Observer variation in the histopathological classification of thymoma: Correlation with prognosis

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Abstract

Aims—To assess the ability of three histopathologists, experienced in thoracic surgical reporting, consistently to classify thymomas as cortical, medullary, or mixed pattern tumours.

Methods—Three histopathologists classified 74 thymomas (none frank carcinomas) as of either cortical, medullary, or mixed pattern, on two separate occasions. Kappa statistics were used to assess inter- and intra-observer agreement. Tumour type was compared with surgical stage as a predictor of biological behaviour.

Results—Inter- and intra-observer agreement were only moderate (κ 0.48 and 0.52, respectively). For only 26 of 74 tumours could a categorisation be consistently agreed on. Follow up information was obtained for 73 cases, with a mean follow up period of five years. The prognoses for those 26 of 74 cases appeared to be at variance from previously reported studies, and showed internal inconsistency, with the mixed pattern category showing a worse survival than the cortical category. For the group as a whole, however, stage at presentation was related to survival, with an overall five year survival of 78% (100% for stage I, 84% for stage II, 27% for stage III and 0% for stage IV).

Conclusions—The classification of thymomas into cortical, medullary, or mixed pattern tumours is difficult to apply. Surgical stage remains a better guide to prognosis.

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Thymomas are rare intrathoracic neoplasms of thymic epithelium, and most histopathologists will see examples of the tumour only rarely. Until recently, the biological behaviour of the tumour was best predicted by the invasiveness at surgery¹⁻⁴ and not by any histologically recognisable determinant. Recently, however, a thymoma classification has been proposed by Marino and Muller-Hermelink.⁵ It links tumour morphology with histogenesis. They proposed that thymomas should be divided into medullary, mixed, and cortical types. Indeed, more recently still, they claim to have recognised a subgroup of well differentiated thymic carcinoma within the tumours of cortical pattern.^{6,7} The classifica-

tion of thymomas into medullary, mixed, and cortical types has been reported by one group to be useful in the prediction of biological behaviour.⁸⁻¹⁰

Despite the plausibility and attractiveness of such a classification, in practice we found it difficult to apply to thymomas in our routine surgical histopathological workload. This study was designed to test the ability of histopathologists to apply the criteria proposed by Marino and Muller-Hermelink and to assess its prognostic value. We studied inter- and intraobserver variation in tumour typing, and correlated surgical stage and tumour type with prognosis.

Methods

The pathology department records of three hospitals (Frenchay Hospital Bristol, and Llandough and University Hospitals, Cardiff) were searched for tumours filed as thymomas, for the period 1966-1990. Eighty tumours were found. Three were misclassified Hodgkin's lymphoma, and a further three proved to be non-Hodgkin's lymphoma after review and immunohistochemistry. The remaining 74 cases formed the basis of the study and the case notes of all of them were obtained.

Of these 74, 63 had had the tumour removed, a procedure which was intended to be curative; the remaining 11 cases had had extensive disease at thoracotomy, and large biopsy specimens were taken. Two blocks of the available tumour tissue were selected for 63 cases; only one block was available for the remaining 11 cases. Fresh 4 μ m sections were cut from each block, stained with haematoxylin and eosin, and marked with a reference number. The same set of slides was examined independently by a panel of three district general hospital histopathologists. All were actively working in reporting thoracic surgical histopathological material and had a mean of 13 years' experience (range seven to 17 years).

Tumours were staged according to the method of Masoaka *et al*¹ into stage I (macro- and microscopically encapsulated); stage II (macroscopic invasion of fat or pleura, or with microscopic invasion into capsule); stage III (macroscopic invasion into adjacent organ); and stage IV (pleural or pericardial or haematogenous or lymphatic metastasis).

Follow up was obtained by reviewing hospital records. The general practitioners of all cases not known to have died were contacted

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with a short questionnaire concerning the current status of the patient, and if applicable, a copy of the death certificate was obtained.

DIAGNOSTIC CATEGORIES

The histopathologists (observers) allocated the thymoma into one of three categories on the basis of the classification proposed by Marino and Muller-Hermelink⁵—namely, cortical, mixed, and medullary types. No attempt was made to identify separately the so-called well differentiated thymic

carcinomas^{6,7} within the cortical category; the study cases included no frankly malignant carcinomas, such as squamous carcinoma, lymphoepithelial carcinoma, of the types described by Rosai.¹¹

Each pathologist was provided with the published detailed descriptions and illustrations of the three tumour types.¹² Briefly, these are as follows. Cortical tumours (fig 1) are composed of epithelial cells with large, clear, round nuclei which have a prominent nucleolus. The lymphoid cells include lymphoblasts. The resulting histological features included "starry sky" pattern. Additional features are the so-called medullary islands. Medullary tumours (fig 2) are composed of epithelial cells with spindled nuclei; the lymphoid cells comprise lymphocytes. Architectural features include rosettes. Mixed tumours (fig 3) contain a mixture of spindled and large round nuclei, and sometimes additional architectural features of perivascular spaces and pseudoglandular structures.

Three months after the first attempt at classification the pathologists were circulated with the same set of slides and asked to classify the tumours for a second time, without reference to their first assessment.

Before this second attempt, they met to discuss aspects of the classification criteria which they found particularly difficult to apply on the first attempt. A definition of cortical or medullary tumour as one containing not less than 80% of the appropriate nuclei was made, with all remaining tumours being classified as mixed (the medullary islands of otherwise typical cortical cases being excepted).

STATISTICAL METHODS

Kappa statistics were used to assess the degree

Figure 1 Cortical pattern thymoma.

Figure 2 Medullary pattern thymoma.

Figure 3 Mixed pattern thymoma.

Table 1 Kappa statistics: interobserver agreement and classification category

	Kappa value	
	First attempt	Second attempt
Interobserver		
Unweighted	0.45	0.48
Weighted	0.53	0.54
Category		
Cortical	0.57	0.54
Mixed	0.33	0.39
Medullary	0.45	0.52

of agreement between observers, firstly between the three pathologists at each of the two attempts at classification, secondly for each individual pathologist separately between the first and second attempt, and lastly for each of the three diagnostic categories. Kappa statistics are corrected for chance—that is, the number of agreements that would be expected to occur by chance alone. The resulting value given for κ is a gauge of degree of agreement: a value over 0.75 indicates excellent agreement; a value under 0.4 poor agreement; and a value of 0.4–0.75 moderate or good agreement.

A weighted κ value was also calculated,¹³ to take into account the seriousness of disagreements. The degree of disagreement is obviously greater if a tumour, classified by the first observer as cortical, is classified by the second observer as medullary, rather than mixed.

Survival for patients was calculated by the actuarial method (Kaplan-Meier¹⁴).

Results

At the first assessment, the three pathologists unanimously classified 37 of 74 cases, giving a κ value of 0.45, indicating moderate agreement (table 1).

During the discussion of the criteria for classification, which occurred before the second attempt, it became apparent that a major difficulty seemed to be the field to field variability of the cellular and nuclear detail of the tumours, and, therefore problems in assigning an overall allocation which also took into account the architectural features apparent at lower power. Almost all tumours seemed to have both the polygonal and spindle types of epithelial cell.

At the second attempt, there was unanimity in classification of 40 of 74 cases, with a κ value of 0.48. There were only 26 of 74 (35%) cases in which all three observers agreed on the same histological categorisation at both attempts.

For the individual pathologist, there was similarly moderate agreement between his first and second attempts, with κ values ranging from 0.42–0.57 (table 2).

Table 2 Kappa statistics: intraobserver agreement

Observer	Unweighted	Weighted
A	0.56	0.62
B	0.42	0.52
C	0.57	0.63
All	0.52	0.59

Table 3 Association between surgical stage and clinical course

Stage	Alive	Non-tumour death	Tumour death	All
I	20	7	0	27
II	19	9	5	33
III	3	0	8	11
IV	0	0	2	2
All	42	16	15	73

For the individual diagnostic groups at the second attempt, the cortical group had a κ value of 0.54, the mixed group one of 0.39, and the medullary group one of 0.52 (table 1).

The 74 cases showed a mean age at presentation of 54 years (range 13–83 years). There were 36 men (mean age 58 years) and 38 women (mean age 51 years), twenty four of 74 (32%) cases had myasthenia gravis, three red cell aplasia, and two hypogammaglobulinaemia, twenty eight of 74 (38%) were stage I, 33 of 74 stage II, 11 of 74 stage III, and two of 74 stage IV.

Follow up information was available for 73 patients; the mean length of follow up was 60 months (range two days to 296 months). Thirty one of 73 patients were known to have died; in 15 of 73 (20.5%) this was due to recurrent or residual tumour. A further two patients were alive with recurrent tumour at the time of last follow up (stages II and III at presentation). Four of 73 died of myasthenia. No deaths from tumours or recurrence occurred in those tumours of stage I (table 3). All the deaths in those in stage III and IV disease were caused by tumour. Stage was thus predictive of survival (fig 4) with an overall five year survival of 78% (100% for stage I, 84% for stage II, 27% for stage III, and 0% for stage IV).

Assessment of the prognostic potential of Marino and Muller-Hermelink's classification was restricted to an analysis of the biological behaviour of those 26 cases on which all of us agreed on both occasions—that is, only those tumours which could be fitted into the classification reproducibly. There were 13 cases of cortical, nine of mixed, and four medullary tumours (table 4). The mean age of those cases of cortical type was 50 years, of mixed type 55 years, and of medullary type 63 years. Myasthenia was restricted to tumours of cortical and mixed type, but red cell aplasia was

Figure 4 Survival curves for thymomas categorised by survival stage.

Table 4 Association between surgical stage and tumour category

Category	Stage			
	I	II	III	IV
Cortical (n = 13)	5	5	3*	0
Mixed (n = 9)	3	5	1†	0
Medullary (n = 4)	3	1	0	0

*One alive and well; one alive with recurrence; one dead.

†Dead.

seen in one cortical and one medullary type. The tendency to invade adjacent organs (stage III) was restricted to the cortical and mixed types, but there was one example of medullary type in the stage II tumours. There were only two deaths from tumour in the 26 consistently classifiable tumours—one of cortical and one of mixed type. One of the patients alive with recurrence had a cortical type tumour. The predictive value of the tumour classification system can be seen in fig 5 with medullary tumours showing excellent prognosis, and mixed pattern tumours the worst prognosis (five year survivals 100% for medullary tumours, 92% for cortical tumours, and 80% for mixed pattern tumours).

Discussion

After studying Marino and Muller-Hermelink's published criteria for the subclassification of thymomas into cortical, mixed, and medullary types we were only able to achieve a moderate agreement in assigning a histological pattern to each of the 74 tumours. Even after discussing our difficulties with the published criteria, there was no significant improvement at the second attempt. Only 26 of 74 (35%) tumours were consistently and reproducibly classified.

The failure of any one of us to achieve a κ value of over 0.75 when our first and second attempts at classification were compared indicates that not only did we interpret the published criteria differently but also inconsistently. Unlike Marino and Muller-Hermelink, who have stated that they found morphological uniformity throughout their tumours,⁵ we found field to field variability in the tumours in this series which made the assignment of tumours to any one type difficult. We therefore doubt the usefulness of histopathologists attempting to classify a thy-

moma in this way in their routine surgical workload.

The slightly higher κ value for the label of "cortical pattern" over the other patterns may indicate that the recognition of the cortical pattern is more reliable than the other patterns—that is, the published defining characteristics of cortical differentiation are easier to recognise. Even for this cortical pattern, however, the κ value does not reach the level of excellent agreement.

The predictive and prognostic value of a classification system like that proposed by Marino and Muller-Hermelink which fails consistently to classify two thirds of cases is at the outset severely limited. Even in those few tumours which were consistently classified this study failed to support its predictive value. We found a 92% five year survival for patients with cortical pattern tumours. This is different from the 52% reported by Ricci *et al*,⁹ who concluded that cortical thymoma behaves like a malignant tumour. We also found that mixed pattern tumours have the worst rather than an intermediate prognosis, which is contrary to the findings of Ricci's group, and is rather difficult to reconcile with the intermediate place given to this type of tumour in Muller-Hermelink's classification. Although we did find that medullary tumours had a 100% five year survival, which would support the belief of Ricci's group that medullary tumour has a benign natural history, we only had four thymomas consistently classified in this category, and one was in stage II.

For the purpose of this study we felt it was justifiable not to attempt to subdivide cortical pattern tumours into cortical thymomas and so-called well differentiated thymic carcinomas.^{6,7} This was because in our view the criteria used to distinguish the so-called carcinomas from the cortical thymomas are even more subjective than those required to divide thymomas into medullary or mixed, or cortical types. (Cortical thymomas lack "predominantly epidermoid differentiation" and have no or minimal cytological atypia, whereas carcinomas have such differentiation and have slight to moderate atypia). We also reason that if our cortical group contains any of the more aggressive tumours of the type Muller-Hermelink would call well differentiated thymic carcinomas, their inclusion would merely tend to worsen the biological behaviour and survival of our cortical category overall. Even with this potential bias our cortical pattern tumours failed to show a worse prognosis than the mixed pattern tumours.

Other workers have also failed to find the cortical/medullary classification of prognostic value. Kornstein *et al* classified 95 thymomas as cortical, medullary, or mixed and found no significant difference in relapse free survival.¹⁵ Hadour showed that cortical, mixed, or medullary epithelial morphology was no predictor of invasiveness in a study of 25 cases.¹⁶ In a review of thymic tumour classification and nomenclature, Otto recommended that a clearcut classification based on stage should

Figure 5 Survival curves for thymomas categorised by histological pattern.

Table 5 Comparison of survivals of patients between our study and other reported studies

	Percentage survival (years)	
	5	10
Present study: n = 73	78	
Stage I	100	
Stage II	84	
Stage III	27	
Stage IV	0	
Masoaka <i>et al</i> ¹ : n = 96	74	57
Stage I	93	67
Stage II	86	60
Stage III	70	58
Stage IV	50	0
Verley <i>et al</i> ² : n = 200		
No invasion	85	80
Invasion	50	35
Maggi <i>et al</i> ³ : n = 169	79	65
No invasion	85	
Invasion	67	
Lewis <i>et al</i> ⁴ : n = 283	67	53
No invasion	75	63
Invasion	50	30

be used instead of subtle histomorphological classifications.¹⁷

Although Muller-Hermelink *et al* have found immunohistological differences between cortical and medullary thymomas which they believe confirm their morphological distinctions,¹⁸ others have found conflicting results. Mokhtar *et al* showed differences in immunostaining between cortical and medullary epithelial cells in normal thymus, but could not specifically delineate thymomas into cortical or medullary type.¹⁹ Hofmann *et al* found that only four of 14 thymomas were classifiable into medullary or cortical type on the basis of immunophenotype, and in three of those the immunophenotype result disagreed with the result of morphological classification.²⁰ Kwast *et al* concluded that thymomas could be classified into medullary or cortical tumours on the basis of immunophenotyping of six cases, but could not correlate staining pattern with biological behaviour.²¹ Wilcox *et al* discovered epithelial cell heterogeneity in an immunohistological study of 30 thymomas, and were unable to relate immunophenotype to biological behaviour with respect to the presence or absence of myasthenia gravis.²²

The correlation of more advanced surgical stage with decreased survival has repeatedly been shown by most large series (table 5), and this correlation was further strengthened by this study. The slightly better outcome for stage I tumours in this study, and the more rapid demise of patients with stage IV tumours, may be partly explained by the smaller numbers of cases and shorter follow up period than Masoaka's group.

In conclusion, we have shown that three experienced thoracic histopathologists were unable to apply in practice the histomorpho-

logical classification of thymomas proposed by Marino and Muller-Hermelink. Furthermore, we were unable to confirm reports of the prognostic and predictive value of this classification. Rather, this study confirms the prognostic value of surgical stage.

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