

Management of invasive thymoma at Groote Schuur Hospital, Cape Town

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Summary

Fifteen patients (median age 55 years; range 23 - 69 years) with macroscopic invasive thymoma or thymic carcinoma were treated at Groote Schuur Hospital between 1969 and 1988. Stage 3 (macroscopically invasive) disease was present in 12 patients (80%) and stage 4 (metastatic disease) in 3 (20%). Ten of the patients with stage 3 disease were treated by combined surgery and full-dose mediastinal irradiation; in 2 resection was not possible and they were treated with irradiation alone. One of the patients with stage 3 disease developed progressive thymoma (median follow-up 74 months). This patient and 2 others died; 1 from mediastinitis after surgery for thymic carcinoma and 1 of unrelated disease. Both patients treated by irradiation alone were free of disease at follow-up. In the patients with stage 3 disease, the relapse rate was 8% (crude) and the 5-year disease-free survival rate 86% (life table).

The patients with stage 4 disease received cisplatin-based combination chemotherapy, which was combined with further irradiation and debulking surgery in 2 of the 3 cases. These patients died of malignant disease at between 5 and 42 months, although 1 had a temporary response to chemotherapy.

Tumour extent is the most important prognostic factor in these patients. A multidisciplinary approach to therapy is required.

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Thymomas are the most common tumour in the anterior mediastinum. Although histologically bland and most often encapsulated, they may be invasive or, rarely, metastatic.¹ When the histological features of malignant disease are present, the term thymic carcinoma is used.¹ The patients with epithelial thymic tumours in the series reported below had macroscopic invasion into surrounding structures, such as the pericardium, great vessels and lungs.

The management of these tumours is controversial. At our institution management has been based on surgical excision or debulking, combined with mediastinal irradiation. Cisplatin combination chemotherapy has been used in recent years for patients with metastatic disease. A retrospective review was undertaken to evaluate the local pattern of disease and review the results of therapy of these tumours.

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Patients and methods

Fifteen patients with macroscopic invasive thymomas or thymic carcinomas were treated between 1969 and 1988 at Groote Schuur Hospital. The results of histological examination of these tumours were reviewed by one of the authors (R.C.).

The median age of the patients was 55 years (range 23 - 69 years). There were 7 men (47%). Seven of the patients were white (47%), 6 were of mixed race (40%) and 2 were black (13%). The patients were staged according to Table I: 12 were stage 3 (80%) and 3 stage 4 (20%). Their initial symptoms are shown in Table II. All patients had an anterior mediastinal mass. The 3 patients with stage 4 disease had pleural, pericardial and lung metastases, respectively. Metastases were diagnosed at the time of thoracotomy in 1 of the 3 patients.

TABLE I. STAGING SYSTEM²

Stage	Description
1	Macroscopic complete encapsulation, microscopic invasion into but not through the capsule
2	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura or microscopic invasion through the capsule
3	Macroscopic invasion into neighbouring structures, i.e. pericardium, great vessels or lung
4	Pleural or pericardial dissemination of metastases

TABLE II. CLINICAL SYNDROMES/SYMPOMS OF PRESENTATION

Presentation	No. of patients	%
Myasthenia gravis	3	20
Polymyositis	1	7
Superior mediastinal syndrome	2	13
Pulmonary symptoms, e.g. cough, chest pain or shortness of breath	7	47
Asymptomatic	2	13

Diagnosis was made by anterior mediastinotomy in 7 patients, by cervical mediastinoscopy in 1, by open biopsy in 3, and after resection in 4.

Thymomas consist of an admixture of cytologically bland epithelial cells and reactive lymphocytes.³ Occasional mitoses and cytological atypia are allowed. Three patients in this series (20%) were diagnosed as having thymic carcinoma on review on the basis of abundant mitoses, prominent nucleoli, vesicular nuclei with dispersed chromatin, markedly increased nuclear to cytoplasmic ratio and numerous foci of necrosis.⁴ All these patients had stage 3 disease. The thymomas in this series (12 cases) were categorised according to the predominant cell type into one of four histological subtypes: (i) predominantly epithelial (more than 50% epithelial cells); (ii) predominantly

lymphocytic (more than 50% lymphocytes); (iii) mixed (50% of each cell type); and (iv) spindle-celled. In this series the thymomas were epithelial in 5 patients (33%), lymphocytic in 3 (20%), mixed in 3 (20%) and spindle-celled in 1 (7%).

Treatment

In the patients with stage 3 disease, the planned therapy was combined surgery and full-dose mediastinal irradiation. Resection was possible in 10 of the 12 patients. The patients with stage 4 disease received cisplatin-based combination chemotherapy, which was combined with further irradiation and debulking surgery in 2 of the 3 cases.

The patients' tumours were explored for surgical excision in 14 cases overall; via median sternotomy in 9 and thoracotomy in 5 (4 right and 1 left). Excision was not attempted in 1 patient with stage 4 disease. Tumour excision or debulking was not possible at surgery in 2 of the patients explored because of mediastinal infiltration (both with stage 3 disease). Tumour was found at surgery to be adherent to the pericardium in 10 patients, pleura in 7, major vessels in 6, lung in 4, phrenic nerve in 3, sternum in 3, lung hilum in 2, oesophagus in 1 and the trachea in 1.

In the 12 patients undergoing resection (10 with stage 3 and 2 with stage 4 disease), gross tumour was known to remain at the termination of the procedure in 6 patients. Concomitant lung resection was performed in 4 cases and segments of major vessels were removed and reconstructed in 2 patients.

Irradiation was given in the stage 3 cases, pre- and post-operatively in 8 patients, and postoperatively only in 4. The 2 patients with stage 3 disease in whom resection was not possible, were treated with irradiation alone. Irradiation was via anterior and posterior portals on cobalt 60 with shielding of the spinal cord at tolerance. The total radiation dose was in the order of 50 Gy in 2,5 Gy fractions. Patients treated with pre-operative irradiation received 25 Gy pre-operatively and 25 Gy postoperatively.

Results

In the patients with stage 3 disease, 9 of 12 are alive and free of disease at a median follow-up of 74 months (range 12 - 224 months). In the stage 3 patients who died there was 1 post-operative death (see below), 1 from coincidental cardiovascular disease while free of thymoma at 9 months and 1 from progressive thymoma. This patient relapsed at 20 months with lung disease and died of malignant disease at 63 months. She had presented with an epithelial tumour and had debulking surgery and pre- and postoperative irradiation. In the patients with stage 3 disease, the relapse rate was 8% (crude) and the 5-year disease-free survival rate was 86% (life table).

One patient with thymic carcinoma and an extensive tumour, thought to be irresectable at the time of surgery, died after operation. A staphylococcal mediastinitis led to fulminant sepsis.

All the patients with stage 4 disease died of malignant disease between 5 and 42 months after diagnosis. One of these patients, with a spindle-cell tumour, had an objective response to chemotherapy, which was of 20 months' duration.

Discussion

Invasive epithelial tumours of the thymus are rare — only 15 cases were seen at our institution over a 20-year period. The most direct method of establishing the diagnosis is anterior mediastinotomy⁵ and this was the most frequently used method

in this series. Distant metastases are relatively rare in patients with thymomas. Three patients in this series had metastases at presentation (all intrathoracic) and 1 of the patients with stage 3 disease developed metastases during follow-up. This emphasises the importance of achieving local control with therapy.

The treatment of invasive disease is controversial. Total surgical excision is adequate for patients with stage 1 thymoma (non-invasive) with an anticipated 100% local control rate.^{2,5} This procedure is possible in some patients with invasive tumours but the reported rates of subsequent relapse, however, vary widely.⁶⁻⁸ It seems likely that local control rates are improved by the addition of full dose mediastinal irradiation. Curran *et al.*² have pooled the results from 7 studies and reported a 28% relapse rate for stage 2 and 3 thymomas treated by total excision alone and a relapse rate of 5% when this was combined with irradiation.

Patients whose tumours are not totally resectable are usually treated by irradiation. A number of small series have been reported in which prolonged disease-free survival was noted.⁹⁻¹¹ It is unclear, however, whether these patients should be treated by irradiation alone or irradiation combined with aggressive debulking surgery. Curran *et al.*² found in their series of 20 patients, 10 of whom had undergone postoperative irradiation after biopsy alone and 10 subtotal resection, no difference in mediastinal recurrence rate (20%) or overall relapse rate (40 - 50%).² We achieved local control in both patients treated with surgery followed by radiotherapy. Too few cases have, however, been treated by biopsy and irradiation alone and we therefore elect to continue with aggressive surgical tumour resection. This allows postoperative irradiation to be given with smaller treatment portals.

Irradiation may be given in a split course (pre-operatively and postoperatively) or in a single continuous course post-operatively. Pre-operative irradiation may facilitate surgery through tumour shrinkage and does not appear to cause increased complications. The known areas of tumour invasion should be marked with clips at surgery to facilitate radiation.

In this study of aggressive surgery where possible combined with mediastinal irradiation the relapse rate in patients with stage 3 disease was 8% and the 5-year disease-free survival rate was 86%.

The prognostic significance of histological subtypes has been the subject of considerable debate. Opinions vary from no correlation^{12,13} to studies showing that epithelial subtypes confer a poorer prognosis.^{3,14,15} It would seem from published reports and our series that capsular invasion together with intra-operative or biopsy evidence of spread (i.e. metastases) is the most important prognostic factor.¹ This far outweighs cell type, pleomorphism and mitotic count.

Chemotherapy has a role in patients with metastatic disease and responses may be seen.^{16,17}

This series supports the need for a multidisciplinary approach in treatment of patients with invasive thymic tumours.

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