MALIGNANT THYMOMA – A STUDY OF 30 CASES

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SYNOPSIS

Malignant thymoma is a rare tumour. This article examines a series of 30 patients with malignant thymomas treated at the Radiotherapy Department, Singapore General Hospital, between 1981 and 1985. All the cases except one were treated by radiotherapy. The actuarial survival of this series at 5 years was 32.1%.

The criteria for malignancy include the surgical finding of invasion or the presence of metastases. All the cases were either lymphoepithelial or epithelial in nature, there being no case of lymphocytic thymoma. The various prognostic factors are discussed. The presence of symptoms other than myasthenia gravis and an invasive or remnant tumour after surgery were the most important factors.

Key Words: Radiotherapy, Prognostic Factors.

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INTRODUCTION

Malignant thymoma is a rare disease with an incidence locally of less than 10 cases a year. In a recent review from the Mayo Clinic which looked at 283 cases of all thymomas, 93 were classified as malignant. Their series was collected over a period of 40 years from 1941 to 1981 (1).

The fascinating aspect of this tumour is the difficulty in classifying it as malignant based on the histology alone. It requires the help of the clinician and surgeon to provide the evidence that it is malignant (1). It must have evidence of either metastases or of invasion. Various authors have expressed frustration over predicting the prognosis of patients with thymomas (1) because of the poor correlation with the histology. Recent articles looked at prognostic factors that will eventually streamline treatment (1,2). A more aggressive approach can be used for those patients with poor prognostic factors. Yet another interesting aspect of thymomas is the association with various autoimmune phenomena besides myasthenia gravis.

Our patients were referred to the Radiotherapy Department based on the following criteria:

1) Invasion of surrounding structures;
2) Presence of metastases either intra- or extra-thoracic; and
3) Histological evidence of malignancy.

The last point may have resulted in the inclusion of cases of what is termed "thymic carcinoma" and these tumours have a very poor prognosis.

MATERIALS AND METHOD

The medical records of all cases of malignant thymomas seen at the Radiotherapy Department, Singapore General Hospital between 1981 and 1985 were reviewed. Six cases were referred initially as thymomas. Of these six patients, two had no histological confirmation. Two had doubtful histology and, upon review and other clinical evidence, one was re-classified as a lymphoma and the other a germ cell tumour. One patient had a metastatic mucinous carcinoma and one was a carcinoid tumour of the thymus.

The remaining cases were referred primarily from the cardiothoracic unit in the hospital with some cases from the private sector and some from overseas. The total number of patients included in this study is 30. However, two patients were excluded from the survival analysis as they returned overseas, but their operative and histological findings were included.

Of the 30 patients, one received only chemotherapy consisting of intravenous cisplatinum, adriamycin and cyclophosphamide. This patient had concomitant Chronic Lymphocytic Leukaemia. She also had liver and bone metastases.

The rest of the patients were treated by radiotherapy using anterior and posterior parallel opposing fields or with a single anterior field (Table 1.) Megavoltage irradiation was given, using either the 10 MeV Linear Accelerator or Cobalt machine.

Eight patients were treated with a 250 cGy fractionation to a total dose of between 3000 to 5000 cGy. Nineteen patients were treated with the conventional fractionation of 180 to 200 cGy to a total dose of between 4000 to 5000 cGy. One patient was incompletely treated to a dose of only 900 cGy while there were no data for another patient. The dose prescribed was to the midplane or to the tumour volume.

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TABLE 1
DISTRIBUTION OF TREATMENT FIELDS AND TOTAL DOSE

	Anterior Field only	Anterior/Posterior Fields	Total
< 5000 cGy	2	12	14
> 5000 cGy	2	12	14
Total	4	24	28

RESULTS

Clinical Features

Table 2 shows the age distribution of patients with malignant thymomas. It is a disease of middle age with a peak incidence at between 40 and 60 years. It is extremely uncommon in childhood.

Table 3 shows the ethnic and sex distribution. There is a predominant number of Chinese. There is also a larger number of males.

Table 4 shows the distribution by sex of patients presenting with myasthenia gravis. Forty one percent of the males presented with this syndrome.

Other symptoms at presentation included chest pain, (16.7%), cough (13.3%) and chest symptoms such as breathlessness and tightness of chest (43.3%). Incidental finding on chest radiograph accounted for only 10% of the cases. Symptoms other than myasthenia gravis play a part in prognosis, (Table 5).

TABLE 2
AGE AND SEX DISTRIBUTION

	Male	Female	Total
0- 9 years	0(0%)	0(0%)	0(0%)
10-19 years	0(0%)	0(0%)	0(0%)
20-29 years	2(9.1%)	0(0%)	2(6.7%)
30-39 years	2(9.1%)	2(25.0%)	4(13.3%)
40-49 years	9(40.9%)	2(25.0%)	11(36.7%)
50-59 years	6(27.3%)	0(0%)	6(20.0%)
60-69 years	3(13.6%)	4(50.0%)	7(23.3%)
TOTAL	22(100%)	8(100%)	30(100%)

Gross Pathology and Histological Features

Table 6 shows the distribution of sites of invasion by histological types. The commonest findings at surgery are invasion of the lung and pleura (60%), pericardial invasion (46.6%) and venous involvement (40.0%). Three patients had no invasion on surgical findings but were referred because of deficient capsule in one patient, malignant elements in another patient and a fairly large tumour with an almost entirely epithelial histology in the third patient.

Table 7 shows the various histological types. Most of the cases were lymphoepithelial in nature (63.3%). There were eight cases of epithelial histology (26.7%) and three cases described as malignant thymomas. No lymphocytic histology was reported in our series. Various authors (3, 4) have classified these tumours, and the simplest consists of lymphocytic, epithelial, and lymphoepithelial.

It is unusual to find metastases outside the thoracic cavity in malignant thymomas, (Table 8). Of the four patients who had extra-thoracic metastases, one had bone and liver metastases together with pleural effusion at presentation. She also had a mediastinal mass and biopsy of the pleura showed a metastatic lymphoepithelial tumour. Two patients presented subsequently with bone metastases: one had epithelial histology and the other was diagnosed as malignant thymoma. The fourth patient had liver metastases with an epithelial histology.

TABLE 3
ETHNIC DISTRIBUTION BY SEX DISTRIBUTION

	Male	Female	Total
Chinese	19(86.4%)	8(100%)	27(90.0%)
Malay	1(4.5%)	0(0%)	1(3.3%)
Indian	2(9.1%)	0(0%)	2(6.7%)
Others	0(0%)	0(0%)	0(0%)
TOTAL	22(100%)	8(100%)	30(100%)

TABLE 4
PRESENCE OF MYASTHENIA GRAVIS BY SEX DISTRIBUTION

	Male	Female	Total
Myasthenia Gravis	9(40.9%)	1(12.5%)	10(33.3%)
No Myasthenia Gravis	13(59.1%)	7(87.5%)	20(66.7%)
TOTAL	22(100%)	8(100%)	30(100%)

TABLE 5
SYMPTOMS OTHER THAN MYASTHENIA GRAVIS BY SEX DISTRIBUTION

	Male	Female	Total
Chest pain	5(22.7%)	0(0%)	5(16.7%)
Cough	2(9.1%)	2(25.0%)	4(13.3%)
Chest symptoms	6(27.3%)	7(87.5%)	13(43.3%)
Incidental	3(13.6%)	0(0%)	3(10.0%)
TOTAL NO. OF PATIENTS	22	8	30

TABLE 6
SITES OF INVASION BY HISTOLOGICAL TYPES

	Epithelial	Lympho-epithelial	Malignant Thymoma	TOTAL
Effusion	2	2	1	5(16.7%)
Pericardial	4	8	2	14(46.7%)
Lung, pleura	4	12	2	18(60.0%)
Vein	5	5	2	12(40.0%)
Aorta	1	3	1	5(16.7%)
Bone	2	2	1	5(16.7%)
Incidental finding	—	3	—	3(10.0%)
Unknown	1	—	—	1(3.3%)
TOTAL NO. OF PATIENTS	8	19	3	30

TABLE 7
DISTRIBUTION OF HISTOLOGY BY SEX

	Male	Female	TOTAL
Epithelial	5(22.7%)	3(37.5%)	8(26.7%)
Lympho-epithelial	15(68.2%)	4(50.0%)	19(63.3%)
Malignant Thymoma	2(9.1%)	1(12.5%)	3(10.0%)
TOTAL	22(100.0%)	8(100.0%)	30(100.0%)

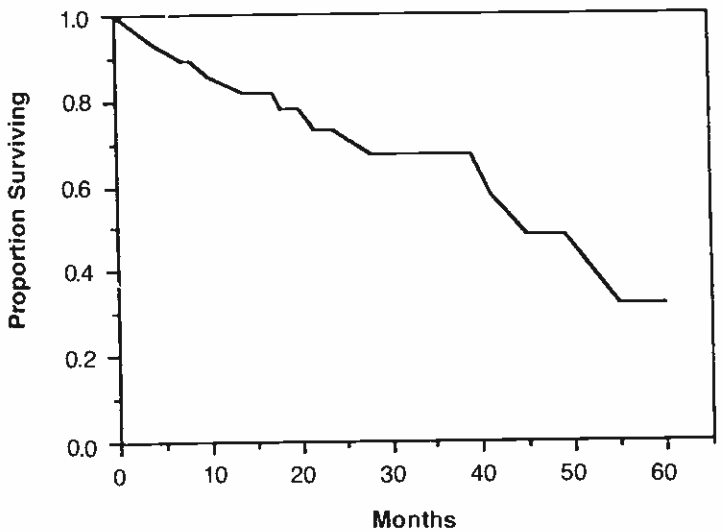
TABLE 8
SITES OF EXTRA-THORACIC METASTASES

Patient 1	Bone
Patient 2	Bone
Patient 3	Bone, liver
Patient 4	Liver

SURVIVAL

The median follow up for the 28 patients in our series was 26 months. The actuarial survival was 32.1% at 60 months. (Fig. 1.) The survival dating from the time of histological proof of diagnosis has been calculated by the life-table method (Kaplan Meier). Myasthenia gravis as a cause of death has not been regarded as intercurrent deaths in this series. Although two patients were excluded because of short follow up times due to their return overseas, one patient who died at four months while on treatment had been included. She was initially diagnosed as malignant thymoma which was well encapsulated and was sent to the Radiotherapy Dept. four months after surgery because of worsening myasthenia gravis. She was started on irradiation but had only 900 cGy when she developed respiratory complications secondary to myasthenia.

Fig. 1 — Survival Curve of Patients



DISCUSSION

The rarity of malignant thymoma makes a definitive conclusion about the treatment policy difficult. The recent large series from the Mayo clinic (1) included all thymomas regardless of their malignant potential. Attention was drawn to several prognostic factors similar to the findings from the Christie Hospital (2), with its series of 26 patients. Patients who are referred for radiotherapy are already selected for having a poorer outlook.

The median age of patients with this tumour is 50 years. (2, 5) It generally occurs in the age group 40-60 (6). Less than 10% of thymomas occur in patients before 20 years of age (7). Up to 1979, there were only 22 reported cases of thymomas in children. (8, 9)

Although the numbers are small, we have a predominantly larger number of Chinese (90%). The sex ratio in our series is 3:1. The series of malignant thymomas from the Christie Hospital also shows a male predominance of 3:2 (2). Other series which include all thymomas show an almost equal sex ratio (1, 5). Perhaps if malignant thymomas are analysed separately, a difference in sex ratio may become more apparent.

Myasthenia gravis as a presenting symptom occurred in one third of our patients. It occurred in 41% of our males and only 12.5% of the females. Generally, about 80% of myasthenia gravis will have an abnormal thymus. Fifteen percent of these will be a thymoma while the rest (i.e. 85%) will be thymic hyperplasia (10). The presence of thymoma in a patient with myasthenia gravis carries a poorer prognosis (11), but the corollary is not true. Thymoma patients who have myasthenia gravis do not have poorer prognosis than those who are not myasthenic (12). Two other common autoimmune associations are red cell aplasia and hypogammaglobulinaemia. One of our patients had Systematic Lupus Erythematosus.

The age of patients with myasthenia gravis and thymomas is older than myasthenic patients without thymomas. Thymomas in patients with myasthenia gravis are usually smaller than those in non-myasthenic patients possibly because they are brought to the attention of the physicians earlier (6).

Other symptoms including chest pain, chest discomfort, cough and dyspnoea not due to myasthenia gravis are important prognostic factors. The best prognosis are those with tumours found incidentally. Symptoms as a prognostic factor were analysed in the Mayo Clinic series by multivariate analysis and were discovered to indicate a poorer prognosis.

Among the most important prognostic factors is the presence of invasion. (1, 13) Patients with invasion or metastases were weighted for a poorer prognosis amongst all thymomas in a recent series. In our cases, only three did not have invasion as a surgical finding and were referred for other reasons. These three patients on follow up at 8, 18 and 58 months showed no evidence of disease. In fact, of these three patients, two were discovered incidentally on routine chest radiographs. They highlight findings in other studies that the presence of invasion with remnant tumour left behind carried a much poorer prognosis.

Histology is the one criterion which has caused some confusion. As the histology does not usually show the typical findings of malignancy, there is difficulty classifying the thymoma as a malignant tumour. Secondly, varying amount of epithelial elements, lymphocytic elements and combinations of both may be used to classify the types of thymomas. As such, most studies have concluded that the various elements that make up the tumour do not help in prognostication. Even tumours with the spindle cell variant are not more aggressive (14). There also appears to be no correlation with autoimmune phenomena. Two studies did indicate that the epithelial type had a poorer prognosis (1, 15), but it did not add to the other known factors such as invasion or symptoms at presentation in indicating a poorer outcome (1). Up to 1976, only 30 reported cases of blood-borne metastases to extra-thoracic sites have been documented. (3). These involved organs include liver, bone, kidneys and brain.

The tumour lies in an area where there are many normal structures and radiotherapy to these tumours requires great care in avoiding these normal tissues. Some of the structures include the lung, the pleura, the heart and the spinal cord. It is best to give radiation in conventional fractionations as these tumours are sometimes slow growing and the detrimental late effects of radiation are best avoided. Eight patients received a slightly larger fractionation of 250 cGy. No undue side effects were apparent after a period of up to five years follow up in some of these patients. Since we have not used unduly large fraction size nor a high total dose, we would not expect more than the usual late side effects.

The total dose used from 4000 to 5000 cGy depending on field and fraction size. The total dose was limited primarily by the presence of normal structures. No planned fields avoiding the spinal cord were made and thus the total dose was to spinal cord tolerance levels. It was generally felt that the dose was also adequate to control microscopic disease as well as small macroscopic disease left behind at surgery.

There has been a proposal to use a larger field size because of local recurrences occurring outside the present usual treatment fields. Hemithorax irradiation has been proposed and the total dose of 15 cGy given in 15 fractions over 17 to 19 days has been proposed (16).

Chemotherapy has also been tried on malignant thymomas and a cisplatinum-based combination is the usual regime. (17-20) Various combinations have been used with partial or complete responses, but generally recurrences occur. As such, radiation has been used to consolidate some of these gains or has been used where extensive tumour has been shrunken by chemotherapy and a higher radiation dose could be given to a smaller area.

The survival of our series is not unlike that seen in a series from a radiotherapy centre where cases were referred because of invasion, remnant tumour or metastases. No attempt was made to exclude intercurrent deaths in our data although they are expected to occur in these patients who have concomitant autoimmune disease (5, 13). It compares favourably with this series from the Christie Hospital, which reviewed its 26 cases between 1965 and 1981 (2). Their overall uncorrected survival was 26% at 5 years; survival corrected for intercurrent death at 5 years was 35%.

CONCLUSION

The thymoma is a very interesting tumour which presents problems in diagnosis as a mediastinal mass. Unfortunately, it is rare and data about the natural history of these tumours and the effects of treatment are scanty. Although the tumour is generally radiosensitive (16, 21-23), failures have occurred outside the field. Perhaps the use of hemi or whole thorax irradiation may be useful. The surgeon also plays a very important part as near complete removal of these growths makes controlling them with lower doses easier. Even lower doses may be used for microscopic disease in the mediastinum, because the proposed hemithorax irradiation uses low doses which are effective for extra-thoracic microscopic disease. The scheme of determining prognosis based on various factors is also a useful contribution. Perhaps those tumours with an extremely poor outlook could be treated differently with an effective chemotherapy combination and consolidation by radiotherapy.

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