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RADIATION THERAPY IN THE MANAGEMENT OF MALIGNANT THYMIC TUMORS

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Thymic tumors were described by COOPER in 1832 and VIRCHOW in 1890. About 300 cases were published up to 1947 and more than 700 cases up to 1976 (LE GOLVAN & ABELL 1977).

Confusion concerning these tumors derives principally from their low incidence and from difficulties in histopathologic classification. The first classifications were proposed by MATRAS & PRIESEL (1928), WORMS & KLOTZ (1935), ANDRUS & FOOT (1937), and BUSINCO (1938)—quoted by BARIETY & COURY (1958). Since then, attempts at simplification have been made by CASTLEMAN (1955), THOMSON & THACKRAY (1957), LATTES & JONAS (1957), and RENAULT (1968).

Several authors have tried to estimate the prognostic indicators, all agreeing that the single most important factor is the extension of the tumor outside the organ (LATTES 1962, LEGG & BRADY 1965, BERNATZ et coll. 1973, BATATA et coll. 1974, SALYER & EGGLESTON 1976, LE GOLVAN & ABELL). Another factor could be the association with a general syndrome, especially myasthenia gravis (LATTES, BERNATZ et coll., BATATA et coll.).

The results of treatment vary in published series, which may be explained by the confusion mentioned. However, all authors agree that surgery is the most important single therapeutic procedure in the management of thymic tumors.

In the series now presented the histopathologic material has been reviewed. A simplified classification of thymic tumors is proposed. The therapeutic

results and the complications observed have made possible an attempt to define the role of radiation therapy in the management of these tumors.

Material and Methods

Histopathology. The material consisted of 24 patients treated at this Institute from 1966 to 1979, including 4 malignant lymphomas confined to the thymus. One source of confusion is the term thymoma itself. The thymus is formed by lymphocytic and epithelial cells. Tumors derived from the lymphocytes are malignant lymphoma while tumors derived from the epithelial cells are carcinoma. The malignant tumor has a monoclonal origin and in fact no mixed tumors exist. Lymphocytic infiltration of some carcinomas is a reactive phenomenon. Therefore, no specific tumor is derived from the thymus; the microscopic types of tumors found in the thymus are also found elsewhere and the term thymoma should be avoided.

Following this concept, a simple classification was used, that divides these tumors into two major categories: benign tumors or pseudo-tumors of the thymus, which are not dealt with in the present context, and malignant thymic tumors (Table 1).

The 4 malignant lymphomas, including 3 cases of Hodgkin's disease (formerly called granulomatous thymoma) have been excluded. The remaining 20

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Accepted for publication 5 March 1981.

Table 1*Classification of thymic tumors*

	No. of cases
Benign thymic tumors	
Pseudo-tumors	
Thymic hyperplasia	
Pseudo-cyst	
Benign tumors	
Thymolipoma	
True cyst	
Malignant thymic tumors	
Malignant lymphomas	
Non-Hodgkin's lymphoma	1
Hodgkin's disease	3
Carcinoma	
Undifferentiated carcinoma	7
Poorly differentiated carcinoma with lymphocytic infiltration (lymphoepithelioma or UCNT)	10
Large cell carcinoma (pseudoseminoma)	1
Pseudosarcomatous carcinoma (spindle-cell carcinoma)	—
Pseudo-carcinoid	—
Secondary tumors	
Germinal tumors of the anterior mediastinum	
Seminoma	2
Choriocarcinoma	—
Malignant teratoma	—
Rare	
Carcinoid	—
Embryonal rhabdomyosarcoma, etc.	—

Table 2

Distribution of symptoms in malignant thymic tumors. Due to the small number of cases in each group, the percentages within parentheses are intended as guidelines only

	No. of cases
Symptoms	
Thoracic pain	6 (30)
Dyspnea	5 (26)
Cough	5 (26)
Fever	5 (26)
Obstruction of superior vena cava	4 (21)
Loss of weight	3 (16)
Dysphagia	2 (10)
Hoarseness	2 (10)
Asymptomatic	4 (21)
Associated syndromes	
Myasthenia gravis	1
Erythroblastopenia	1

Table 3*Malignant invasive thymic tumors. Sites of tumor involvement*

Site	No. of cases	Alive without evidence of disease
Pleura	9	4
Pericardium	4	1
Lung	4	2
Neck	4	3
Chest wall	2	0
Trachea	1	1

cases (10 males, 10 females) include 7 undifferentiated carcinomas, 10 poorly differentiated carcinomas with lymphocytic infiltration (these tumors being microscopically identical with the so-called lymphoepithelioma of the Waldeyer's ring and designated in modern nomenclature as UCNT—undifferentiated carcinoma of the nasopharyngeal type), one large cell carcinoma or pseudo-seminoma and 2 true seminomas. No spindle cell carcinoma was included in the present series.

Clinical findings. The age distribution ranged from 18 to 72 years (mean 40 years). The delay between the onset of symptoms and the diagnosis varied between one and 5 months, with an average of 2 months, one patient with symptoms of myasthenia gravis 5 years before the diagnosis not being taken into account.

Of the 20 patients, only 2 had an encapsulated tumor. This term is synonymous with benign thymoma, for some authors. In fact, these tumors are true carcinoma (one undifferentiated carcinoma and one UCNT). It seems preferable to use the term encapsulated tumor as opposed to invasive carcinoma.

The patients were operated upon whenever it was possible; postoperatively, invasive tumors were irradiated. Unresectable tumors were given radiation therapy alone.

The 2 true seminomas were invasive and could not be completely resected. Sixteen were invasive carcinoma. Complete resection was possible only in 3 of them and 8 were unresectable. This fact reflects the general recruitment of this Institute which mostly receives patients with advanced malignant tumors referred from general hospitals for supplementary treatment.

Table 4

Local recurrences in 7 malignant thymic tumors. UC = Undifferentiated carcinoma. UCNT = Undifferentiated carcinoma of the nasopharyngeal type. RT = Radiation therapy. S = Surgery. CT = Chemotherapy

Microscopy	Macroscopy	Treatment	Dose (Gy)	Treatment-recurrence interval	Comments
UC	Unresectable	RT+CT	45	6 months	Died from recurrence and radiation pneumonitis
UC	Invasive	CT	-	11 months	Probably uncontrolled by RT. Died from distant metastasis
UC	?	RT	30	19 years	Uncontrolled by second RT
UC	Unresectable	RT	45	0	Uncontrolled
UCNT	Invasive	S+RT	50	4 months	Field-border recurrence. Local control after second RT. Died from complications
UCNT	Encapsulated	S	-	6 years	Control after second S+RT
UCNT	Unresectable	CT	-	0	Uncontrolled

The relative frequency of symptoms appears in Table 2. Four patients were asymptomatic and in the whole series only one patient had myasthenia gravis.

The relative frequency of tumor extension for invasive tumors is given in Table 3. The structure most commonly involved is the pleura.

Most of the patients (16/20) were irradiated because they had locally advanced tumors. In 9 of 16 cases a combination of high energy roentgen rays and electrons of convenient energy was used. The volume generally irradiated was the mediastinum plus the supraclavicular nodes with the doses to the mediastinum lying between 40 and 55 Gy.

Results

Clinical response. Most of the patients with invasive tumors were treated by combined surgery and irradiation. Complete clinical regression was always obtained in these cases. Complete regression was also obtained in 5 of the 7 patients with unresectable tumors who were treated by radiation therapy alone.

Chemotherapy was primarily used in 2 patients because a diagnosis of malignant lymphoma had firstly been proposed but without response.

Local recurrence. Seven local recurrences occurred: 4 of the 7 cases with undifferentiated carcinoma and 3 of the 10 with UCNT (Table 4). The original tumors were advanced and only 2 benefited from surgery. One patient had an encapsulated tumor and was primarily treated by surgery alone. Recurrence

occurred 6 years after the treatment and was controlled by a second operation and postoperative radiation therapy. In one patient who received radiation therapy alone the recurrence occurred 19 years after the initial treatment.

Local control at 2 years. The highest proportion of long term control (6/7) was observed in the group of invasive carcinoma treated by surgery and postoperative irradiation. Two of 4 patients given radiation therapy alone are controlled at 2 years, but in 3 other patients the follow-up is too short to permit a conclusion.

Survival. Sixty per cent of the whole series survived at 5 years, 78 per cent of the UCNT cases, and only 36 per cent of the cases with undifferentiated carcinoma (Fig. 1). However, due to the small number of patients, this difference is not significant ($p=0.12$).

Patients treated by surgery and postoperative irradiation or by irradiation alone have the same survival up to 3 years (Fig. 2). However, the numbers are too small to allow a significant conclusion.

Long term survivors did not present signs and symptoms that were considered as indicators of poor prognosis by BATATA et coll.

No evidence was found that age could be a prognostic factor.

Cause of death. Associated syndromes at the time of diagnosis were rare (2 cases). Most of the patients died of local problems including therapeutic complications. Only one death was caused by distant metastases. Another patient is still living with dis-

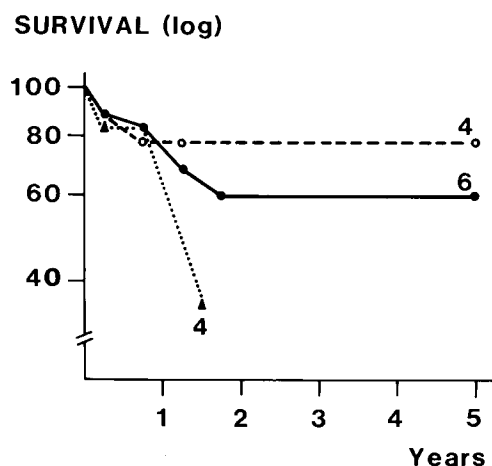


Fig. 1. Actuarial survival (in per cent). UCNT (---). UC (···). Overall (—).

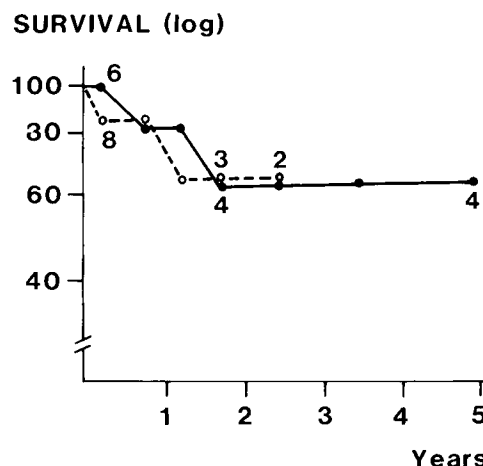


Fig. 2. Actuarial survival (in per cent) following irradiation alone (---) or irradiation combined with surgery (—).

Table 5

Review of the literature on malignant thymic tumors

Reference	No. of cases	Invasive tumor (per cent)	Complete resection (per cent)	Local recurrence (per cent)	5-year survival (per cent)
BATATA et coll. (1974)	18	0	100	0	83
LUOSTO et coll. (1977)	19	10	90	10	84
LE BRIGAND (1973)	38	100	76	?	60
LE GOLVAN & ABELL (1977)	46	43	50	26	65
PENN & HOPE-STONE (1972)	15	100	47	?	66
GEREIN et coll. (1978)	17	100	35	53	58
BATATA et coll. (1974)	36	100	30	75	54
Institut Gustave-Roussy (1979)	18	100	16	33	45
PONS et coll. (1977)	12	100	8	66	11

tant metastases. Both of them had undifferentiated carcinoma.

Complications. Two major complications observed following doses of 45 and 50 Gy may be explained by the large volume of lung tissue irradiated at high doses. These patients developed severe pneumonitis, one of them also pericarditis in a complex clinical picture with uncontrolled local disease. The latter case had no evidence of recurrence at necropsy. This patient had been irradiated three times because of uncontrolled and life-threatening disease: an advanced thyroid infiltration with tracheal constriction and asphyxia needed a tracheostomy. The mediastinum and a large volume of the left lung received 50 Gy in 42 days. The initial diagnosis was malignant lymphoma, but when the slides were reviewed a UCNT of the thymus was

diagnosed. In 2 of 4 patients given 55 Gy to the mediastinum, clinical pneumonitis occurred, responding to corticosteroid treatment. Two other lung complications were revealed only at radiologic examination, without clinical manifestation.

The overall clinical complication rate was 33 per cent.

Discussion

Tumors derived from the thymus are not specific to this organ. At microscopy, the normal thymic tissue is recognized, but on a cytologic basis it is not possible to discriminate whether or not the malignant tumor is of thymic origin. The diagnosis in these cases should be supplemented with the history and the clinical and surgical findings. The thymus is

an organ and it seems that the term thymoma is misleading, as would be such terms as uteroma or brainoma. Furthermore, some authors include non-neoplastic disease such as thymic hyperplasia under the term benign thymoma. Consequently, the term thymoma is not used in this review, in order to avoid confusion still present in current literature.

Five-year survival, in different published series, varies between 11 and 83 per cent and the crude 5-year survival for invasive tumors in the present series is 45 per cent. These differences are easily explained when the percentage of complete surgical resection is taken into account (Table 5). The lower the percentage of complete resection, the lower is the 5-year survival and the higher is the percentage of local recurrence. In the present series the percentage of complete resection is low, 16 per cent, but the percentage of local recurrence is moderate: 33 per cent. In fact, the local control at 2 years is 72 per cent. This relatively high rate of local control may be explained by the use of radical irradiation, whether associated or exclusive. This figure confirms that the single most important prognostic factor in the tumors of the thymus is the extension to the mediastinum. Related to this factor is the possibility of complete surgery. This is an additional fact to consider in comparing different treatment results.

Only one case in the present series was associated with myasthenia gravis.

The results suggest that UCNT could do better than undifferentiated carcinoma. This fact is also suggested by other series (JAIN & FRABLE 1974, LE GOLVAN & ABELL), but the correlation is probably weak (LATTES, LEGG & BRADY).

The treatment of choice of thymic tumors is surgery as complete as possible. In fact, surgery permits the histopathologic diagnosis, determination of the extension of the disease, and it is the single most important therapeutic procedure in the management of these tumors.

The present data suggest that when the tumor is invasive, even if completely removed at surgery, postoperative radiation therapy is indicated. The volume to be treated should be the mediastinum, the supraclavicular nodes and all the thoracic extensions found at the operation. Special attention should be directed to the fact that the volume of lung included in the treatment volume should be as small as possible. In case of extensive pulmonary lesion shrinking fields should be used. The use of electrons to boost the anterior mediastinum could decrease

the risk of pulmonary and spinal cord irradiation. When the tumor is completely removed postoperative irradiation should deliver 45 to 50 Gy. On the other hand, when the resection is incomplete or the tumor unresectable, a risk may be taken and 50 to 55 Gy delivered to the anterior mediastinum. Doses to the spinal cord should not exceed 45 Gy. In the present series, chemotherapy was not of value; however, this statement is based on 2 patients only. It might have a value in reducing the size of the tumor, to facilitate radiation therapy alone.

The treatment of supraclavicular areas seems justified because 5/20 cases had evidence of neck involvement. The systematic treatment of these areas could decrease the recurrence rate in this region.

The principle problem concerning thymic tumors is their low incidence. Series are too small to allow a valid analysis of the prognostic factors; moreover, differences in concepts and classifications introduce difficulties in comparison between different series.

An International or European Registry of Thymic Tumors with an Advisory Pathology Board might be a relevant first step toward initiating a broad scientific investigation of these tumors.

SUMMARY

A review of 20 patients with malignant thymic tumors is presented. A simplified classification is used avoiding the term thymoma, which is considered misleading. Most of the patients were treated by a combination of surgery and radiation therapy while 7 were treated by irradiation alone. Postoperative radiation therapy is indicated when the tumor is incompletely removed. This is also advised in invasive tumors even when they are considered completely resected. Irradiation alone of inoperable tumors should be carried out with high doses (55 to 60 Gy) to decrease the risk of local recurrence.

The investigation was presented at the European Group of Radiotherapists, Helsinki, Finland 1979.

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