Atypical and malignant meningiomas: importance of micronecrosis as a prognostic indicator

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Twenty-eight patients with a diagnosis of either atypical or malignant meningioma, according to the World Health Organisation (WHO) classification, were followed up to relate histopathological features with times to recurrence and death. Five year disease-free survival was 41% with a median disease free survival of 27 months. Micronecrosis was the only histopathological feature associated with increased risk of recurrence (rate ratio, 3.73; 95% confidence interval 1.03-13.6). At 36 months, 32% of patients with micronecrosis were alive compared with 71% of patients without micronecrosis. Brain invasion was not associated with disease-free survival. After recurrence, median survival was 7 months and was not correlated with any histopathological feature. The prevalence of micronecrosis was estimated from random samples of benign, atypical and malignant meningiomas to be 8%, 42% and 71% respectively. The relevance of these findings and the current WHO classification is discussed.

Keywords: atypical meningioma, malignant meningioma, micronecrosis, brain invasion

Introduction

The current World Health Organisation (WHO) classification of primary central nervous system tumours divides meningiomas into benign, atypical and malignant tumours. Atypical meningiomas show an increased cellularity, mitotic rate and nuclear-cytoplasmic ratio, prominent nucleoli and areas of necrosis. Previous studies of atypical meningiomas have shown an overall increased risk of recurrence following complete resection compared with benign meningiomas. The main defining feature of malignant meningiomas in the WHO classification is invasion of the underlying brain parenchyma. Despite use of the term malignant, invasion has not been clearly established as indicating aggressive behaviour. This has been due to the low frequency of malignant meningiomas and the difficulty of establishing brain invasion with certainty. The malignancy of the papillary meningioma subtype is accepted.

Previous studies of individual histopathological features of meningiomas have suggested that high cellularity is an indicator of poor prognosis. However, there has been no consistent finding in the assessment of mitotic activity, nucleolar prominence or cellular pleomorphism as prognostic indicators. These features are subject to significant inter-observer variability. In addition, some studies have included haemangiopericytomas and subtotally resected tumours, further clouding the analysis of recurrence related solely to histopathological features. Haemangiopericytomas are no longer regarded as a subtype of meningiomas in the WHO classification, and subtotal resection has been clearly established as increasing the risk of recurrence. To determine the independent prognostic importance of histopathological features, we analysed the survival of 28 patients, 15 with atypical and 13 with malignant meningiomas, as classified by the present WHO criteria.

Materials and methods

Between 1986 and 1990, the Australian Brain Tumour Registry was notified of 2031 meningiomas. Only 133 of these (63 males and 70 females) were graded as either atypical or malignant by a panel of neuropathologists.
using the WHO criteria. Two series of meningiomas were selected for analysis.

The first series included 28 of the 133 atypical/malignant meningiomas which had been completely resected (the dural attachment had also been removed in 25 cases) and for which adequate follow-up data were available. These comprised 15 males and 13 females with an average age of 54 years, range 21–88 years. The following histopathological features were recorded for each case: 1 invasion of brain, rounded extensions of tumour infiltrating brain beyond the arachnoid or Virchow–Robin spaces without a fibrous connective tissue layer present between tumour and underlying parenchyma (Figure 1); 2 mitotic activity, any mitotic figures present in five high power fields; 3 pleomorphism, variation in size and shape of tumour nuclei; 4 micronecrosis, foci of up to 200 cells showing karyorrhexis with central necrosis (Figure 2); and 5 nucleolar prominence, prominent nucleoli in the majority of tumour cells seen at × 200 magnification. All histological sections were examined using haematoxylin and eosin stained preparations.

Two sets of Kaplan–Meier survival analyses were performed. The first computed survival until first recurrence or death and the second computed survival from the first recurrence to death. Additional analyses were stratified by the presence or absence of one of the five histopathological features. Survival curves were calculated and plotted using Splus software. Rate ratio estimates and confidence intervals were calculated using the proportional hazards model.

A second series of tumours was selected to determine the proportion of benign meningiomas with micronecrosis. This comprised a random sample of 89 of the original 1898 benign meningiomas and 20 of the remaining 105 atypical/malignant meningiomas. Of the latter, 12 were atypical and eight were malignant. Altogether 109 meningiomas were assessed and the occurrence of micronecrosis in each sub-category was recorded.
Atypical and malignant meningiomas

Results

All 13 malignant meningiomas in the first series exhibited nuclear pleomorphism and hypercellularity; 12 (92%) had increased mitotic activity, 8 (62%) micronecrosis and 6 (46%) prominent nucleoli. All 15 atypical meningiomas were hypercellular; 9 (60%) had an increased mitotic count, 7 (46%) micronecrosis, 3 (20%) prominent nucleoli and 12 (80%) pleomorphism. The combined prevalence of each of these features in all 28 meningiomas is given in Table 1. In the random sample of cases (second series) 7 (8%) of 89 benign, 15 (42%) of 12 atypical, and 5 (71%) of 8 malignant tumours showed micronecrosis.

Overall, there were 14 recurrences, including one death. Median disease-free survival was 27 months and 5-year disease-free survival was 41% (Figure 3). The median disease-free survival of meningiomas with brain invasion was 21 months compared with 24 months in cases with no invasion. It was not possible to establish accurate survival probabilities on the basis of this feature alone. Disease-free survival rate ratio estimates and their 95% confidence intervals are shown in Table 1 for each histological feature. Micronecrosis was the only feature associated with an increased risk of recurrence with 32%

Table 1. Survival rate ratios, by histological feature, in the follow-up series of 28 atypical/malignant meningiomas

<table>
<thead>
<tr>
<th>Histopathological feature</th>
<th>No. of cases</th>
<th>Rate ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasion</td>
<td>13 (46%)</td>
<td>0.97</td>
<td>0.33-2.8</td>
</tr>
<tr>
<td>Mitotic activity</td>
<td>21 (75%)</td>
<td>1.26</td>
<td>0.35-4.6</td>
</tr>
<tr>
<td>Micronecrosis</td>
<td>15 (54%)</td>
<td>3.73</td>
<td>1.03-13.6</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>9 (32%)</td>
<td>0.51</td>
<td>0.16-1.7</td>
</tr>
<tr>
<td>Pleomorphism</td>
<td>25 (89%)</td>
<td>0.28</td>
<td>0.07-1.1</td>
</tr>
</tbody>
</table>
of patients with foci of micronecrosis alive at 36 months compared to 71% if micronecrosis was not present (Figure 4). As seen in Table 1 the recurrence rate in tumours with micronecrosis was on average almost four times that of the 13 tumours with no micronecrosis.

In the analysis of survival after first recurrence, there were seven deaths amongst 11 cases within 14 months (median 7 months). No individual histopathological feature correlated with survival.

Discussion

The proportion of meningiomas described as atypical/malignant (8.6%) in the Australian Brain Tumour Registry is within the range (1–9%) of previous published estimates. A sex ratio close to unity has also been observed in other series and contrasts with the female preponderance of benign meningiomas. Five-year survival from atypical/malignant meningiomas in our series was 41%, about half that of benign meningiomas. Recurrence rate was 50% at 27 months, as compared with 40% at 3 years, and 71% at 8 years in two previous studies.

We combined the 15 atypical and 13 malignant meningiomas into one group and found that micronecrosis was the single histopathological feature predicting poor outcome. Microscopic foci showing central necrosis were often multiple and consisted of up to 200 karyorrhectic tumour cells. Larger areas of necrosis are probably less specific as they may be due to large vessel occlusion unrelated to tumour biology and were not assessed in this study. Large areas of necrosis may also be seen in large, entirely benign meningiomas. Some studies have also indicated that small foci of necrosis have been associated with meningiomas that recur more frequently. Foci of necrosis have also been noted in 10% of 185 non-recurrent meningiomas. However, from the data presented, it is not possible to determine the size of these necrotic foci or whether they occurred in what would now be classified as benign, atypical or malignant meningiomas. In the data from our second series of 109 meningiomas 8% with no other atypical features and classified as benign, had foci of micronecrosis. Using the current WHO criteria for diagnosis of an atypical meningioma, this single feature alone would not alter the diagnosis from benign. Further study of micronecrosis is required to determine if this feature is indicative of poor prognosis in otherwise benign meningiomas.

Micronecrosis, being multifocal and definable at medium power, has less inter-observer variability than other features used to define atypical or malignant meningiomas. Mitotic activity and brain invasion in meningiomas have been particularly subject to inter-observer variability. Mitotic figures are difficult to quantify uniformly in histological sections. In meningiomas, they are often clustered and widely dispersed throughout the tumour in small, high growth foci. Most previous studies have not been able to specify what constitutes a high mitotic rate. Owing to these factors, the prognostic significance of mitotic figures is difficult to assess. However, cytokinetic studies have shown a positive correlation between labelling indices provided by bromo-
deoxyuridine uptake\textsuperscript{14} and Ki-67 immunoreactivity and rapidity of tumour recurrence\textsuperscript{15}. Maier et al.\textsuperscript{16} correlated silver-stained nucleolar organizer region (AgNOR) numbers and recurrence with 23 benign, 35 atypical and 40 anaplastic meningiomas and found overlapping AgNOR numbers in all groups. This finding limits the usefulness of AgNOR counts in predicting prognosis in meningiomas, Maier’s subjective categorization of meningiomas defined ‘atypical’ as showing a focal increased cellularity and at least five atypical mitotic figures per 10 high power fields and ‘anaplasia’ as tumours with high cellular density, high mitotic rate, cytological anaplasia and necrosis. The current WHO classification is more widely accepted in defining the categories of meningioma\textsuperscript{1}.

Brain invasion appeared histologically as rounded extensions of tumour infiltrating beyond the arachnoid or Virchow–Robin spaces without a layer of fibrous connective tissue intervening between tumour and underlying parenchyma. Compression of the molecular layer by tumour on a broad front did not constitute invasion. The most convincing feature of invasion was tumour in white matter or, if confined to cortex, the presence of a reactive astrocytic response. Multiple blocks were examined for accurate assessment of invasion. All the meningiomas showing brain invasion in our study had other features defining atypical meningioma. Owing to poor histological definition of brain invasion and low numbers in previous studies, the veracity of basing a distinction between atypical and malignant meningiomas on invasion can be questioned\textsuperscript{2,5-8,10,17}. In our analysis of 28 meningiomas, brain invasion as an individual factor was found to be of little prognostic significance.

In meningiomas with atypical features, with or without brain invasion, our study has shown that foci of micronecrosis are the most prognostically informative individual histopathological feature prior to recurrence. The relevance of brain invasion as the major defining feature of malignant meningiomas in the WHO classification requires review. Where there was true brain invasion in our study, other atypical features were always present. Brain invasion alone was of little prognostic significance. We consider that tumours showing brain invasion in addition to atypical features should not be segregated from atypical meningiomas.

The current features of atypical meningiomas, including hypercellularity, increased mitotic count, prominent nucleoli, an increase in the nuclear–cytoplasmic ratio and areas of necrosis, clearly define a group of meningiomas with a poorer survival compared with benign meningiomas. Considering meningiomas as a whole, a practical prognostic classification of meningiomas could be simplified to benign and atypical with or without brain invasion. If a further comment on prognosis is required this could be based on the presence of micronecrosis.

References