

# Thymoma: A clinico pathological study of 21 cases and assessment of prognostic features

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**Summary.** This is a retrospective and comprehensive study of 21 cases of thymoma treated during a period of 30 years (1954-1984). The tumors were staged into 3 categories: stage 1 for encapsulated completely resectable tumor, stage 2 for nonresectable intrathoracic tumor and stage 3 for tumor with extrathoracic spread. According to their lymphocytic content tumors were separated into 3 groups: 1) predominantly epithelioid (PE); 2) mixed cellular (MC) and predominantly lymphocytic (PL). Incidence of recurrence and survival were correlated with various treatment modalities. The tumor occurred in all age groups with highest incidence in the fourth decade. Six cases were asymptomatic. Myasthenia gravis was present only in one case. The most important prognostic factor was the stage of the tumor. Five-year survival was 69% for stage 2 and 0% for stage 3. All 12 patients who died with evidence of residual disease had PE tumors. Lymphocytic participation might be indicative of a residual functional competence and appears to confer a more favourable prognosis. This is a tumor of uncertain malignant potential which should be excised or debulked, and staged. Post-operative radiotherapy appears to prevent recurrence and improve the prognosis in stage 2. No therapeutic benefits were seen in the stage 3 cases. The value of chemotherapy is uncertain.

**Key words:** Thymoma, Staging, Grading, Prognosis

## Introduction

Primary tumors of the mediastinum are uncommon, and thymoma heads the list as being the commonest of these tumors. Thymus is normally situated in the superior mediastinum, lying closely applied to the superior vena cava, phrenic nerve and upper part of the

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parietal pericardium. The tumor arising from thymus is primarily situated in the superior mediastinum and, depending on its size, may extend to the anterior mediastinum.

The term thymoma was originally used in a generic sense to describe any tumor arising in the thymus. Presently it is used in a narrower histogenetic sense by restricting it to tumors originating from the thymic epithelium (Bell, 1917; Mottet, 1964; Rosai and Levine, 1976). The neoplastic tissue is epithelial although a variable amount of lymphoid tissue may be associated with it. Various synonyms e.g. lymphoepithelioma are therefore considered obsolete. The clinical course may be prolonged, attended by recurrence, metastases, and may be complicated by the appearance of a second malignancy (Jain and Frable, 1974). The biological behaviour of this tumor is uncertain and shows no definite correlation with its histological appearance. The most striking feature of this tumor is the assortment of histological structures. Less commonly it may be totally monomorphic presenting diagnostic problems. The object of this study is to categorise the tumor according to its lymphocytic content, stage, and assess response to various treatment modalities with a view to determining factors influencing prognosis.

## Materials and methods

During the period 1954-1984 28 cases were treated for thymoma. The diagnostic criteria were based on the generally accepted concept that this tumor takes its origin from the thymic epithelium (Rosai and Levine, 1976). Six cases were considered as metastatic carcinoma and were excluded from this study along with one who died in early post-operative phase. The following parameters were examined with a view to detecting any prognostic trends.

Presenting clinical features, associated syndromes, complications and incidence of second malignancies were reviewed.

The extent of tumor was staged as follows:

stage 1: encapsulated tumor, completely resectable

stage 2: invasive tumor, but not extending beyond thorax

stage 3: tumor extending beyond thorax

Paraffin sections stained with hematoxylin and eosin were examined. Approximate percentage of lymphocytes in each tumor was assessed in 10 high power fields ( $\times 400$ ) and grouped into three categories: 1) predominantly lymphocytic (PL) when lymphocytes were in excess of 70%; 2) mixed cellular (MC) with lymphocyte population varying between 30 and 70% (Fig. 1); 3) predominantly epithelioid (PE) with lymphocytes less than 30% (Fig. 2). These histological assessments were performed blind by one of the authors (RSM).

There was considerable variation in therapeutic approach of the 21 patients entered into this study. Nineteen patients had surgical excision of the tumor followed by radiotherapy with doses varying from 1200 to 6000 rads. One patient had radiotherapy after a diagnosis mediastinoscopy while the other had no post-excision radiotherapy. In 3 cases post-operative radiotherapy was delayed until there was recurrence of tumor. Four patients received chemotherapy as well.

Autopsies were performed on 5 cases.

## Results

### Presenting clinical features

The incidence was slightly higher in the females, with a sex ratio of 4:3. The average age was 44. The youngest patient was 6 and the oldest 78. The highest incidence was in the 4th decade. In 6 cases the tumor was discovered

by routine chest X-ray. Six patients complained of symptoms related to local pressure such as heaviness in chest, substernal discomfort and pain. In 3 patients persistent cough was the presenting symptom. Recurrent bronchitis in a child led to the discovery of the tumor. Clinical presentations were generally non-diagnostic except when there were associated syndromes such as myasthenia gravis which was present only in one patient. Abdominal pain was the presenting symptom in 2 patients who were found to have intra-abdominal metastases.

### Stage and clinical outcome

Of 21 cases studied only one stage 1 tumor was found. He remained free of tumor until his death 27 years later, due to cerebro-vascular accident.

Sixteen cases (76%) belonged to stage 2 category. Eight patients (50%) from this group died with evidence of residual disease. Five of these patients (31%) died within 5 years, while the other three lived up to 12 years before succumbing to the disease. Two patients with no residual thymoma died of carcinoma of the cervix, and aplastic anemia. Six patients (37%) with one of them suffering from myasthenia gravis were alive and free of tumor.

All 4 patients in stage 3 category died of metastases within 28 months.

### Histopathology

In 14 cases (66%) tumors were of PE pattern. MC pattern was seen in 5 cases (23.7%) and PL pattern in 2 cases (Table 1). All 12 patients who died with evidence of

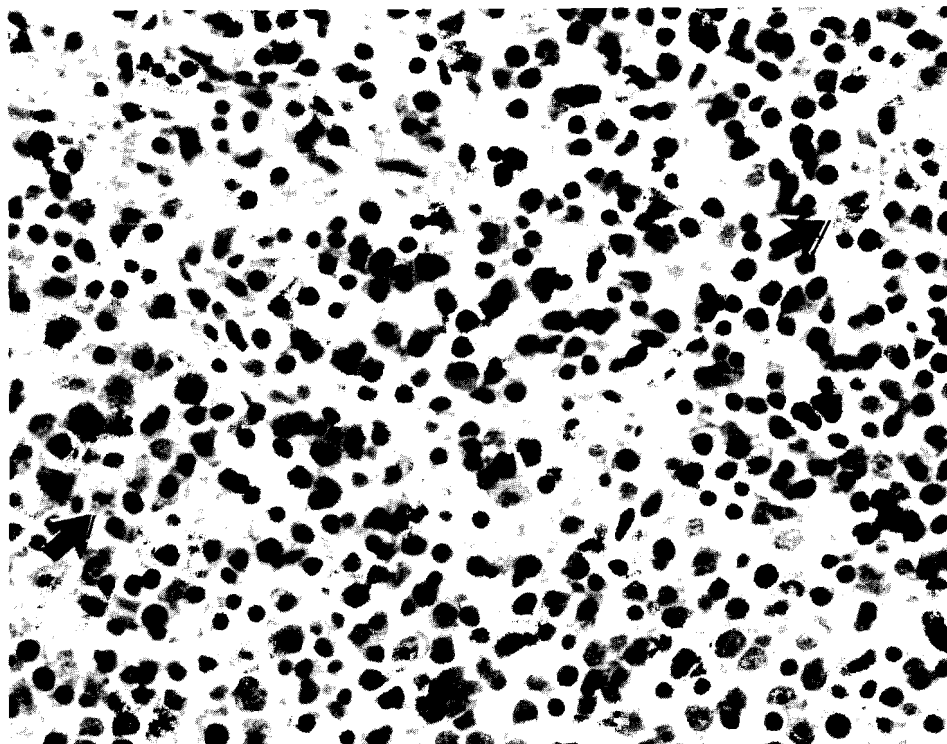
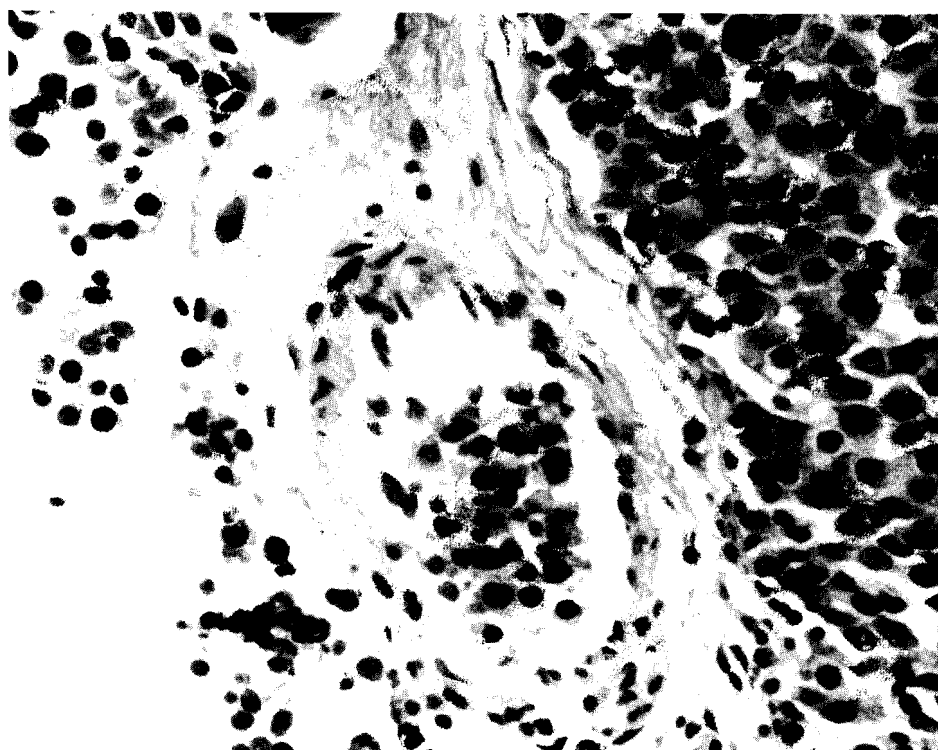


Fig. 1. Mixed cellular pattern (MC) consisting of both epithelioid cells and lymphocytes. Arrows indicate mitosis in epithelioid cells. H&E,  $\times 400$



**Fig. 2.** Tumor showing predominantly epithelioid pattern (PE) with vascular invasion. A close relation between epithelioid cells and lymphocytes appears to be present in the tumor embolus. H & E, × 400

**Table 1.** Relation between stage, histological type and survival.

Stage	Number of cases	Histological types* (number)	5-year Survival	10-year Survival
1	1	MC (1)	1	1
2	16	MC (4)	4	4
		PL (2)	2	2
		PE (10)	5	3
3	4	PE (4)	0	0

\* PE = predominantly epithelial; M = mixed cellular; PL = predominantly lymphocytic

**Table 2.** Distribution of treatment modalities and stages.

Treatment	cases	Stage 1	Stage 2	Stage 3
Surgery	2 (9.5%)	—	2	—
Radiotherapy	1 (4.7%)	—	1	—
Surgery and Radiotherapy	14 (65.8%)	1	11	2
Surgery, Radiotherapy, Chemotherapy	4 (18.8%)	—	2	2
Chemotherapy	None	—	—	—

disease, had PE tumors. Necrosis and increased mitoses were observed in tumors of stage 3 patients. No relation between the cell pattern and associated syndromes was evident.

### *Treatment*

Therapeutic approach varied a great deal. The most favoured approach was an excisional biopsy followed by radiotherapy (Table 2). The radiation dose varied from 1200 to 6000 rads. The stage 1 tumor was successfully irradiated by simple excision followed by radiation dose of 1244 rads. All 4 cases of recurrence had stage 2 tumor. Three of these patients had not received postoperative radiotherapy. Re-excision followed by 2600 rads of radiation prevented further recurrence. The fourth is a case of a 13-year-old girl who had a predominantly epithelioid tumor resected. The tumor recurred at the 7th and 12th year. Both were resected. Radiotherapy of 1200 rads and chemotherapy were given after the second recurrence by which time she was in terminal phase with metastases. The reluctance to give radiotherapy was probably influenced by her young age. An interesting contrast is the case of a 6-year-old girl who had a MC tumor resected and followed by 4500 rads of radiotherapy and chemotherapy (endoxan, actinomycin D). For 14 years she has been free from clinically detectable disease. Her physical and sexual development have apparently been within normal limits in spite of the heavy dose of radiation.

In stage 3 disease, both surgery and radiotherapy were of no benefit. The clinical state rapidly deteriorated in all 4 patients despite surgical debulking of the primary tumor and post-operative radiotherapy. Two of these patients also received chemotherapy with no apparent therapeutic benefit.

The overall survival was 43%. The leading cause of death was metastases which was observed in 5 cases. Metastases were more often found in the lower thoracic vertebrae and liver. Two patients died of sepsis. Other causes of death were cardiac tamponade, superior vena caval obstruction, aplastic anemia and lymphoblastic leukemia. Hypogammaglobulinemia was seen in one patient.

### **Discussion**

The major problem that confronts one, engaged in the study of thymoma, is the small number of cases that are available for such a purpose. In our cancer center only 21 well-documented cases were treated during the period between 1954-1984. In the references cited in this publication it appears that approximately 850 cases were studied in various major institutions during the past 20 years.

The diagnosis of thymoma is facilitated when a patient with myasthenia gravis is found to have an anterior or superior mediastinal tumor. Many of these patients are then referred to specialized centers. This selection of

cases probably accounts for the higher associated incidence of myasthenia reported by these centers. Bernatz et al. (1973) found myasthenia in 44% of 181 cases while Verley and Hollmann (1985) reported an incidence of 52% in 200 cases. We believe that the true incidence of myasthenia is less frequent. In our study the only case of myasthenia was found in association with a predominantly epithelioid thymoma. Thirty per cent of our patients were asymptomatic at the time of discovery of the tumor.

Histological diagnosis of thymoma is often difficult in the absence of the characteristic protean appearance especially when the tumor is composed entirely of epithelial cells. Multiple sampling might be necessary to demonstrate these features. For this reason we prefer an excisional biopsy, as it has diagnostic as well as therapeutic value.

The heterogenous pattern of the tumor may be explained by embryological considerations. The main pharyngeal component of the primitive thymus is a membrane consisting of ectoderm and endoderm with no intervening mesoderm (Patten, 1964). As it descends into the mediastinum the epithelial character is lost by incorporation of mesoderm. The three germ cell layer participation would explain the confusing array of histological presentation of a thymoma. The tumor may consist of patterns varying from monomorphic epithelial mass to a complex one consisting of glands, squamous epithelium, rosettes, cysts, etc. (Patten, 1964; Pascoe and Miner, 1976; Rosai and Levine, 1976). This complex pattern was evident in all 12 cases where the tumor pursued a relatively indolent course with survival exceeding 5 years. The monomorphic epithelial pattern was present in the tumors of all 9 patients who died within 5 years. In this context it is tempting to speculate that mediastinal teratoma, which has a benign outlook, belongs to the most differentiated end of this histological spectrum. A variable amount of lymphocytes is commonly found within thymoma. High lymphocytic content has been reported as a favourable prognostic feature (Bernatz et al., 1973). All five cases (24%) from our series with MC pattern and two cases with PL pattern survived five years.

It is possible that the presence of lymphocytes indicates some residual functional competence within the tumor and therefore an indirect evidence of a better differentiation. Thus, PL tumor could be graded as 1, MC as grade 2, and PE as grade 3.

Recent studies with monoclonal antibodies have shown several phenotypes among epithelial, lymphoid and mesenchymal cells of thymus (Van der Kwast et al., 1985). Cortical epithelium is HLA-DR antigen positive whereas medullary epithelial cells are HLA-DR negative. This heterogeneity in phenotypes would explain the apparent lack of correlation between histological appearance and biological behaviour including unexpected associated syndromes such as myasthenia gravis.

We believe that thymoma, regardless of its size or state of encapsulation, should be treated as a malignant

tumor. In 1962 Lattes following his analysis of 107 cases, concluded that gross features were more important than histology in assessment of the prognosis. Subsequent publication (Mottet, 1964; Batata et al., 1974) and our impression are essentially in agreement with this contention.

We found it useful to stage the extent of tumor. In our series complete encapsulation (stage 1) was found only in one patient who lived 27 years free from tumor. Stage 2 was the commonest form of presentation. In this stage the tumor is found attached to the neighbouring structures such as pleura, lung, and pericardium. The margins of the tumor often show varying amounts of fibrous tissue. It is not uncommon to find small islands of viable tumor within this fibrous wall, thus probably contributing to recurrence following excision of an apparently encapsulated tumor. Postoperative radiotherapy would seem to be effective in destroying these remnants of this radiosensitive tumor. In our series the incidence of recurrence was higher when radiotherapy was either omitted or delayed (Table 2). It appears that true encapsulation is infrequent and complete excision of the tumor is seldom possible. The figures for this attribute of the tumor vary from 7% (Rosai and Levine, 1976) to 50% (Bergh et al., 1978). In our series 31% of the patients with stage 2 disease died within 5 years. We believe the prognosis in stage 2 can be significantly improved if an incisive therapeutic approach is undertaken. The tumor should be debulked and followed by radiotherapy (Chahinian et al., 1981; Arriagada et al., 1984). Extension of tumors beyond the thorax (stage 3) significantly reduced the survival. All 4 patients of this group showed little response to various treatment modalities and succumbed to the disease within 28 months.

This is an uncommon tumor and any study will inevitably be based on a collection of cases spread over a very long period. The treatment modalities will be heterogeneous causing difficulties in forming conclusions. A collaborative study of recent cases involving several institutions would be worth while.

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