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Invasive Carcinoma of the Thymus. A Multicenter Retrospective Review of 56 Cases

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Abstract—*This multicenter retrospective study included 56 cases of histologically reviewed invasive epithelial thymic tumors. All these patients underwent surgical treatment or exploration and were referred for complementary radiotherapy. The majority received a dose higher than 4000 rad. Twenty-three out of 50 patients (46%) with incomplete resection received some chemotherapy. The local recurrence rate at 2 yr was 34%. The overall 5-yr actuarial survival was 46%. There was no evidence of any relationship between radiation dose and local control. No difference in survival was observed with or without chemotherapy, nor according to histological type or lymphocytic infiltration, except cases with very undifferentiated carcinomas which presented a worse prognosis. Nor was any difference in survival observed between patients benefiting from incomplete resection and those only having undergone exploratory thoracotomy and biopsy. Radiotherapy seems to decrease the rate of local recurrence in invasive carcinoma of the thymus. The role of chemotherapy is still debatable, but it could have a role in decreasing tumor volume before radiotherapy. This study has shown the necessity of histological review by a panel of histopathologists in an attempt to better define terminology and diagnosis. A prospective study is necessary in order to solve the problems of concepts and management in epithelial thymic tumors.*

INTRODUCTION

THYMIC tumor is the most common neoplasia of the anterior mediastinum [1, 2]. Invasive carcinoma represents 10–66% of all thymic tumors, depending on recruitment [3–5]. Most of the confusion concerning this disease results from a discord in terminology; thus, most papers present heterogeneous material, even including Hodgkin's disease of the thymus. The commonly used term 'thymoma' is actually misleading [6]. Rosai and Levine's proposition [7] to restrict its use to "neoplasms of thymic epithelial cells" has not been widely adopted.

The authors report a series of 56 cases of invasive carcinoma of the thymus referred to several radiotherapy departments for post-surgical irradiation.

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MATERIALS AND METHODS

Fifty-six patients were treated from 1951 to 1980 in the radiotherapy services of the following centers: Gustave-Roussy Institute (Villejuif), Tenon Hospital and Pitié-Salpetrière Hospital (Paris), and the Val-de-Grâce Military Hospital in Paris.

The retrospective inclusion criteria of the study were: (a) invasive epithelial tumor of the thymus; (b) histological slides reviewed by the same histopathologist; and (c) patients treated by surgery and radiotherapy as primary treatment.

The total number of cases of carcinoma of the thymus was 65, but 9 patients were excluded because radiotherapy was given for recurrence or

because the first post-surgical treatment was chemotherapy.

Histopathological findings

The histological review of this series of 56 cases has led to the use of the term 'thymic carcinoma' for the following reasons: (1) all of these tumors were macroscopically invasive; (2) the normal architecture of the thymus was altered if not completely destroyed by the tumoral proliferation; (3) invasive microscopic signs were observed in 68% of cases: tumoral infiltration of fat or muscular tissues or pulmonary parenchyma; intravascular invasion; tumoral infiltration of fibrotic intratumoral tracts; and (4) nuclear abnormalities were present in 33% of cases: large nuclei, large nucleoli, hyperchromatism and/or irregular chromatin. Abnormal mitoses were less frequently observed (11%).

In two recent publications [8, 9] the term of thymic carcinoma was applied exclusively to the epithelial thymic tumors with cytological signs of malignancy. The term of 'malignant thymoma' was reserved to the epithelial thymic tumors without cytonuclear atypia but with extrathymic extension. In our series the term 'thymic carcinoma' was used in epithelial thymic tumors with local extrathymic invasion, irrespective of the cytonuclear abnormalities and lymphocytic population.

The histological material was divided into 5 types according to the epithelial cell morphology and irrespective of the lymphocytic population: type I (30 cases): similar morphology to normal epithelial cells of the thymus, with small nucleolus; type II (15 cases): large cell size, with a spherical nucleus (>20 μm) and a large nucleolus; type III (1 case): spindle cell aspect; type IV (4 cases): clear cytoplasm, well-defined cellular membrane, nucleus with small nucleolus; and type V (6 cases): hyperchromatic nucleus with fine chromatin. The aspect was similar to very undifferentiated carcinoma.

These types can coexist in the same tumor in approximately one-third of cases and the classification was carried out according to the predominant type.

Lymphocytic infiltration was evaluated and the cases were divided into 3 categories: 0, 1 (33 cases): absence of lymphocytes or a number of lymphocytes lower than the number of epithelial tumor cells; 2 (18 cases): an equivalent number of lymphocytes and epithelial tumor cells; and 3 (5 cases): a higher number of lymphocytes than of the epithelial tumor cells. This evaluation is not always easy and bias can be introduced because the lymphocyte population is not homogeneous within the same tumor. Moreover, the quantity of tissue examined was very different in each case.

Table 1 shows the case distribution according to histological type and lymphocyte infiltration.

Clinical findings

The series consisted of 27 men and 29 women. The age distribution ranged from 15 to 72 yr, the mean age being 39.7 yr.

The relative frequencies of initial symptoms were: thoracic pain, 25%; superior vena caval obstruction, 25%; cough and/or dyspnea, 22%; fever, 18%; associated syndromes, 13%; loss of weight, 7%; cardiac tamponade, 2 cases; cervical mass, 2 cases; and distant metastases, 1 case. Eight patients were asymptomatic (15%). The seven associated syndromes were: 6 myasthenia gravis and one erythromelalgia.

Table 1. Case distribution according to histological type and lymphocyte infiltration

Histological type	Lymphocyte infiltration 0–1	2	3	Total
I	14	13	3	30
II	10	3	2	15
III	1	–	–	1
IV	2	2	–	4
V	6	–	–	6
Total	33	18	5	56

The delay between the onset of symptoms and the diagnosis varied from 1 to 72 months, excluding patients with associated syndromes. In fact, 3 patients with associated syndromes presented a delay longer than 5 yr. However, approximately 60% of symptomatic patients were diagnosed within the first 3 months after appearance of clinical disorders.

Surgical findings

The relative frequencies of thoracic structures involved by the tumor were as follows: pleura, 75%; large vessels, 51%; lung, 45%; pericardium, 45%; mediastinal or cervical involvement, 16%; chest wall, 6%. The trachea, the esophagus or the phrenic nerve were involved respectively in 3 patients.

Eighty-four percent of patients presented at least 2 structures involved, and 54% at least 3.

Only 6 patients benefited from a complete resection, 22 had an incomplete resection and 28 received exclusive radiotherapy after surgical exploration and biopsy.

Radiotherapy

Cobalt units or linear accelerators were used for treatment. Doses varied from 2500 to 6500 rad, 54

cases receiving a dose over 4000 rad. The fractionation varied from 5 × 150 rad per week to 3 × 330 rad per week; this difference is due to the multicenter recruitment and the duration of the study. Radiation fields with large security margins were defined, taking into account the radiological or surgical and pathological data; to deliver high doses shrinking field techniques avoiding the spinal cord were used. Most patients received irradiation of internal supraclavicular nodes. Large fields were used in case of pleural extension or pleural metastases, but radiotherapy to one hemithorax was not prescribed systematically.

Chemotherapy

Twenty-three out of 50 patients (46%) with incomplete or no resection received some chemotherapy. Six received MOPP and the others received different monochemotherapies. The heterogeneity of these indications reflects the absence of a defined policy.

RESULTS

Local control

The overall rate of local recurrence was 30% (17/56). These 17 cases are summarized in Table 2. In fact, 8 out of 17 patients did not respond to radiotherapy. The other 9 patients suffered recurrence secondarily from 2 to 228 months after treatment.

Only 1 patient out of 6 benefiting from a complete surgical resection developed a local recurrence. In 28 patients treated by radiotherapy alone the rate of local control at 2 yr was 80%.

No clear relationship between radiation dose and local control was observed. In fact, the rate of local recurrence at 2 yr was 42% (5/12) for patients receiving less than 4800 rad, 35% (6/17) for those receiving between 4900 and 5900 rad and 0% (0/3) for those receiving more than 6000 rad. The number of patients is too small to get significant figures.

Distant metastases

Twenty-one patients developed extrathoracic distant metastases (37.5%). Metastases appeared before 6 months after treatment in 12 patients and before 1 yr in 18. The median delay to appearance of distant metastases was 6 months.

Sites of distant metastases are listed in Table 3. These metastases were not histologically verified.

Survival

Overall actuarial survival at 5 yr was 46% (Fig. 1). Five-year survival for histological type I was 47.3%, for types II + V, 43.2% and for type II alone, 63.8%. These differences are not statistically significant. Only patients presenting type V had a poor prognosis, these 6 patients dying before 30 months of follow-up.

Table 3. Site of distant metastases

Site	No.
Liver	9
Bone	6
Brain	5
Pelvis	3
Abdomen	2
Para-aortic nodes	2
Skin	1
Kidney	1
Diffuse metastases	1

Table 2. Local recurrences in 17 cases of invasive carcinoma of the thymus

Treatment	Dose (rad)	Treatment-recurrence interval (months)	Distant metastases	Survival (months)	Comments
RT*	4500	0	0	2 D	uncontrolled
RT + CT	5800	0	YES	3 D	uncontrolled
RT	2500	0	0	3 D	uncontrolled
S + RT + CT	5350	0	YES	10 D	uncontrolled
S + RT	2600	0	YES	4 D	uncontrolled
RT + CT	5300	0	YES	12 D	uncontrolled
RT	4900	0	YES	12 D	uncontrolled
RT + CT	5500	0	YES	16 D	uncontrolled
S + RT	5000	2	YES	9 D	liver metastases
RT	5000	3	YES	19 A	controlled by RT and CT
RT	4500	4	0	54 A	controlled after S and CT
S + RT	5700	5	0	14 D	peripheral lung
S + RT + CT	5500	7	YES	13 D	peripheral lung
S + RT	5500	21	0	24 A	peripheral pleura
RT + CT	4100	24	0	30 D	mediastinal involvement
S + RT	6100	27	YES	45 D	liver metastases
RT	3000	228	0	240 D	uncontrolled by second RT

*RT: radiotherapy; CT: chemotherapy; S: surgical resection; D: dead; A: alive.

Table 4. Cause of death

Cause	No.
Local failure	5
Local failure + distant metastases	8
Distant metastases	8
Complications	2
Unknown	2

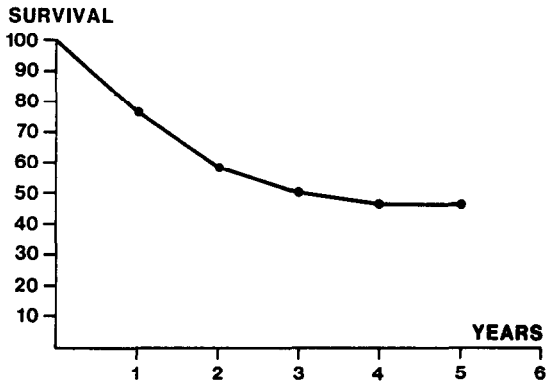

Fig. 1. Overall actuarial survival.

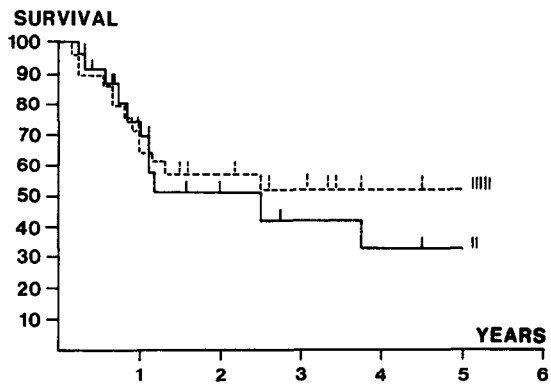

Fig. 2. Actuarial survival for patients having incomplete resection (———) and those without tumoral resection (– – – – –). No significant difference was observed.

No significant difference in survival was observed between patients with tumors showing little lymphocytic infiltration (groups 0 and 1) and those with tumors showing extensive lymphocytic infiltration (groups 2 and 3): 43.2 and 51.5% 5-yr survival respectively.

Excluding patients with complete resection, survival was compared between patients having incomplete resection and those without tumoral resection. No significant difference was observed up to 5 yr (Fig. 2): 34 and 52% at 5 yr respectively. The 3- and 5-yr survival rates for the 6 patients having complete resection were 83 and 66% respectively.

No difference in survival was observed between patients receiving chemotherapy and those who did not.

The causes of death are presented in Table 4. The most frequent cause of death was distant metastases (64%).

Complications

In two cases complications due to radiotherapy were probably the cause of death. These patients developed radiation pneumonitis, accompanied in 1 case by pericarditis; in these cases large thoracic volumes were irradiated at relatively high doses due to very large mediastinal masses.

DISCUSSION

Rosai and Levine [7] defined 'thymoma' as a neoplasm derived from the epithelial cells of the thymus. However, for a long time the term 'thymoma' has been used for various types of thymic tumors, and even now is widely considered a synonym of thymic tumor. From the histogenetic point of view the denomination of thymoma does not take into account the two populations of the thymus: lymphocytes and epithelial cells. The term 'thymoma' does not implicate an epithelial origin. The use of terms such as 'Hodgkin's disease of the thymus' or 'non-Hodgkin's lymphoma of the thymus' is widely accepted; similarly, it seems reasonable to propose the term 'epithelial tumor of the thymus'. These tumors should be called carcinoma if they have histological and clinical characteristics of malignancy. In our series we observed only malignant epithelial tumors with local invasion of the mediastinum, and the term 'thymic carcinoma' seemed justified. There is at present an on-going study to determine the cytological grading of malignancy as it has been established for bladder epithelial tumors [10]. If successful, it would then be possible to define thymic carcinomas of grades I–III. This cytological grading should be complemented by an anatomo-clinical staging, taking into account the clinical, radiological and surgical data. An attempt to clarify concepts of thymic tumors seems necessary for a better understanding and to place these tumors within the framework of current histological nomenclature.

This retrospective study has collected an unusually large number of cases of invasive thymic carcinoma; most of the patients presented with very large tumors, only 11% benefited from complete surgical resection and 50% were considered unresectable. The majority of patients were referred to radiotherapy because surgery was incomplete or exploratory.

No histological criteria of prognosis were found in this series. However, patients presenting very undifferentiated carcinoma (type V) died in a

relatively short period. Some studies [4, 6, 11] have suggested that lymphocyte infiltration could be a sign of favorable prognosis, but this was not confirmed in this series. However, only a small number of patients had 5 yr of follow-up.

Most authors [3, 6, 12–15] consider complete surgical resection of invasive tumors to be the most important therapeutic act with a clear effect on prognosis. In spite of this fact, the rate of local recurrence in this series is relatively low (34%) and the survival rate at 5 yr is 46%.

It seems that radiotherapy has an important role in the local control of invasive tumors of the thymus, as has been recognized by several authors [3, 6, 11, 16–22]. In fact, as presented in Fig. 2, there was no difference in survival between patients benefiting from incomplete resection and those without tumoral resection. It could be speculated that radiotherapy was able to supress this difference, thereby obtaining the same local control in both groups in spite of the difference in tumor volume.

Patients of this series were treated at doses varying between 4000 and 6000 rad. No significant correlation between dose and local tumor control could be found, probably related to the small number of patients and bias in patient selection, and to the different techniques used due to the multicenter recruitment. Most patients received doses over 5000 rad. The rate of local control obtained (70%) seems satisfactory when taking into account the extension of the treated tumors. If we consider that these tumors are from epithelial origin, we can postulate that doses of approximately 6000 rad are needed to obtain consistent local control. In fact, some of these tumors with an important lymphocytic population can give a spectacular response to chemotherapy or low-dose radiotherapy, but the tumor cell population—from epithelial origin—might need a higher dose to achieve a long-term local control. A randomized trial demonstrated this fact for epithelial bronchial tumors [23].

Large fields should be used to avoid border recurrence, but it is recommended to shrink the fields during radiotherapy in an attempt to decrease the incidence of severe complications. Although no evidence has been found concerning optimal doses, we deliver high doses because these tumors are of epithelial origin. We give 5000 rad in classical fractionation by post-operative radiotherapy in cases without macroscopic residual tumors and 5500–6000 rad if macroscopic residual disease is present. A dose of 6000 rad could be necessary for unresectable tumors.

Distant metastases are considered to be exceptional in thymic tumors, but Batata *et al.* [3] observed a 30% rate in a series of 36 invasive tumors. In our series a similarly high rate of distant metastases (37%) was recorded. This fact could be related to the advanced local disease of these patients and underlines the poor prognosis initially established.

Chemotherapy was used in almost half of the patients. Unfortunately chemotherapy schedules were very different and no valid conclusion can be drawn based on these data. Patients treated by chemotherapy did not present a different survival rate but this fact could be due to a bias in treatment, more advanced cases being more likely to receive chemotherapy. Since 1977 the proportion of patients treated by adjuvant chemotherapy has increased (58%, vs 26% before 1977). Because of the small number of patients treated by chemotherapy no consensus in the role of chemotherapy has been reached in the current literature [24–27].

Chemotherapy could have a role in reducing the volume of large tumors requiring radical radiotherapy; in order to determine this role, well-defined therapeutic trials should be carried out.

Because of difficulties in histopathological diagnosis and in related definitions, it was necessary to critically review all slides before including patients in the study. However, other biases remain in the interpretation of results. This retrospective study demonstrates the usefulness of collecting patients from different centers when dealing with rare tumors such as thymic epitheliomas. Nevertheless, most of the unsolved questions in the management of invasive thymic tumors should be raised in prospective, well-defined multicenter studies; thus an effort by all specialists concerned is highly desirable.

Such a multicenter prospective study has been undertaken in an attempt to solve the questions raised by the retrospective study: histopathological concepts, anatomoclinical staging, distant metastases rate, role of radiotherapy and chemotherapy.

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