb disease. Chemotherapy regimens consisted of either (A) or (B) below. (A) Cisplatin 100 mg/m^2 as a 4-hour infusion on day 1, and continued infusion of 5-fluo-

rouracil 1000 mg/m²/day for 4 consecutive days on the first cycle. Then, we adjusted the dosage with cisplatin 60-80 mg/m2 as a 4-hour infusion on day 1, and continued infusion of 5-fluorouracil 600-800 mg/m²/day for 4 consecutive days on the following cycles. (B) Doxorubicin 30 mg/m² intravenous bolus on day 1, cisplatin 50 mg/m² as a 3-hour infusion on day 1, vincristine 0.6 mg/m² intravenous bolus on day 3, and cyclophosphamide 500 mg/m² as a 3-hour infusion on day 4. Courses were repeated every 4 weeks for at least 2 cycles. The median cycle of chemotherapy was 3, ranging from 2 to 6 cycles. A total 58 cycles were given in 16 patients. The exact number of cycles of chemotherapy were 2 cycles for two patients, 3 cycles for seven patients, 4 cycles for four patients, 5 cycles for one patient, and 6 cycles for two patients.

All patients received external beam radiotherapy concurrently. The treatment volume included the entire mediastinum which was irradiated through individually shaped anteroposterior and posteroanterior portals. Radiation doses to the mediastinum were 23.4 to 44.0 Gy (median: 36 Gy). Fifteen patients subsequently received additional irradiation of 12.0 to 37.8 Gy to the gross tumor site. The remaining patient deeveloped lung metastases post-CCRT debulking surgery. Additional irradiation was delivered with a three-dimensional conformal radiotherapy technique in 12 patients. The total dose to the primary tumor site ranged from 34.2 to 70.0 Gy (median: 64.0 Gy). External beam radiotherapy was delivered with 10 MV photons and the daily fraction was 1.8 or 2 Gy, 5 fractions per week.

Chest computed tomography to assess response was performed one month after the end of CCRT. A complete response was defined as disappearance of all measurable disease based on imaging studies. A partial response was defined as a 50% or greater decrease in the sum of the products of the largest perpendicular diameter of all measurable lesions, or a decrease of at least 50% of one dimension of the evaluable lesions for at least 4 weeks without the appearance of new lesions. Stable disease was defined as a decrease in lesions for at least 4 weeks, which did not reach the criteria of PR, or a less than 25% increase in lesions. Progressive disease was defined as a 25% or greater increase in the size of one or more evaluable lesions, or the appearance of new lesions. Toxicity was evaluated according to commonly accepted WHO criteria. The survival time was calculated from the start of therapy to the date of death, and the survival pattern was established using the Kaplan-Meier method.

RESULTS

Patient data are shown in Tables 2 and 3. The clinical outcomes of the sixteen patients who under-

Table 2. Clinical Profiles, Histology and Stage of 16 Patients with Unresectable Thymic Carcinomas

No.	Gender	Age	Presenting symptoms	Histology	Masaoka stage
1	F	46	Chest pain	SCC, NK	III
2	M	52	Chest pain	SCC, K	III
3	M	46	Dyspnea	undifferentiated carcinoma	IVb
4	M	55	Chest pain	undifferentiated carcinoma	III
5	M	64	-	SCC, K	III
6	M	63	Cough	SCC, NK	III
7	M	47	Cough	SCC, NK	III
8	M	53	Dyspnea	SCC, NK	III
9	F	46	Cough	undifferentiated carcinoma	IVb
10	F	45	-	SCC, NK	III
11	M	58	Cough	SCC, NK	III
12	M	55	Chest pain	SCC, NK	III
13	F	62	Chest pain	SCC, NK	III
14	F	66	Cough	SCC, NK	IVb
15	M	50	Dyspnea	small cell-squamous carcinoma	IVb
16	F	50	Dyspnea	SCC, NK	III

Abbreviations: SCC: squamous cell carcinoma; NK: non-keratinizing; K: keratinizing

Table 3. Patient Characteristics

	Number (N=16)
Age	
Median (years)	53
Range (years)	45-66
Gender	
Male	10
Female	6
Stage*	
III	12
IVb	4
Histology	
Squamous cell carcinoma, non-keratinizing	10
Squamous cell carcinoma, keratinizing	2
Undifferentiated carcinoma	3
Small cell-squamous cell carcinoma	1

*Stage according to the modified Masaoka staging system

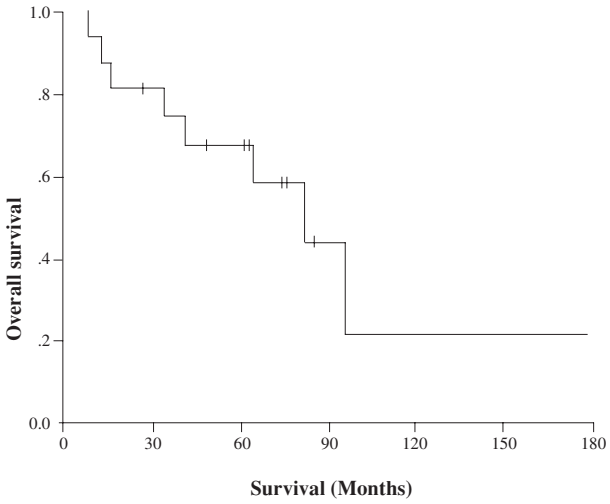

Fig. 1 Kaplan-Meier plot showing the overall survival for all patients. The median survival of all patients was 82 months.

Table 4. Treatment Modalities and Results of 16 Patients With Unresectable Thymic Carcinomas

No.	Type of surgery	Concurrent chemoradiotherapy		Response	Sites of recurrence	Status	Survival time (months)
		Chemotherapeutic agents	Radiotherapy dose (Gy)				
1	Debulking	CF	56.3	CR	-	NED	177
2	-	ADOC, CF	70.0	SD	Mediastinum	Dead	96
3	Debulking	CF	70.0	SD	LN	Dead	64.5
4	Debulking	CF	64.0	PR	LN, Bone, Liver	Dead	82
5	Debulking*	C, CF	34.2	PD	Lung	Dead	12.5
6	Debulking	CF	66.0	SD	Lung, Brain	AWD	85
7	-	CF	66.4	SD	LN, Bone	Dead	41.5
8	Debulking	CF	64.0	PR	Mediastinum	AWD	74
9	-	ADOC, CF	60.0	SD	Brain	AWD	61
10	Debulking	CF	66.6	CR	-	NED	76
11	Debulking	CF	64.0	CR	-	NED	49
12	Debulking*	CF	66.0	PR	Bone	Dead	16
13	Biopsy	CF	59.4	SD	Mediastinum, Liver	Dead	34
14	Biopsy	CF	59.4	CR	-	NED	63
15	-	CF	61.2	PD	Bone, LN	Dead	8
16	-	CF	60.0	PR	†	AWD	27

Abbreviations: ADOC: doxorubicin, cisplatin, vincristine, cyclophosphamide; C: cisplatin; CF: cisplatin, 5-Fluorouracil; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; LN: lymph node; NED: no evidence of disease; AWD: alive with disease.

*: post concurrent chemoradiotherapy debulking; †: At the end of this study, patient #16 had stationary residual disease after obtaining PR.

went CCRT are shown in Table 4. Four (25%) patients had complete responses, 4 (25%) had partial responses, 6 (38%) had stable disease and 2 (13%) had progressive disease. The overall response rate (CR+PR) was 50%. The median follow-up was 64 months (range, 8-177 months). The median survival was 82 months. The overall cumulative survival rates at 1, 2, 3, and 5 years were 93.8%, 81.3%, 74.5%, and 67.7%, respectively) (Fig. 1). Eight patients were still alive, and 4 patients were alive without

evidence of disease at the end of this study. During the follow-up, there were 11 patients with recurrence of disease. The sites of recurrence were bone (4 patients), lymph node (4 patients), mediastinum (3 patients), lung (2 patients), liver (2 patients), and brain (2 patients). The 16th patient had stationary residual disease after obtaining partial response.

No scheduled chemotherapy was postponed due to hematological toxicities. No fever was noted during the course of CCRT. Acute toxicities were grade I/II nausea, vomiting, fatigue, and esophagitis, which were managed with fluid supplements and pain control. No grade III non-hematological toxicities or life-threatening side effects were noted. Unfortunately, radiation pneumonitis was experienced by all 16 patients with the manifestations of chronic cough, and mild respiratory distress. After completing CCRT, 8 of 16 patients (50%) were admitted to the hospital for radiation pneumonitis during follow-up.

DISCUSSION

Thymic carcinomas are thymic epithelial neoplasms with cytologic malignant features and include various histologic types. They are distinct thymic neoplasms that differ from ordinary thymomas. The clinical course of thymic carcinoma tends to be much more aggressive than that of thymoma. The histology of Rosai's and Muller-Hermelik's 1978 classification is subdivided into low grade carcinoma, such as squamous cell carcinoma, mucoepidermoid carcinoma, and basaloid carcinoma; and high grade carcinoma, such as lymphoepithelioma-like carcinoma, small cell carcinoma, clear cell carcinoma, and poorly differentiated carcinoma.[5] Suster and Rosai presented 60 patients with thymic carcinoma who underwent various treatment modalities and were followed at least 3 years. These patients were divided into prognostic groups based on pathologic criteria (low-grade versus high-grade histologic type). They stated that the histologic grade was the best prognostic indicator; and absence of a lobular pattern, greater than 10 mitoses per 10 high power fields (40×10 per high power field), necrosis and atypia were also found to be associated with a poor prognosis.[5] Some authors reported that the stage and resectability of the tumor and performance status were also significant predictive factors for the effectiveness of treatment.[14-15]

There are multiple treatment modalities for thymic carcinoma including surgical resection, postoperation radiotherapy and chemotherapy. Initial surgical resection followed by local irradiation was used in most studies for localized lesions.[4-8,16-17] The best survival rates were seen with complete resection of early stage lesions. However, the outlook for unresectable thymic carcinoma is unsatisfactory because of advanced invasive disease, distant metastasis and a high relapse rate. There is no uniform treatment modality for unresectable thymic carcinoma. Debulking surgery followed by irradiation is commonly the mainstay of treatment in advanced thymic carcinoma. In addition, adjuvant chemotherapy followed by surgical resection with or without postoperation radiotherapy for advanced thymic carcinoma has been reported in a small number of patients.[7,20-21] Although the postoperative treatment has been investigated as well as that of thymoma, the published research on chemotherapy has been limited. Case reports and several prospective trials have demonstrated that thymic carcinomas are chemotherapy-sensitive diseases, especially with cisplatin-based combination chemotherapy.[6,11,20-22] But, the clinical benefit of systemic chemotherapy for unresectable thymic carcinoma remains controversial. No definite chemotherapeutic agents have yet been established. Several chemotherapeutic agents have been used, including cyclophosphamide, doxorubicin, vincristine, cisplatin, etoposide, 5-Fluorouracil and leucovorin.[7] Overall survival rates based on Suster's study at 1 year, 3 and 5 years were 56.6%, 40.0% and 33.3%, respectively.[5] Nevertheless, few reports have addressed the efficacy of CCRT for unresectable thymic carcinoma. Akiyama et al.[23] reported that a 59-year-old woman with inoperable thymic squamous cell carcinoma was effectively treated with preoperative CCRT. In several recent trials, CCRT was shown to improve the overall survival and disease-free survival when compared with radiation alone in the setting of locally advanced nasopharyngeal carcinoma.[24-26] We used the same modality to treat unresectable thymic carcinoma.

Our results with CCRT are promising and show a tendency toward improvement in overall survival. In comparison with previous studies, CCRT seems to be beneficial for patients with advanced unresectable thymic carcinoma (Table 5). Further randomized

Table 5. The Long-Term Results of Different Treatment Modalities for Thymic Carcinoma

Study	Patient number	Modality	Response Rate (%)	Median survival (months)	5-year survival (%)
Suster S et al. 1991(5)	60	Sx±RT±CT	NR	NR	33.3
Chang HK et al. 1992(27)	16	Sx±RT±CT	NR	30*	31
Hsu CP et al. 1994(4)	20	Sx±RT	NR	39†	34.4
Ogawa K et al. 2002(15)	40	Sx+RT±CT	NR	NR	38
Liu HC et al. 2002(14)	38	Sx	NR	24.1	27.5
Hsu HC et al. 2002(28)	26	Sx+RT	NR	NR	77
Our series	16	CCRT	50	82	67.7

Abbreviations: Sx: surgery; RT: radiotherapy; CT: chemotherapy; NR: not report; CCRT: concurrent chemoradiotherapy.

*: The median survival of patients with pure squamous cell carcinoma was more than 49 months.

†: The median survivals of patients with complete and incomplete resections were 39 months and 14.3 months, respectively.

study is mandatory to elucidate whether CCRT is superior to other treatment modalities. Although the overall response rate was 50% with only a 25% complete response, we had a promising survival rate of 67.7% at 5 years. The study could have been affected by a limitation in our evaluation technique. We had three patients with partial responses with long response durations, of 28, 55, and 27 months. They had stationary residual density over the mediastinum on the follow-up chest computed tomography. It is difficult to differentiate residual tumor from radiation fibrosis without biopsy or resection. According to the evaluation criteria, we defined them as having a partial response rather than a complete response, which may have resulted in underestimation of the number of patients with complete responses. There is increasing evidence to show that functional imaging with positron emission tomography may define the response status more accurately than structural imaging in many kinds of malignant tumors. We will consider applying this technique for those patients with a questionable response status in the future.

CCRT seems effective for unresectable thymic carcinoma. Our experience, although preliminary, is encouraging and merits conducting a randomized trial to determine the impact of CCRT on unresectable thymic carcinoma. Positron emission tomography will be used to assess patients with a questionable response status.

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對於無法手術切除之胸腺癌以同步化學及放射線治療之效果

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背 景： 胸腺癌是一種罕見的前縱隔腔腫瘤，相較於傳統之胸腺瘤，其較具侵襲性，預後較差，由於診斷時常廣泛的侵犯周邊器官或遠端移轉，往往無法做根除性的手術切除，然而化學治療的角色及最適當的治療模式目前尚未有定論，我們分享以同步化學及放射線治療來處理無法手術切除之胸腺癌的經驗。

方 法： 於1989年7月至2003年7月共收集了29例於高雄長庚醫院診斷爲無法手術切除之胸腺癌作回朔性的分析，共有16人接受同步化學及放射線治療，其中10位男性6位女性，中位年齡53歲。

結 果： 共有4人達到完全緩解，4人部份緩解，反應率爲50%，中位存活期爲82個月，第1年、第2年、第3年、及第5年存活率分別爲93.8%、81.3%、74.5%、67.7%，放射性肺炎是最常見的副作用，但沒有第三級和第四級的毒性出現危及生命副作用。

結 論： 同步化學及放射線治療對於無法手術切除之胸腺癌似乎是有效的治療模式可延長病人的存活期，但是仍需要大規模研究來證實之。

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關鍵字：胸腺癌，化學治療，放射線治療，同步化學及放射線治療。

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