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Single Centre Experience in the Management of Thymic Tumours

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Abstract

Background: Thymoma and thymic carcinoma are relatively rare tumours of the anterior mediastinum. Optimum treatment options for these tumours remain unresolved, although at present, a multimodality approach involving aggressive surgical resection, platinum-based combination chemotherapeutic interventions and radiotherapy represents the preferred therapeutic approach.[1-3] This study evaluates the treatment outcome of patients with thymic tumours at our centre.

Methods: We retrospectively reviewed clinical case notes, electronic patient records, imaging and radiation treatment records of patients treated at Clatterbridge Cancer Centre.

Results: A total of 21 patients diagnosed with thymic tumours were treated at Clatterbridge Cancer Centre between June 1990 until June 2011. There were 12 (57%) out of 21 patients who received multimodality therapy (chemotherapy and/or radiation therapy and/or surgery), 7 (34%) received single modality treatment and 2 (9%) did not receive any treatment. Relapse occurred in 10 (47%) patients with a median time from primary diagnosis to relapse of 28 months (10 to 104 months). Among those who relapsed, 6 died with a median survival of 58 months (53 to 64 months). Out of 12 patients in the multimodality treatment group, 9 (75%) remain alive with a median follow up of 45 months. In 7 patients who received single mode therapy, 5 (71%) died with a median survival of 45 months. 2 patients who did not receive any treatment died. Overall median survival in 10 of 21 patients who died was 42 months (2 to 192 months).

Conclusion: Multimodality treatment for thymic tumours represents the preferred therapeutic approach and should be considered in suitable patients. Further randomized trials are necessary to define the optimum treatment options.

Keywords: Thymoma, Thymic carcinoma, chemotherapy, Radiotherapy

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Introduction

Thymoma and thymic carcinoma are relatively rare tumours of the anterior mediastinum, which together represent 0.2% to 1.5% of all malignancies.[1]

Thymoma can occur at any age, from 8 month-old patients to those aged 90 years, with a mean age of 53 years.[2-4] Patients may be completely asymptomatic or can present with local or systemic symptoms of

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paraneoplastic disease. Local symptoms include pain, cough, hoarseness, dyspnoea and superior vena cava syndrome. The most common paraneoplastic syndrome is myasthenia gravis in 30% to 45% of patients.[2, 5] Other common paraneoplastic presentations include red cell aplasia and hypogammaglobulinemia.[6] Vascular invasion, encasement and pleural dissemination on CT scan usually favour invasive malignancy.[7] MRI and PET scan are not used routinely for staging of thymic tumours.

Optimum treatment options for these tumours remain unresolved, although at present, a multimodality approach involving aggressive surgical resection, platinum-based combination chemotherapeutic interventions and radiotherapy represent the preferred therapeutic approach.[8-10]

Surgery remains gold standard treatment for resectable tumours and complete resection should be attempted, but is not always possible.[11] Adjuvant radiotherapy is considered effective for invasive tumours. These tumours are reported to be chemotherapy-sensitive in many case reports, retrospective and prospective studies. Platinum-based combination chemotherapy has been used but its clinical benefit remains debatable.[12-15]

Materials and Methods

Patients with histologically confirmed thymic tumours were identified on a retrospective review of an electronic data base and clinical notes at Clatterbridge Cancer Centre (CCC), a regional centre serving a population of 2.1 million. Patients diagnosed from June 1990 to June 2011 were included. Patient demographics, clinical variables, treatment and survival data were documented.

Data was collected on date of diagnosis, histology, Masaoka staging, initial site of involvement, pre- and postoperative chemotherapy, pre- and postoperative radiotherapy, type of surgery, date and site of relapse, treatment of relapse, association with myasthenia gravis and date of death. Relapse-free survival was measured from the diagnosis of the primary tumour and development of relapse. Median survival in relapsed group was calculated from date of diagnosis to date of death. The radiotherapy dose, the number of primary chemotherapy cycles for relapse were recorded. Survival estimates were calculated using the Kaplan-Meier method and log-rank test. The Cox regression model was used to calculate the hazard ratio and 95% CI. Statistical analysis was performed with SPSS version 19. Because of the small sample size we combined our results for thymomas and thymic carcinomas.

Results

A total of 21 patients were identified in the

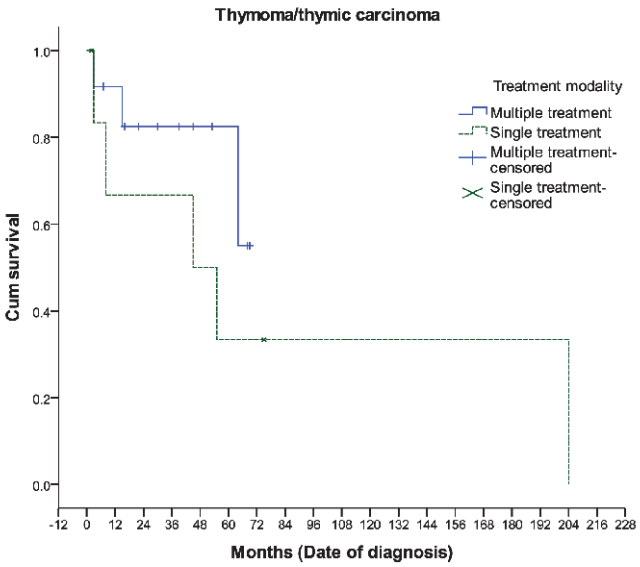

Figure 1. Survival associated with treatment modalities.

Table 1. Treatment of thymic tumors according to stage.

Stage	Resected margins	Treatment (n=number)	Patients	Diagnosis
I	R0	S	1	Thymoma
IIA	R0	S	1	Thymoma
	R1	S+RT	1	Thymoma
IIB	R0	S+RT	1	Thymoma
	R1	S+RT	1	Thymic carcinoma
	R2	S+RT	1	Thymoma
	R2	S+RT	1	Thymic carcinima
III	-	Observation	1	Thymoma
	-	CT	1	Thymoma
	R2	S	1	Thymoma
	R2	S+CT+RT	1	Thymic carcinoma
IVA	-	Observation	1	Thymoma
		RT	1	Thymoma
	-	RT	1	Thymic carcinoma
	-	S+RT	1	Thymic carcinoma
		S+RT	1	Thymic carcinoma
	-	CT+RT	1	Thymic carcinoma
	-	CT+S+RT	1	Thymic carcinoma
		CT+S+RT	1	Thymic carcinoma
IVB	-	CT+RT	1	Thymoma
	-	CT	1	Thymic carcinoma

S= Surgery; RT= Radiotherapy; CT= Chemotherapy

period from June 1990 to June 2011. The median age at diagnosis was 61 (26-81) years. Out of 21 patients, 8 (38%) had thymoma and 13 (62%) had thymic carcinoma. Twelve (57%) patients were males and 9 (43%) patients were females. Most of the patients presented with Masaoka stage IV disease (n=10, 48%). Of patients, 4 (19%) had stage III disease and 6 (28%) had stage II disease. Only one (5%) patient had stage I disease. Three patients each presented with metastatic disease in the pleura, lungs and axillary nodes. Median overall survival was 64 (2-204) months. Three (14%) of 21 patients had associated myasthenia gravis.

Multimodality therapy (chemotherapy and/or radiation therapy and/or surgery) were received by 12 (57%) out of 21 patients, 7 (33%) patients received single modality treatment for primary disease and 2 (9%) did not receive any treatment. Among the patients who received multimodality therapy, 3 patients received neoadjuvant chemotherapy. Surgery mainly involved a thymectomy in 9 patients for stages I, II, and III disease and partial resection in 4 patients with stage IV disease. Eight patients did not have surgery. R0 resection was achieved in 3 patients. R1 resection was accomplished in 2 patients, whereas R2 resection was achieved in 4 patients.

Decision about the treatment modality was mainly based on tumour stage. One patient in stage I had only surgery (R0). In stage IIA, one patient had surgery (R0) and another patient had surgery (R1) followed by radiotherapy. All 4 patients in stage IIB disease were treated with surgery followed by postoperative radiotherapy. In this group of patients, 2 had R2 resection and one each with R0 and R1 resection. Treatment of patients in stages III and IV disease varied from surgery alone (n=1), chemotherapy only (n=2), radiotherapy only (n=2), surgery and radiotherapy (n=2), surgery, chemotherapy and radiotherapy (n=3), chemotherapy and radiotherapy (n=2) and 2 patients did not receive treatment due to poor performance status. Four patients with stage IV disease received platinum-based combination chemotherapy (Table 1).

There were 10 (47%) patients who relapsed with a median time from primary diagnosis to

Table 2. Treatment of Relapse.

Masaoka stage	Initial treatment	Relapse site	Treatment for relapse	Time from diagnosis to relapse (months)	Diagnosis
I	S	Local	S+RT	104	Thymoma
II	S+RT	Bones	RT	26	Carcinoma
II	S+RT	Lungs	CT	14	Carcinoma
III	CT	Local	RT	12	Thymoma
III	S	Thorax	CT	42	Thymoma
IV	RT	Local	RT	41	Carcinoma
IV	S	Pleura	CT	10	Carcinoma
IV	CT+S+RT	Pleura+bone	CT	34	Carcinoma
IV	Observation		CT	55	Thymoma
IV	S+RT	Mediastinal l ymph nodes	RT	19	Carcinoma

S= Surgery; RT= Radiotherapy; CT= Chemotherapy

relapse of 28 months (10 to 104 months). Four patients relapsed locally and 6 relapsed with metastatic disease. All 4 patients with local relapse were treated with radiotherapy. In addition to radiotherapy 1 patient underwent surgical resection for localized disease. Five of 6 patients with metastatic disease received platinum-based combination chemotherapy. One patient with just bone metastases was treated with radiotherapy. Relapse was more common in patients with thymic carcinoma (n=6). Initial staging of 5 (50%) patients in the relapsed group was stage IVA; 2 patients each had initial presentations with stages II and III disease. One patient had stage I disease. According to Table 2, 6 out of 10 patients in the relapsed group that died had a median survival of 58 months (53 to 64 months).

Out of 12 patients who were treated with multimodal therapy, 9 (75%) remain alive with median follow up of 45 months. Of 7 patients who received single mode therapy, 5 (71%) died with a median survival of 45 (2 to 204) months (HR: 0.44; 95% CI: 0.1-2.0). Two patients who did not receive treatment died (Figure 1).

Overall median survival in 10 patients who died was 42 months (2 to 204 months). Our results showed that more patients survived after treatment with multimodal therapy compared to single modal therapy. These results should be interpreted with caution because of the small sample size. The reason for the small sample size was rarity of these tumours and collection of data from only one cancer centre.

Discussion

The mainstay of therapy for thymic tumours is complete surgical resection for early stage lesions. Complete resection of thymic carcinoma significantly increases the survival rate.[3-6] Therefore early diagnosis remains a key factor for improving the survival of thymic tumours following surgical treatment. Optimum treatment options remain unclear but literature search has revealed that multimodality approach offers better outcome. Our study reports similar results. The combined modality treatment allows prevention of local and distant recurrence and enhances long-term survival.

Kondo and Monden reported treatment modalities of 1093 patients with thymic tumours. Multimodality therapy was reported to be the preferred mode of treatment for these tumours. Most patients with stages I, II, III were treated with surgery followed by radiotherapy while patients in stage IV disease were offered chemotherapy in addition to surgery and radiotherapy.[16]

Neo-adjuvant chemotherapy can be beneficial in patients with invasive thymoma or thymic carcinoma who have measurable disease on imaging scans. It is effective in patients with unresectable lesions. It allows a higher incidence of complete resections and reduces the recurrence

rate improving survival.[17-19] Neo-adjuvant regimens are mostly cisplatinum based but cyclophosphamide, doxorubicin, vincristine, etoposide or epirubicin have also been used in different studies. Macchiarini and colleagues reported a 50% reduction of tumour size after three cycles of three weekly cisplatin, epirubicin and etoposide neoadjuvant chemotherapy in seven patients with advanced-stage thymic tumours.[18] There were two complete pathologic responses and complete resection was reported in four patients. All patients received postoperative radiotherapy (45 Gy after complete resection and 60 Gy in case of incomplete resection). An MD Anderson study on 22 patients with stages III and IVA thymoma reported a complete resection rate of 76% and complete pathological response in two patients. The five-year overall and disease-free survival rates were 95% and 77%, while at seven years it was 79% and 77%, respectively. In our study three patients received neoadjuvant chemotherapy. Of these, two achieved partial response and underwent surgical resection followed by adjuvant radiotherapy. Both of them were alive at the time of writing this paper, more than five years after treatment. The third patient progressed on neoadjuvant chemotherapy and died seven months after diagnosis.

Radiotherapy is usually not recommended in completely resected stage I thymic tumours and adjuvant radiotherapy for stage II disease is controversial.[17] Patients with macroscopic invasion of the capsule and surrounding mediastinal fat, or gross adhesions to the mediastinal pleura are at increased risk of recurrence and they can benefit from radiotherapy. Haniuda and colleagues have reported a recurrence rate within the mediastinum of 0% with radiotherapy versus 36.4% without radiotherapy in stage II disease.[20] In another study a recurrence rate of 29% has been reported for patients with resected stage II thymoma who did not receive adjuvant radiation therapy, compared with an 8% recurrence rate for those who had postoperative radiotherapy.[21] At stages III and IV, there is more evidence supporting the need for postoperative radiation therapy. Urgesi and colleagues have reported no local recurrence in 33 patients who had adjuvant radiotherapy after complete resection of stage III thymoma.[22] Monden and colleagues reported a recurrence rate of 20% after adjuvant radiotherapy compared to 50% in those without adjuvant radiotherapy among patients with stages III and IV thymoma. Most recurrences were outside the irradiated field. Some authors reported an 8% recurrence rate in stage II disease among patients treated with surgery and postoperative radiotherapy.[2, 21, 23] No difference in disease-free survival was reported between surgery alone and surgery followed by radiotherapy in an Italian study.[24] In our study only 1 (20%) out of 5 patients with stage II disease who received postoperative radiotherapy relapsed. This was in accordance with most other studies.

Studies on multimodality therapy for stages III and IV disease reported improvement in survival.[25-29] In our study 12 patients with stages II, III and IV disease received multimodal therapy. Three died with a median survival of 15 months. Nine (75%) patients are still alive with a median follow up of 45 months. There were 5 out of 7 patients who received single mode of therapy that died with a median survival of 45 months.

In summary, resectability and survival might be improved with multimodality treatment. Limitations to our study were small sample size and collection of data from a single centre however our results have shown that multimodal therapy is a better treatment option for patients with stages II, III and IV thymic tumours. Neoadjuvant chemotherapy improved resectability and adjuvant radiotherapy in stage II has prevented or delayed relapse. As mentioned previously, these results should be interpreted with caution because of the small sample size. There is a need for prospective randomized controlled studies to identify the optimal management of these tumours.

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