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Managements of Locally Advanced Unresectable Thymic Epithelial Tumors

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Background. Surgery is the treatment of choice for thymic epithelial tumors (TET), but the resectability is about 60-70%. For those with locally advanced unresectable TETs (LAU-TETs), some controversies about the prognostic factors and treatment modalities existed. The aims of this study are to elucidate the roles of various therapeutic options and to determine the survival and prognostic factors of LAU-TETs.

Methods. Twenty-seven patients diagnosed with LAU-TETs underwent treatment in Taipei Veterans General Hospital between 1979 and 1997. Multiple treatment modalities, including surgical intervention, irradiation and chemotherapy, were advocated for these patients. The clinicopathological factors and the effects of the treatment modalities were evaluated retrospectively.

Results. Twenty seven cases of LAU-TETs, included 18 thymomas (12 at stage III and 6 at stage IVa) and 9 thymic carcinomas (4 at stage III and 5 at stage IVa), were enrolled for study. The overall 5-year and 10-year survival rates were 54.6% and 35.1%, respectively. Patients receiving debulking surgery and those with irradiation dosage higher than 4400 cGy had significantly better survivals ($P = 0.021$ and $P = 0.016$, respectively).

Conclusions. Aggressive debulking surgery and sufficient irradiation dosage provide better survivals for patients with LAU-TETs, especially for those with thymoma.

Thymic tumors consist of a heterogeneous group of uncommon tumors that derived from the thymic epithelium. The classification of thymic tumors has spawned at least 21 different proposals since 1916, and continued to generate vigorous debate until recent years when new concepts for classification of thymic epithelial tumors (TETs) implicated features of prognostic relevance.[1,2] Nowadays, the degree of disease progression for TETs can be predicted by anatomic and clinical staging[3] or by the histological classification.[4] According to the histological typing of thymic tumors published by the World Health Organization (WHO) in 1999, TETs contain thymoma and thymic carcinoma.[5] As described by Shimosato and Mukai in 1997,[2] thymomas retain relatively normal histological structures and even functional characteristics, whereas thymic carcinomas reveal obvious histological atypia. In addition, there are evidences that differentiation between medullary and cortical thymomas has impacts prognosis.[6]

It is widely consented that complete surgical resection is the treatment of choice for TETs, and can provide a better chance of long-term survival. Unfortunately, complete resection of advanced-stage tumors is difficult, and a high incidence of tumor recurrence is inevitable.[7] Thus, locally advanced unresectable TETs (LAU-TETs) remain challenging to clinical oncologists and surgeons. It has been advocated that the LAU-TETs should be approached in a multidisciplinary fashion. However, the therapeutic options and factors affecting the prognosis continue to be matters of controversy, and are not fully clarified.

METHODS

From a computerized TET registry at Taipei Veter-

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ans General Hospital between 1979 and 1997, 140 patients with histologically confirmed TETs underwent surgical operations at Division of Thoracic Surgery. Twenty seven (19.3%) of them were LAU-TETs in stages III and IVa. The stage of tumors in this study was classified according to the Masaoka staging system.[3] Stage III was defined as patients with tumor invading into neighboring organs (i.e., lungs, pericardium or great vessels) and stage IVa denoted tumor dissemination confined to the intra-thoracic cavity (i.e. pleural seeding or pericardial seeding). The preoperative work-up included chest radiography, blood cell counts, biochemistry studies, chest computed tomography (CT) and pulmonary function test. Radionuclide scanning of bone and ultrasound of whole abdomen were also performed if needed. The modes of surgical operation comprised a debulking surgery or an open biopsy. Debulking surgery was defined to remove at least 90% of the main tumor and wedge resection of all the seedings. In addition to surgery, the majority of patients received perioperative adjuvant treatments, including radiotherapy, chemotherapy or both. Radiation was administered to the main tumor and sites of tumor seeding before or after surgery. Twenty-three patients (85.3%) received irradiation, with a mean dose of about 4400 cGy (range: 1600 to 9800 cGy). A combination of chemotherapy with various regimens was instituted in 15 (55.6%) patients. The cisplatin-based formula was administered in 13 (86.7%) patients and non-cisplatin-based formula (including cyclophosphamide, vincristine, or adriamycin) was administered in 2 (13.3%) patients (Table 4). The initial dosage of cisplatin was 50 mg/m^2, which was adjusted according to the patients' tolerance and serum creatinine levels. The irradiation dosage was established dependent on the tumor size and tumor location. The clinical response to radiotherapy or chemotherapy, including complete response (CR), partial response (PR), no change (NC) or disease progression (DP), was recorded according to the WHO criteria.[8]

STATISTICAL ANALYSIS

The relationships between clinicopathological factors and histological types were analyzed by *Chi-square* test or Student's *t* test. Survival curve was plotted by the Kaplan-Meier method. Log-rank and Breslow tests were used to analyze the long-term and short-term survival differences, respectively. Statistical significance was assumed for a p value less than 0.05.

RESULTS

Clinicopathological features

Among the 27 patients with LAU-TETs, the male/female ratio was 17/10 and their mean age was 53.7 ± 15.5 years (ranges: 29-85 years). All patients were regularly followed after treatment for a median of 62.3 months (ranges: 0.5 - 197 months). Upon admission to the hospital, only 3 (11.1%) patients were asymptomatic. The most frequent clinical features were cough (37%), chest pain (26%) and an association with myasthenia gravis (MG, 26%) (Table 1). Five of 7 MG patients were female. These MG patients were significantly younger (mean age: 40.1 ± 9.5 years) than those without MG (58.5 ± 14.4 years, $p = 0.02$).

All the 27 patients had direct tumor invasion to the adjacent organs and 11 of them also got tumor seedings. The most frequent sites of tumor invasion or seeding were great vessels (62.3%) and pleura (26.0%) (Table 2). The histopathological patterns consisted of 18 thymomas and 9 thymic carcinomas. In thymoma group, 12 were at stage III and 6 at stage IVa; whereas in thymic carcinoma group, 4 were at stage III and 5 at stage IVa. Their clinical variables are shown in Table 3. There was no statistical differ-

Table 1. Clinical features in 27 patients with LAU-TETs

Clinical features	No. (%)
Asymptomatic	3 (11.1)
Symptoms	24 (88.9)
Cough	10 (37.0)
Chest pain/distress	7 (25.9)
Myasthenia gravis	7 (25.9)
SVC syndrome	5 (18.5)
Dyspnea	4 (14.8)
Hoarseness	1 (3.7)
Fever	1 (3.7)

LAU-TETs = locally advanced unresectable thymic epithelial tumors; SVC = superior vena cava.

Table 2. Summary of organs or tissues invaded by TETs

Organs/Tissues	No. (%)
Direct invasion	27 (100)
Great vessels	17 (62.3)
Lung	16 (59.3)
Pericardium	7 (26.0)
Pleura	6 (22.2)
Phrenic nerve	5 (15.8)
Diaphragm	2 (7.4)
Recurrent laryngeal nerve	1 (3.7)
Sternum	1 (3.7)
Tumor seeding	11 (40.1)
Pleura	7 (26.0)
Diaphragm	3 (11.1)
Pericardium	1 (3.7)
Chest Wall	1 (3.7)

TETs = thymic epithelial tumors.

Table 3. Distribution of clinical characteristics according to histological types

	Thymoma (n = 18)	Thymic carcinoma (n = 9)	*p* value
Sex (M/F)	12/6	5/4	NS
Age (years)	51.7 ± 17.7*	57.7 ± 9.0	NS
Associated symptoms			
Myasthenia Gravis	7 (38.9)†	0 (0)	0.03
SVC syndrome	4 (22.2)	1 (11.1)	NS
Tumor stage			NS
III	12 (66.7)	4 (44.4)	
IVa	6 (33.3)	5 (55.6)	
Treatment modality			
Surgical operation			NS
Debulking	7 (38.9)	4 (44.4)	
Biopsy	11 (61.1)	5 (55.6)	
Radiotherapy	16 (88.9)	7 (77.8)	NS
Chemotherapy	9 (50.0)	6 (66.7)	NS

SVC = superior vena cava.; *Mean ± S.D.; †Data in the parentheses represent percentages.

ence in sex, age, presence of superior vena cava (SVC) syndrome, or tumor stages between thymoma group and thymic carcinoma group. However, MG occurred only in the thymoma group.

Managements

The treatment modalities comprised 3 components including surgical resection, radiotherapy and chemotherapy. The therapeutic status and results of each patient are briefly demonstrated in Table 4.

Surgical resection

An aggressive debulking surgery was accomplished in 11 (40.7%) cases, including 7 (38.9%) of the 18 patients with thymomas and 4 (44.4%) of the 9 patients with thymic carcinomas. In the remaining 16 (59.3%) patients, only a simple biopsy was performed. There was no surgical mortality or major complication in the debulking group. Tumor resections for intrathoracic recurrences were further performed in 2 patients with thymoma.

Radiotherapy

Irradiation was instituted in 23 patients (16 thymomas and 7 thymic carcinomas). Among these patients, 4 (3 thymomas and 1 thymic carcinoma) underwent irradiation before operation. Two of them (1 thymoma and 1 thymic carcinoma) then had successful debulking surgery but the other 2 patients with thymoma received open biopsies due to direct invasion of great vessels or bony metastasis identified after primary treatment. Furthermore, 17 patients (12 thymomas and 5 thymic carcinomas) received irradiation dose more than 4400 cGy.

Chemotherapy

Fifteen patients (9 thymomas and 6 thymic carcinomas) received peri-operative chemotherapy. Thirteen patients underwent cisplatin-based chemotherapy and 2 patients with thymomas underwent non-cisplatin-based chemotherapy. Among them, 2 patients with thymomas received neoadjuvant chemotherpy (both had cisplatin-based formula) and 1 then underwent successful debulking surgery subsequently. Two patients with thymoma undergoing second operation for recurrent tumors received another course of chemotherapy.

Survival analysis

At the end of this study, 15 patients (10 thymomas and 5 thymic carcinomas) died and 2 with thymomas were lost to follow-up. Ten patients (6 thymomas with 5 receiving debulking and 4 thymic carcinomas with 3 receiving debulking) are still alive currently. The median follow-up time was 62.3 months (ranges: 0.5 - 197 months) in this series. The overall 5-year survival rates in thymoma and thymic carcinoma were 61.1% and 37.0%, respectively. Among the 15 deceased patients, 7 died of tumor recurrence or dissemination, 1 died of gas-

Table 4. Clinicopathological parameters and outcome in 27 patients with LAU-TETs

No.	Age/Sex	Cell Type	Stage	Duration (m)	Present Status	Operation	Irradiation (cGy)	Chemotherapy	Response*
1	59/M	thymoma	III	62.3	Expired	biopsy	6000 †	C	yes
2	70/M	thymoma	IVa	10.3	Expired	biopsy	6700	C	No
3	42/F	thymoma	IVa	13.0	Expired	biopsy	3300 †	Nil	No
4	35/M	thymoma	III	49.6	Expired	biopsy	4000	Nil	yes
5	47/F	thymoma	III	83.4	Expired	biopsy	5000	Nil	yes
6	54/F	thymoma	III	43.0	Expired	biopsy	5098	Nil	yes
7	29/M	thymoma	III	7.0	Expired	biopsy	3756	A	No
8	66/M	thymoma	III	13.4	Expired	biopsy	1950	C	No
9	64/M	thymoma	III	102.0	Lost	biopsy	0	Nil	yes
10	35/M	thymoma	IVa	55.0	Alive	biopsy	6130	C	yes
11	85/F	thymoma	III	68.8	Alive	debulking	4930	Nil	yes
12	42/F	thymoma	III	197.0	Alive	debulking	0	Nil	yes
13	59/M	thymoma	III	41.0	Expired	debulking	5997	Nil	yes
14	44/M	thymoma	IVa	69.8	Expired	debulking	6000	Nil	yes
15	36/F	thymoma	III	57.9	Alive	debulking	5200	C	yes
16	34/M	thymoma	III	145.2	Alive	debulking	6000 †	C	yes
17	63/M	thymoma	IVa	113.8	Alive	debulking	6000	C	yes
18	31/M	thymoma	IVa	96.0	Lost	biopsy	6000	A	yes
19	52/F	carcinoma	IVa	7.4	Expired	biopsy	2550	C	No
20	62/M	carcinoma	III	22.9	Expired	debulking	5800	C	No
21	41/M	carcinoma	IVa	22.5	Expired	biopsy	1600	C	yes
22	62/F	carcinoma	III	52.9	Expired	biopsy	6403	C	yes
23	61/M	carcinoma	III	0.5	Expired	biopsy	0	Nil	NE
24	62/M	carcinoma	IVa	53.6	Alive	biopsy	9800	Nil	yes
25	57/F	carcinoma	IVa	52.0	Alive	debulking	5000	Nil	yes
26	72/M	carcinoma	IVa	66.1	Alive	debulking	0	C	yes
27	50/F	carcinoma	III	41.2	Alive	debulking	5000 †	C	yes

LAU-TETs = locally advanced unresectable thymic epithelial trmors; C = cisplantin based adjuvant chemotherapy; A = adjuvant chemotherapy with non-cisplantin based formula; NE = not evaluated; *disease under control longer than 1 year; †neoadjuvant radiotherapy.

tric cancer, 1 died of postoperative respiratory failure after open biopsy and the remaining 6 deaths were associated with other miscellaneous causes.

Among the 18 thymoma patients, the cumulative 5-year and 10-years survival rates for patients undergoing debulking surgery (n = 7) were better than those received open biopsies only (85% *vs*. 45%, and 64.2% *vs*. 22.2%, $p = 0.075$). There seemed to make no significant difference in survival with gender, tumor stages (stage III *vs*. IVa), adjuvant chemotherapy, and an association with MG or SVC syndrome. Four of the 9 thymic carcinoma patients received debulking surgery, they tended to have a better 5-year survival rate than those with biopsy only (75% *vs*. 20%, $p = 0.14$). No statistical significance could be reached, because of the limited cases analyzed.

For the overall LAU-TETs (n = 27), there was no significant survival difference in histopathological patterns

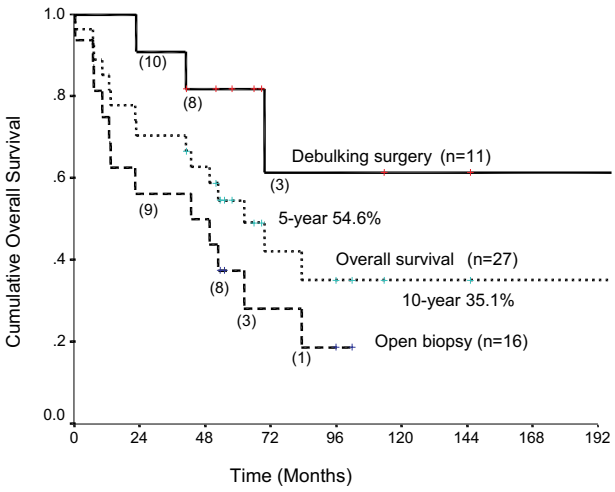

Fig. 1. Overall survival curve of the 27 patients. Survival curves of patients, receiving debulking surgery and open biopsy ($p = 0.021$). The numbers in parentheses represent the humber of patients at risk every 2 years.

(thymoma *versus* thymic carcinoma)(p = 0.37) and clinical stages (III and IVa)(p = 0.60,). To sum up, the cumulative survival rates for LAU-TET patients undergoing debulking surgery in 2 years, 5 years and 10 years were 90.9%, 81.8% and 61.4%, respectively. The cumulative survival rates for patients undergoing biopsy in 2 years, 5 years and 10 years were 56.3%, 37.5% and 18.8%, respectively. Compared with debulking surgery group, the biopsy group had significantly worse survival rates (p = 0.021) (Fig. 1). Additionally, the LAU-TET patients receiving irradiation dose larger than 4400 cGy (n = 17) had better short-term survival rates than those receiving lower irradiation doses less than 4400 cGy (n = 10) (p = 0.016). Nevertheless, these 2 groups showed no difference in long-term survival rate (p = 0.101) (Fig. 2). Neither were the survival rates affected by the following factors such as gender, adjuvant chemotherapy, and an association with MG or SVC syndrome. Using the multivariate analysis

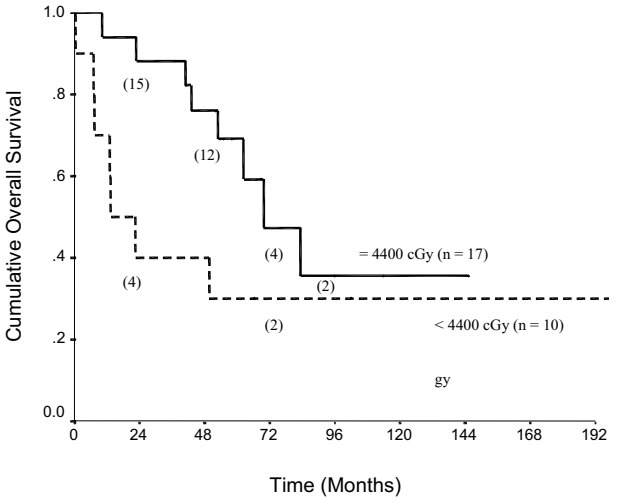

Fig. 2. Survival curves of patients receiving irradiation, with a cutoff value of 4400 cGy (p = 0.016, Breslow test and p = 0.101, Log-rank test). The numbers in parentheses represent the number of patients at risk every 2 years.

Table 5. The median survival and survival rates according to various factors

Factors	Survival		Survival rates			*p* value	
	Number of patients (%)	Median ± SD (months)	2 - year %	5 - year %	10 - year %	*p* (Log-rank)	*p* (Breslow)
Overall	27 (100)	62.3 ± 12.3	70.4	54.6	35.1		
Sex						0.7680	0.5869
Male (n = 17)	17 (63.0)	62.3 ± 16.0	64.7	52.9	36.3		
Female (n = 10)	10 (37.0)	83.4 ± 20.8	80.0	54.9	27.4		
Histological Type						0.3700	0.3652
Thymoma (n = 18)	18 (66.7)	69.8 ± 9.1	77.8	61.1	38.8		
Thymic carcinoma (n = 9)	9 (33.3)	52.9 ± 30.3	55.6	37.0			
Stage						0.6041	0.7669
Stage III (n = 16)	16 (59.2)	52.9 ± 11.0	75.0	48.1	30.0		
Stage IVa (n = 11)	11 (40.8)	69.8 ± 44.2	63.6	63.6			
Operation Mode						0.0209	0.0195
Biopsy (n = 16)	16 (59.2)	43.0 ± 27.1	56.3	37.5	18.8		
Debulking (n = 11)	11 (40.8)	141 ± 27.4	90.9	81.8	61.4		
Irradiation Dose						0.1011	0.0161
≥ 4400 cGy (n = 17)	17 (63.0)	69.8 ± 13.5	88.2	69.1	35.5		
< 4400 cGy (n = 10)	10 (37.0)	13.4 ± 7.5	40.0	30.0			
Chemotherapy						0.9049	0.6716
Yes (n = 15)	15 (55.6)	62.3 ± 30.8	60.0	52.5	42.0		
No (n = 12)	12 (44.4)	69.8 ± 22.9	83.3	58.3	29.2		
MG						0.1539	0.0777
Yes (n = 7)	7 (25.9)	131.0 ± 27.6	100.0	87.5	51.4		
No (n = 20)	20 (74.1)	40.3 ± 11.5	60.0	43.3	28.9		
SVC syndrome						0.2290	0.1971
Yes (n = 5)	5 (18.5)	43.0 ± 32.9	60.0	20.0	0		
No (n = 22)	22 (81.5)	69.8 ± 14.3	72.7	63.3	37.5		

with Cox regression, surgical resection was the only independent prognostic factor of LAU-TETs (Table 5).

DISCUSSION

Thymoma and thymic carcinoma are both TETs, and most authors thought thymoma had a better prognosis. For LAU-TETs, as in the current series, there seemed to be no survival differences between thymoma and thymic carcinoma. It has been suggested that the factors affecting the prognosis of TETs may include the invasiveness of the tumor, clinical stage, tumor size, resectability, histological nature, an association with MG, and postoperative radiotherapy and chemotherapy.[3,7-10] Nevertheless, whether debulking surgery plays a significant role remains debatable. In this study, we documented that aggressive debulking surgery significantly improve survival for those patients with LAU-TETs.

Thymomas and thymic carcinomas are rather radiosensitive.[7,11,12] The local control rates of postoperative radiotherapy were around 50-80% in the previous reports.[13,14] Radiotherapy is indicated for patients with unresectable tumors or residual tumors following incomplete resection. Extended postoperative radiotherapy may control residual tumors, offer a lower relapse rate and provide a long-term, disease-free survival in a subset of patients after incomplete resection.[15,16] A median dose of 4500 cGy has been suggested for adjuvant treatment of completely resected invasive TETs.[10] For patients with grossly residual tumors after resection, irradiation doses greater than 6000 cGy have been recommended.[15] Due to some differences in body size between various ethnic populations, a relatively lower irradiation dosage has been advocated for most of our patients with LAU-TETs and some patients seemed to benefit in survival. However, it deserves further study to find whether it is related to ongoing side effect of radiotherapy or radio-resistance acquired by the tumors later on.

The timing for radiotherapy; namely before or after surgical interventions, is still controversial. Most authors suggested that radiotherapy should be reserved after surgery to eliminates the need to operate in a radiated field and optimizes biologic effects of radiotherapy by avoiding dose interruption. In our series, pre-operative radiotherapy made the bulky tumors shrink and enabled the debulking surgery to proceed (Cases 16 and 27). However, 1 patient (Case 3) developed bony metastasis after primary radiotherapy.

The constitutional role of chemotherapy in the treatment of TET has remained undefined until the 1990's. Some authors proposed the importance of chemotherapy for LAU-TETs. Chemotherapy provides a favorable outcome for stage III-IVa lesions.[17] Single agent such as cisplatin, doxorubicin, cyclophosphamide or ifosfamide did offer benefits for some patients,[17-20] but others doubted.[21] On the other hand, a combination of cisplatin-based regimen have been applied and improvement of disease control and survival has been noted.[22,23] Meanwhile, in addition to the cytotoxic effects of chemotherapy itself, chemotherapeutic agents such as cisplatin and etoposide have proved to enhance the effect of radiotherapy.[24,25]

MG is a specific paraneoplastic syndrome associated with thymoma. Whether the presence of MG affects prognosis remains disputable. Some authors found that thymomas with MG were at earlier stages and considered it as a positive prognostic factor,[7] whereas some authors could not identify such relationship.[3] In the current series, MG was a marginally prognostic factor (P = 0.078) in LAU-TETs. We regard this as a result of limited cases and conclude that more cases are needed to investigate the prognostic role of MG in LAU-TETs.

In conclusion, our results showed that debulking surgery improved survival in patients with LAU-TETs, especially for thymomas, compared with those who received open biopsy only. A higher dose (≥ 4400 cGy) irradiation combined with cisplatin-based chemotherapy was helpful in improving survival. We therefore recommended that debulking surgery should be advocated, if no contraindication, in the patients with LAU-TETs.

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