Thymic Carcinoma – Analysis of Nineteen Clinicopathological Studies

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Background: Primary thymic carcinomas are rare tumours with nonuniform management protocols and poor prognosis due to delayed diagnosis and highly malignant behaviour. This review summarises the major clinicopathological studies to assess more fully the prognostic importance of tumour histology and staging as well as treatment benefit. **Methods:** A Medline search from 1966 to date was carried out and relevant references gleaned from these. Nineteen clinicopathological studies form the core of this review. Demographic data and clinical features were examined in all studies. Correlation of outcome with histology was possible in fifteen of the studies and with tumour staging in thirteen. **Results:** Thymic carcinomas occur most commonly in the fifth to sixth decades of life, usually presenting with symptoms of space occupation or invasion. Paraneoplastic syndromes are rarely associated, except with the well differentiated thymic carcinoma. Of 140 thymic carcinomas, 40 were squamous cell, 19 were spindle cell and 16 were lymphoepithelioma-like. Completely resected stage I and II tumours demonstrated the best survival. **Conclusions:** Complete surgical resection is taken to be the desired treatment, but the continued high mortality and relapse rates and the variable benefit of adjuvant therapies challenge this strategy.

Key words: Thymus – Thymic carcinoma – Surgery – Radiotherapy – Chemotherapy

Introduction

Thymic carcinomas, defined by their cytological atypia [1], are rare malignancies of the anterior mediastinum, accounting for less than 0.06% of thymic neoplasms [2]. However, their importance lies in their dismal outlook and unsatisfactory prognostic staging and treatment modalities.

Methods

A Medline search was carried out from 1966 to date for all relevant papers and further references taken from the reference lists therein. Nineteen clinicopathological studies [2 – 20] of multiple cases of primary thymic carcinoma form the focus of this review (Table **1**).

Omitting the duplicated data of *Shimosato* et al. [3] and *Kuo* et al. [7], a limited meta-analysis was undertaken. Histological correlation with treatment and outcome was possible for 140 different cases in fifteen of the studies [2 – 7,9 – 13,15,16,19,20]. From the surgicopathological descriptions of individual tumours, prognostic application of the Masaoka staging system [21] was possible in thirteen of the studies [3 – 7,9,11 – 13,15,16,19,20], with 104 different cases being assessed for outcome.

Results

Clinical features

A total of 305 cases were reported in the 19 studies, but this includes complete duplication of those of *Kuo* et al. [7] and *Shimosato* et al. [3] in the studies of *Chang* et al. [9] and *Tsuchiya* et al. [13] respectively, and some rereporting amongst the Rosai/Suster/Moran collaborations [4,8,17,20]. 183 were males and 122 females, with the average age (both mean and median) in the late fifth to early sixth decades and an overall age range of 4 to 83 years (Table **1**).

Histology

Table **2** summarises the histological classification of tumours from fifteen of the studies [2 – 7,9 – 13,15,16,19,20], correlated with tumour stage, treatment and outcome. Squamous cell carcinoma (40 cases), spindle cell (19 cases) and lymphoepithelial-like carcinoma (16 cases) were the most common types and have contrasting outcomes. While at 2 years after diagnosis half, and at 5 years a third, of the patients with squamous cell carcinoma were alive, there were no survivors with lymphoepithelial-like histology at 5 years, and only two patients with spindle cell carcinoma were alive at 5 years.

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Table 1 Clinicopathological studies of thymic carcinomas: clinical features

Author, year	Number of Patients	Age range (years)	Sex (M:F)	Presenting Features			
				None	Compressive/ Invasive	General	Paraneoplastic syndrome
Shimosato et al. [3], 1977	8	39–65	7:1	0	6	7	0
Wick et al. [2], 1982	20	4–72	14:6	2	11	8	0
Snover et al. [4], 1982	8	29–76	4:4	4	4	0	0
Truong et al. [5], 1990	13	30–74	7:6	1	12	0	0
Hartmann et al. [6], 1990	5	38–68	2:3	0	5	2	0
Kuo et al. [7], 1990	13	19–64	9:4	0	13	0	0
Suster and *Rosai* [8], 1991	60	10–76	36:24	19	41	0	2
Chang et al. [9], 1992	16	19–75	11:5	0	16	6	0
Pescarmona et al. [10], 1992	15	27–60	6:9	NA	NA	NA	9
Yano et al. [11], 1993	8	30–66	5:3	3	4	1	0
Weide et al. [12], 1993	5	33–55	3:2	1	3	0	0
Tsuchiya et al. [13], 1994	16	32–68	9:7	NA	NA	NA	0
Hsu et al. [14], 1994	20	34–70	9:11	0	20	0	0
Shimizu et al. [15], 1994	5	50–69	4:1	1	4	0	0
Hasserjian et al. [16], 1995	8	36–84	3:5	3	4	0	0
Suster and *Moran* [17], 1996	22	23–83	16:6	12	8	1	2
Blumberg et al. [18], 1998	43	19–72	27:16	5	24	0	14
Matsuno et al. [19], 1998	4	57–70	2:2	2	1	0	0
Suster and *Moran* [20], 1999	16	23–82	9:7	6	10	3	0

Key: NA – not available

Table 2 Tumour type, stage, treatment and outcome*

Tumour type	Stage						Treatment				Survival			Recurrence		
(Number)	I	II	III	IVa	IVb	NA	SC	SI	R	C	2y	5y	NA	Local	Mets	NA
Low-Grade Thymic Carcinomas																
WDTC (15)	3	8	4	0	0	0	15	0	0	0	6	3	0	2	0	0
Squamous cell (40)	2	2	25	3	5	3	19	15	34	18	21	13	0	8	23	2
Basaloid (3)	1	0	2	0	0	0	3	0	0	0	2	1	1	0	0	1
Mucoepidermoid (1)	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0
High Grade Thymic Carcinomas																
Lymphoepithelial-like (16)	1	0	0	0	2	13	10	1	13	4	3	0	0	6	12	0
Clear cell (11)	1	4	5	0	1	0	6	2	8	5	3	2	0	4	7	0
Spindle cell (Sarcomatoid) (19)	3	4	7	1	3	1	10	3	12	2	9	2	7	4	7	7
Small cell (12)	0	0	6	0	2	4	2	5	9	7	4	2	0	5	7	0
Undifferentiated (Anaplastic) (9)	0	0	5	2	2	0	1	6	6	8	2	0	0	2	6	1
Other Thymic Carcinoma Variants																
Adenosquamous (1)	1	0	0	0	0	0	1	0	0	0	0	0	0	1	1	0
Mixed small cell squamous (6)	0	0	5	0	1	0	3	3	5	2	2	1	1	5	2	0
Mixed small cell adenocarcinoma (1)	0	0	1	0	0	0	0	1	1	1	0	0	0	1	1	0
Mixed small cell adenosquamous (2)	0	0	2	0	0	0	0	2	2	1	1	0	0	2	0	0
Papillary (4)	1	1	1	1	0	0	3	1	1	1	1	1	1	1	1	1

*Based on fifteen clinicopathological studies [2–7,9–13,15,16,19,20]. Key: NA – insufficient details available; SC – surgery, complete resection; SI – surgery, incomplete resection; R – radiotherapy; C – chemotherapy; Mets – metastases (both recurrence or subsequent development from unresected tumour).

Staging and outcome

The Masaoka system for thymomas [21] was applied to 104 patients from thirteen of the studies [3–7,9,11–13,15,16,19,20] (Table **3**). All stage I and and all but one stage II tumours were resected completely. Their median survivals were 36 and 45 months respectively (range 4–86 and 1–205 months) compared with medians of 9, 24 and 36 months respectively (ranges 0–242, 15–67 and 0–242 months) for stage III, IVa and IVb tumours, which were largely incompletely or not resected.

Local recurrence was more common in the more invasive resected tumours. Forty-one (32.03%) of the 128 patients in Table **2** with follow-up data had local recurrence of tumour following tumour resection. Metastases developed in 67 (52.34%) of the patients.

Table 3 Thymic carcinoma staging related to outcome*

Stage		I	II	III	IVa	IVb	NA	Total
Number		10	11	59	6	17	1	104
Complete resection		10	10	23	0	3	0	46
Partial resection		0	1	26	3	7	0	37
No resection		0	0	10	3	7	1	21
Survival[a]	Total	287	580	2022	174	253	12	3328
(months)	Mean	35.86	61.25	37.44	34.80	15.81	12	35.40
	Median	36	45	24	36	9	12	24
Local recurrence[a]		1	4	17	1	5	0	25
Metastases[a]		4	2	24	6	12	0	44

* Based on thirteen clinicopathological studies [3 – 7, 9, 11 – 13, 15, 16, 19, 20]. [a] Follow-up data unavailable for two, one, five, one, and one patients for stages I, II, III, IVa and IVb respectively. Key: NA – Stage not available

Discussion

Definition

Until it was classified as a category II malignant thymoma, characterised by cytological atypia by *Levine* and *Rosai* [1] in 1976, thymic carcinoma was not well defined. Its rarity and the similarity of its histological forms to tumours in other locations, particularly salivary glands and lung, have relegated it, as a primary thymic entity, to a diagnosis of exclusion. It is now accepted that thymic carcinoma implies a thymic epithelial neoplasm showing atypical cellularity, including multiple mitoses, high nuclear/cytoplasm ratio and prominent nucleoli, and necrosis.

Even more unsettled is the well differentiated thymic carcinoma (WDTC) described by the Müller-Hermelink group [22,23], which retains some organotypical features with mild atypical change. This may represent an intermediate stage of dedifferentiation of thymomas and indeed has characteristics more in keeping with thymomas than with other thymic carcinomas.

Incidence

Thymic carcinomas are rare, comprising only 0.06% of thymic neoplasms [2]. There is a slight male preponderance. The peak incidence is in the fifth to sixth decade. Over the 5-year period 1988 – 1992 inclusive, a total of 57 non-thymomatous thymic malignancies were registered for England and Wales (source: Office for National Statistics, London, UK). The number of these that were carcinomas, however, is unavailable.

Histological classification

Kirchner and *Müller-Hermelink* [23] broadly identified WDTCs and other thymic carcinomas. The latter group, termed "proper thymic carcinomas" by *Masaoka* and associates [24] and type II malignant thymomas by *Levine* and *Rosai* [1], comprises two sub-groups based an behavioural patterns (Table **2**). A papillary form of spindle cell carcinoma has recently been described [19].

The identity of WDTC is a subject of current debate. *Suster* and *Moran's* "atypical thymoma" [25] terminology for this intermediate thymic tumour is supported by *Masaoka* and colleagues [24], both groups disagreeing with the designation of thymic carcinoma on histological and behavioural grounds, in addition to the great prevalence of associated myasthenia gravis, absent from the other carcinomas.

While tumours derived from the germinal epithelium (seminoma, teratoma) are generally excluded, some studies of primary thymic carcinomas include the group of neuroendocrine tumours in their analyses.

Neuroendocrine differentiation

Both carcinoid and small cell tumours have been included in reports of thymic carcinomas, but strictly speaking, these are neuroendocrine tumours and have a different behaviours [26,27]. These tumours are currently classified as Grades I – III carcinoids based an the degree of dysplastic morphology, with oat cell tumours amounting to Grade III and having the worst prognosis [27,28].

There is a growing number of reports of neuroendocrine differentiation present in thymic epithelial tumours, as confirmed by immunohistochemical markers (synaptophysin, neuron-specific enolase, chromogranin, alpha subunit of guanine neocleotide-binding protein, Go, and small cell lung carcinoma cluster 1 antigen) [29,30]. This suggests a diverse potential of malignant thymic epithelial tumours to differentiate along neuroendocrine lines [29,30]. The spectral approach of *Travis* and colleagues [31] to classification of neuroendocrine tumours of the lung can thus be extrapolated more widely (Table **4**).

Table 4 Classification of neuroendocrine tumours (after Travis et al. [31])

Tumour	Description
Carcinoid	Mainly composed of well-differentiated cells with little or no mitotic activity; neuroendocrine differentiation readily seen throughout tumour.
Atypical carcinoid	Cytological atypia present: increased mitotic activity and necrosis.
Small cell carcinoma	Undifferentiated small cells, with abundant mitoses and necrosis.
Large cell neuroendocrine carcinoma	Neuroendocrine cytology but more pronounced atypia than atypical carcinoid, especially with regard to mitotic activity.
Carcinoma with neuroendocrine features	Heterogeneous group with identifiable cytoarchitecture but with variable number of neuroendocrine cells. Increased dedifferentiation.

Pathogenesis

The more aggressive behaviour and poorer prognosis of carcinomas suggest that they are distinct entities from thymomas, but noted cases of coexistence and even apparent devolution of the former from the latter may suggest that they are merely different stages of the spectrum of thymic epithelial neoplasia [7,9,17,20,32]. The presence of tumour necrosis within a thymoma should alert to the possibility of carcinomatous change [33]. In the latest of the of the classifications to enter the fray of obscurity surrounding thymic epithelial neoplasia, *Suster* and *Moran* [25] based their classification of thymoma, atypical thymoma and thymic carcinoma on the degree of cellular differentiation, maintaining the premise that all thymic epithelial tumours possess malignant potential. Akin to the classification of carcinoid tumours, in reality this is merely alternative nomenclature for the traditional oncology of well, moderately and poorly differentiated tumours.

It is speculated that, as with lymphoepithelioma-like tumours in other sites, those in the thymus may have a causal association with the Epstein-Barr virus [34].

Clinical features

Thymic carcinomas may be discovered incidentally from abnormal chest radiographs or at operation (e.g. coronary artery bypass grafting). Most commonly, however, patients complain of symptoms of compression or invasion (e.g. superior vena cava (SVC) obstruction, dysphagia, dyspnoea, hoarseness, chest pain, cough). General symptoms of malaise, weight loss and easy fatiguability also occur. Paraneoplastic syndromes are rare [31,36]. However, this does not appear to be the case with WDTC which may be associated with myasthenia gravis (MG) in 60% of cases [10]. All 14 cases of paraneoplastic syndrome reported by *Blumberg* and colleagues [18] occurred in WDTC. This fact challenges the view of the thymoma-WDTC-other thymic carcinoma spectrum of thymic dedifferentitiation and suggests that, at the very least, the transition is not uniform but, rather, many carcinomas arise *de novo*. Thymic carcinoids have a recognised association with Cushing's syndrome [26].

Radiographic imaging

Like other thymic lesions, thymic carcinoma appears as a widened superior mediastinum on chest x-ray (Fig. **1**). Computed tomography confirms the mediastinal mass (Fig. **2**) and may reveal mediastinal lymphadenopathy and extrathymic metastases [37]. Except for neurogenic tumours, magnetic resonance imaging has little more to offer than CT scanning for mediastinal lesions.

Staging

The staging system of *Masaoka* et al. [21], originally described for thymomas, has been adopted for thymic carcinomas but lacks universal support [18]. A TNM system has also been applied [38]. A proposed modification is limited by a study of small numbers (sixteen cases), with only three histological variants and the absence of Stage II tumours [13]. Furthermore, the prognostic value of the nodal status is difficult to assess due to the small numbers involved.

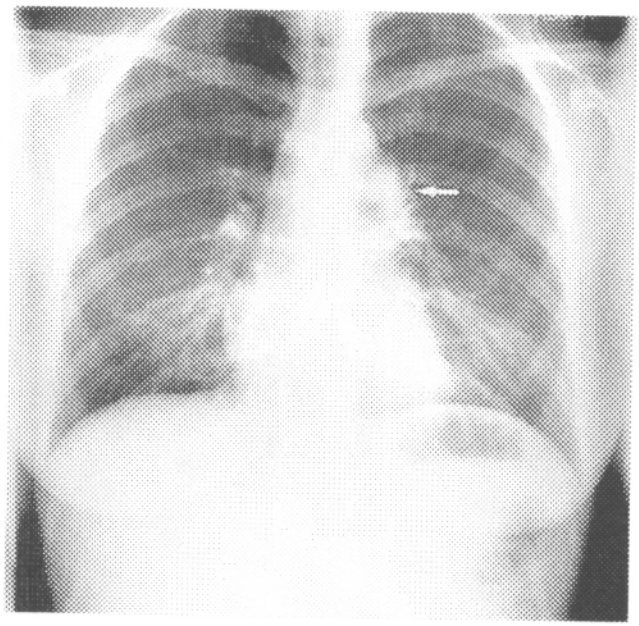

Fig. 1 Chest radiograph of a 38-year-old female with squamous carcinoma of the thymus gland, appearing as mediastinal widening (arrow).

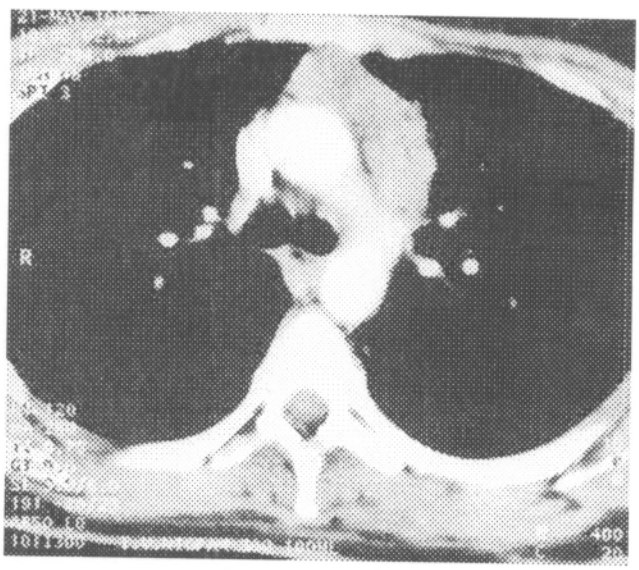

Fig. 2 Computed tomogram of the patient in Fig. **1** showing the thymic carcinoma anterolateral to the ascending aorta and inferolateral to the aortic arch.

Management

Surgery

While surgical intervention is usually viewed as the primary modality of treatment, the extent of the resection itself is variable, depending on tumour spread as well as the attitude of the individual surgeon. Thus, complete resection may involve removal of the thymic lesion proper and thymus gland as well as

a pleuropneumonectomy, pericardiectomy and reconstruction of venous confluences, while partial resection may simply be a debulking procedure in preparation for adjuvant therapies.

Radiotherapy

Few studies have analysed the impact of radiotherapy. The field of irradiation as has been described for invasive thymoma includes both supraclavicular fossae and the whole mediastinum down to the diaphragmatic crurae as well as the predominantly involved hemithorax when pleural dissemination is present [39, 40].

Chemotherapy

The great variety of chemotherapy combinations and small numbers of patients preclude meaningful interpretation of efficacy. Cisplatin-based combination chemotherapy has been used with limited success either as an adjunct or as primary therapy [12, 15, 41]. In other centres, chemotherapy has been used with radiotherapy to treat advanced lesions.

Prognosis

The five-year survival rate is quoted at 31% to 50% [5, 19, 20, 22, 23]. From the survival data in Table **2**, there were 25 (19.2%) of 130 patients (no survival data available on 10 of the 140 patients) alive at 5 years. These figures, however, do not take into account potential survivors who were followed up for less than 5 years.

Histology and differentiation

The division of thymic carcinoma into high and low grade histology is supported by respective high and low recurrence and metastatic rates and deaths from tumour [8]. Absence of lobular pattern, greater than 10 mitoses per 10 high power field, necrosis and atypia were also found to be poor prognosis factors [8]. Although *Blumberg* et al. [18] have downplayed the significance of histological classification, they report a 5-year survival rate of 65% based an 43 patients of which 16 were WDTC.

Staging and surgical resection

Advanced stage carcinomas and corresponding unresectability indicate poor prognosis [13]. All stage I and nearly all stage II tumours were completely resected and have the best median survivals. *Blumberg* et al. [18], however, found only neoplastic invasion of brachiocephalic vessels to significantly correspond with poor prognosis.

Adjuvant therapy

Valid assessment of adjunctive treatments, in particular chemotherapy, is difficult as these modalities are usually applied to advanced, incompletely resected or unresected tumours in systemically unwell patients [6, 12, 13]. In addition, the rarity of thymic carcinomas does not allow for studies of significant size. *Yano* et al. [11] quote an 85.7% partial response rate from radiation doses of 40 to 60 Gy in unresectable and recurrent tumours with response durations of 1 to 10 years. A mean survival of 106 months in 7 patients following adjuvant or neoadjuvant radiotherapy compared with 49 months in 4 patients with no radiotherapy has been achieved [13]. *Hsu* et al. [14] reported a median survival of 39 months for patients with radiotherapy compared with 15 months for those without radiotherapy. There is a trend towards squamous cell carcinomas being radiosensitive [3, 13]. *Shimosato* et al. [3] reported an apparent cure (no evidence of disease 11 years after diagnosis) from radiotherapy for an unresected squamous cell thymic carcinoma with lung invasion.

The positive results of chemotherapeutic strategies are anecdotal at best, with partial responses in a few cases [12] and, very rarely, apparent cures [15, 41].

Recurrence

Death from tumour recurrence several years following complete resection is not unknown [4, 11]. In contrast to thymomas, re-resection for local recurrence has not been described, probably due to the advanced stage and associated debilitating systemic effects of the recurrent tumour. The effect of adjuvant therapy is, at best, short-lived [12].

Conclusions

1. Thymic carcinoma is a rare tumour with poor prognosis.
2. There is a male predominance of about 3 : 2.
3. The clinical presentation usually reflects tumour invasion or compression. Myasthenia gravis is commonly associated only with the well-differentiated form.
4. The concept of the well-differentiated thymic carcinoma as a true primary thymic carcinoma remains controversial.
5. While some evidence suggests thymic carcinoma to represent the extreme of thymoma dedifferentiation, most tumours probably arise *de novo*.
6. Best survival trends are seen in completely resected early stage lesions.
7. Radiotherapy may be helpful in squamous cell tumours, but chemotherapy remains unsubstantiated.
8. High relapse rates add to the poor prognosis.

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