Recent years have witnessed an intense interest in studies aimed at predicting the biological and clinical behavior of meningiomas. Although usually they are benign tumors, meningiomas have the potential for progression and aggressive behavior, and recurrence is not limited to those with atypical or malignant histological features. Sex steroids have been implicated in the growth of meningiomas since early observations of the preponderance of female patients harboring these lesions,\(^\text{15,49}\) the acceleration of tumor growth during pregnancy,\(^\text{7}\) and an association with breast cancer.\(^\text{37,45,48}\) Progesterone receptors have been identified in normal arachnoid tissue,\(^\text{4,80}\) but normal adult meninges express low levels of PRs.\(^\text{44}\) The expression of PRs in meningiomas is well documented.\(^\text{4,11,28,50,73}\) In meningiomas PRs are functional receptors,\(^\text{17}\) but their regulation is still unclear.\(^\text{9}\) Normal meningeal tissues do not have ERs,\(^\text{4,35}\) and controversy still surrounds the presence of ERs in meningiomas.\(^\text{4,11,12,28,42,50,62,73}\) A lack of ERs but an immunoreactivity to estrogen-regulated protein was observed in 65% of the meningiomas reviewed by Bouillot and colleagues.\(^\text{11}\) Using reverse transcriptase–PCR, Speirs and associates\(^\text{72}\) recently showed that meningiomas with hormone receptors have distinct and heterogeneous clinical and biological behaviors.
confirmed that human meningiomas do express gene transcripts for ERs.

The results of some recent studies have indicated that PR expression in meningiomas relates to the tumor’s grade and recurrence. \(1,2,8,9,10,14,17\) The proliferative index in PR-positive meningiomas was found to be lower than that of PR-negative tumors. \(59\) The role of ERs in meningiomas is still undetermined.

Cytogenetic abnormalities have been documented in meningiomas. A loss or mutation of the meningioma locus on chromosome arm 22q is common in 40 to 70% of tumors and is considered to be an early step in tumor genesis. Progression and malignant tendencies are hypothesized to occur with deletion or modification of other genes and the accumulation of genomic aberrations; these alterations have been located by different investigators on chromosomes 1, 6, 8, 9, 10, 14, 17 and \(Y\). \(6,14,36,37,60,61\) Aggressive meningiomas are believed to follow a multistep tumor progression model involving genes on 1p, 1q, and 22q. \(97\) These abnormalities, however, are also found at the beginning of tumor development. \(1\) How these cytogenetic abnormalities relate to sex steroids, however, is unknown. In this study, we investigated the relationship between clinical behavior and cytogenetic findings for meningiomas in three categories: tumors expressing PRs only, those with no receptors, and those expressing ERs.

Materials and Methods

Patient Population

We studied receptor status in tumor specimens collected from 239 patients with cerebral meningiomas who underwent surgery between January 1993 and July 2004 at our institution. In 221 patients, the meningioma was located at the skull base; in 97 of these, the tumor involved the cavernous sinus. Eight patients had a convexity meningioma and 10 had a parasagittal meningioma. Fifty-seven patients had undergone surgery at other institutions and harbored recurrent tumors when they came for treatment. In cases of basal meningioma, the extent of tumor removal depended on the location of the tumor, especially for those lesions located in the cavernous sinus or the petroclival area. Subtotal resection implied visible residual tumor, whereas gross-total resection included cases in which a small piece of tumor was detected on postoperative MR imaging studies and was adherent to important vital structures such as the carotid or basilar arteries or the brainstem. Any increase in the size of a residual tumor on follow-up MR images or any growth of tumor in cases in which no residual tumor had been found was counted as a recurrence.

Patients were divided into three groups according to the receptor status of the tumor they harbored. Group 1 included 162 patients (67.8%) whose tumors demonstrated a positive reaction to markers for PRs alone. Group 2 comprised 59 patients (24.7%) with receptors for neither progesterone nor estrogen. Group 3 included 18 patients (7.5%) whose tumors had ERs with or without PRs. Only two patients (1%) had tumors that displayed a positive reaction for ERs alone. The other 16 patients in Group 3 had tumors with both ERs and PRs.

Histological Studies

The histological grade of each tumor was classified according to the WHO 2000 classification. \(60\) We classified atypical, chordoid, and all cases of brain invasion as Grade II. Malignant, papillary, and rhabdoid meningiomas were classified as Grade III. The immunohistochemical method used to detect ERs, PRs, PCNA, and Ki67 is an indirect biotin–streptavidin system for detecting mouse immunoglobulins G and M, and rabbit polyclonal primary antibodies in paraffin-embedded sections. We used an automated diaminobenzidine detection system (Ventana Medical Systems, Tucson, AZ), which is used to detect mouse and rabbit antibodies bound to an antigen in tissue sections. The specific antibody is located by using a biotin-conjugated secondary antibody. This step is followed by the addition of a streptavidin enzyme conjugate, which binds to the biotin present on the secondary antibody. The complex is then visualized with a precipitating enzyme product. The receptor status was defined for all 239 patients. The PCNA was measured in 98 cases and Ki67 was measured in 77.

Cytogenetic Analysis

A cytogenetic analysis was performed on 154 specimens using standard in situ culture techniques and G-banding, as described elsewhere. \(66\) Cytogenetic abnormalities were defined as any change in the chromosome that showed more than two cells with the same structural or numerical abnormality. The presence of a single cell with an abnormal karyotype was not considered a true clone.

Statistical Analysis

Statistical analysis and comparisons between groups were performed using the Student t-test and the Fisher exact test with the aid of MedCalc statistical software (version 7; MedCalc Software, Mariakerke, Belgium).

Results

Progesterone Receptor–Positive Meningiomas

Group 1 comprised 116 women (72%) and 46 men (28%) (female/male ratio 2.5:1) who harbored tumors positive for PRs alone. The ages, sexes, locations, and extents of resection in this group are shown in Table 1.

Group 1 included 26 patients (16%) with recurrent tumors prior to our treatment and 136 patients (84%) with de novo tumors (Table 2). In the women in this group, 89% of the tumors were de novo; in the men, 72% were de novo. The greater number of recurrent tumors at presentation in the men in this group was statistically significant (\(p < 0.016\); Table 2).

In 145 cases, the pathological analysis showed a Grade I meningioma with various benign variants. Fourteen of the remaining 17 tumors were Grade II and three were Grade III. Of these tumors, 19% occurred in men and 8% in women (Table 2). In the men, atypical or malignant types of tumors were more frequent (\(p < 0.024\)).

In the PR-positive group, tumors thus had a predilection for women (female/male ratio 2.5:1) and most were de novo (de novo/recurrent tumor ratio 5.2:1). The overall recurrence rate after surgery was 19%. In patients in whom residual tumors had been seen on postoperative MR images the recurrence rate was 36%, whereas in patients in whom there was no such finding the recurrence rate was 5% (\(p <
Sex receptors as prognostic indicators in meningiomas

TABLE 1  
Clinical characteristics of patients with meningiomas with differing receptor statuses

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PR-Positive Tumor (Group 1)</th>
<th>Receptor-Negative Tumor (Group 2)</th>
<th>ER-Positive Tumor (Group 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>total</td>
<td>162 (68)</td>
<td>59 (25)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>male</td>
<td>46 (28)</td>
<td>20 (34)</td>
<td>9  (50)</td>
</tr>
<tr>
<td>female</td>
<td>116 (72)</td>
<td>39 (66)</td>
<td>9  (50)</td>
</tr>
<tr>
<td>mean age in yrs (± standard deviation)</td>
<td>47.11 ± 12.27</td>
<td>45.65 ± 16.69</td>
<td>55 ± 19.01</td>
</tr>
<tr>
<td>male</td>
<td>51.86 ± 10.77</td>
<td>50.18 ± 11.26</td>
<td>52.77 ± 10.92</td>
</tr>
<tr>
<td>tumor located in skull base</td>
<td>153 (94)*</td>
<td>55 (93)</td>
<td>13 (72)*</td>
</tr>
<tr>
<td>w/ cavernous sinus involvement</td>
<td>65 (42)</td>
<td>24 (44)</td>
<td>8  (62)</td>
</tr>
<tr>
<td>convexity meningioma</td>
<td>4 (2)†</td>
<td>1 (2)</td>
<td>3  (17)†</td>
</tr>
<tr>
<td>parasagittal meningioma</td>
<td>5 (3)</td>
<td>3 (5)</td>
<td>2  (11)</td>
</tr>
<tr>
<td>gross-total resection</td>
<td>150 (92)</td>
<td>57 (97)</td>
<td>16 (89)</td>
</tr>
<tr>
<td>small residual lesion on MRI</td>
<td>58 (39)</td>
<td>20 (35)</td>
<td>5  (31)</td>
</tr>
<tr>
<td>no residual lesion on MRI</td>
<td>92 (61)</td>
<td>37 (65)</td>
<td>11 (69)</td>
</tr>
<tr>
<td>subtotal resection</td>
<td>12 (7)</td>
<td>2 (3)</td>
<td>2  (11)</td>
</tr>
<tr>
<td>breast cancer</td>
<td>4 (2)</td>
<td>0 (0)</td>
<td>1  (0.5)</td>
</tr>
<tr>
<td>lesion growing during pregnancy</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0  (0)</td>
</tr>
</tbody>
</table>

* Statistical significance between indicated groups (p = 0.006437).
† Statistical significance between indicated groups (p = 0.022978).

0.00001; Table 2). Only 10% of the tumors in this group were aggressive, and these occurred more often in men than in women. Death from progression of disease occurred in 3% of patients in Group 1.

The PCNA index in Group 1 was 4.60 ± 5.96 and the overall Ki67 index was 1.95 ± 1.88 (Table 3).

In five patients in this group, the receptor study was performed after each of two surgeries. In two of these five patients, the tumor changed its receptor status. In the first patient, the specimen examined after the first surgery was PR-positive only, but the one examined following the second surgery showed the presence of ERs. In the second patient PR positivity was identified in the specimen examined after the first surgery and the lesion resected at the second surgery had a receptor-negative status. These findings suggest that a tumor can change its receptor status with progression.

Chromosomal Changes. The results of the cytogenetic analysis, which was performed on specimens from 103 patients (69 women and 34 men) with PR-positive meningiomas, are shown in Tables 2 and 4. Differing chromosome aberrations were identified in approximately 50% of patients (26 men and 25 women) with a statistically significant difference in the distribution of chromosome abnormalities between men (76%) and women (36%) (p < 0.0002), especially for chromosomes 7 and 14. Based on these findings, it appears that in men PR-positive tumors accumulate more changes in karyotype and have the potential for a worse clinical progression than in women. Changes involving chromosomes 1, 6, 11, 14, or 19 were statistically significantly higher in patients who presented to us with recurrent tumors than in those with de novo tumors (Table 4). In all but one case, chromosome 19 was the only chromosome to exhibit changes in the same region of the long arm (q13).

Thus, in the PR-positive group, chromosome changes were dominant in cases of recurrent tumor, compared with cases of de novo lesions, and were more dominant in men than in women.

Receptor-Negative Meningiomas

Group 2 comprised 59 patients with receptor-negative meningiomas. There were 39 women (66%) and 20 men (34%), for a female/male ratio of 1.95:1. In the receptor-negative group, tumors still predominated in women but the female/male ratio was lower than that in Group 1. A summary of the clinical findings for this group is shown in Table 1. At presentation, in 25 patients (42%) the tumor was recurrent, and in 34 (58%) it was de novo. There was a statistically significant difference between cases of de novo and recurrent lesions, with a larger percentage of cases of recurrent tumor at the time of presentation compared with Group 1 (p < 0.00001), especially among women (p < 0.0001).

The pathological examination showed that 41 tumors (69%) were benign and 18 (31%) were aggressive (13 Grade II lesions and four Grade III lesions). There was a statistically significantly higher proportion of aggressive tumors in this group compared with those in the PR-positive group (p < 0.00009), and in women in this group compared with women in Group 1 (p < 0.0033). There was no difference, however, in the proportion of aggressive tumors between men and women in this group or between men in this group and men in Group 1.

Twenty-three patients (39%) had a recurrence of disease after surgery. Twelve (52%) of these had recurrence from a residual tumor, and in 11 (48%) no residual tumor had been seen on the postoperative MR images (Table 2). There was a statistically significant difference between the PR-positive group and Group 2 in the overall number of recurrences (p < 0.0025), especially in women (p < 0.0074) as well as in patients without residual tumor (p < 0.00045; Table 2). Five patients (8%) died of progression of the disease.

The average proliferative indices in this group were 13.44 ± 22.50 for PCNA and 3.13 ± 2.87 for Ki67 (Table
3). In comparison with the PR-positive group, the PCNA index was statistically significantly higher for this group \((p < 0.004)\); the Ki67 index tended to be higher overall, but the difference was not statistically significant. In comparison to women in the PR-positive group, there was a statistically significant increase in the Ki67 index \((p < 0.002)\).

### Chromosomal Changes

A chromosome analysis was performed in 37 cases of receptor-negative tumor. Chromosome abnormalities were present in 31 patients (84\%; Tables 2 and 4). The increased number of cases with an abnormal karyotype in this group was statistically significant compared with the PR-positive group overall \((p < 0.0004)\) and for de novo tumors \((p < 0.0135)\). There was a statistically significant increased number of tumors with abnormal karyotypes among the de novo tumors in women in this group compared with women in the PR-positive group \((p < 0.0246)\).

### Estrogen Receptor–Positive Meningiomas

Group 3 comprised 18 patients harboring meningiomas with ERs alone (two tumors) and both ERs and PRs (16 tumors)
Sex receptors as prognostic indicators in meningiomas

lesions. Of these patients, nine (50%) were women and nine (50%) were men, with a female/male ratio of 1:1. A summary of clinical findings for this group is shown in Table 1.

When the patients came for treatment, six (33%) had recurrent tumors and 12 (67%) had de novo tumors. Twelve lesions (67%) were classified as benign, whereas six (33%) were Grade II (three lesions) or Grade III (three lesions). There was a statistically significant increase in the number of aggressive tumors in this group when compared with the PR-positive group (p < 0.014844), especially for men (p < 0.0022) compared with the PR-positive group. Recently, some studies have addressed the role of PRs as a prognostic indicator of the biological behavior of meningiomas.13,22,28,77 An analysis of our data with involvement of chromosome 14 or 22 was statistically significant for women. The ER-positive group had an increase in the distribution of recurrent lesions compared with the PR-positive group. In the receptor-negative group, but female predominance was still present, with a female/male ratio of 1.95:1. There was no significant increase between this group and the receptor-negative group.

In seven patients (39%) there was tumor recurrence after surgery: in five patients (71%) this occurred from a residual tumor, and in two patients (29%) no residual tumor had been detected on the postoperative MR images. Despite the small number of cases, this group had a statistically significant increase in the number of recurrences without residual tumor in comparison with Group 1 (p < 0.00383) (Table 2). Four patients (22%) died of progression of disease, and this is a statistically significant difference in comparison with the PR-positive group (p < 0.0066).

The proliferative indices, based on the presence of PCNA and Ki67, in the ER-positive group were 9.83 ± 10.72 and 6.80 ± 7.85, respectively. These numbers were statistically significantly higher than those in the PR-positive group. Furthermore, the PCNA index was significantly higher among men (p < 0.0022) compared with the PR-positive group. In women, the Ki67 index was significantly higher than the indices in both the PR-positive and receptor-negative groups (Table 4).

Chromosomal Changes. The results of a chromosome analysis were available for 14 patients (Tables 2 and 4). In 12 patients (86%) there was an abnormal karyotype. There was a statistically significant increase in the number of cases with an abnormal karyotype compared with Group 1 (p < 0.02) but not when compared with Group 2. Despite the fact that this was a small group, the number of cases with involvement of chromosome 14 or 22 was statistically significantly higher than that of the PR-positive group overall and in de novo cases (Table 4).

Discussion

Presence of PRs and ERs in Meningiomas

The presence of PRs in meningiomas has been documented in many studies, with rates of occurrence ranging from 48 to 88%.8,9,22,24,28,44,62,73,81,86 Nevertheless, the presence of ERs in these lesions is still subject to discussion. Most investigators have found meningiomas to lack ERs,4,11,12,15,50,68 but others have located ERs in 5 to 33% of these tumors.28,62,23,81 Very sensitive analyses, such as the ligand-binding assay,4,8,62 have shown the presence of ERs in 11.1 to 36% of tumors, and PCR and reverse transcriptase–PCR46,34,72 have allowed the detection of messenger RNA coding for ERs in 68 to 100% of tumors.

In our study, PRs were present alone in 68% of tumors. Estrogen receptors were detected in 8% of tumors, but only two lesions (1%) had ERs alone. Only 25% of meningiomas had no evidence of PRs and ERs, a number in accordance with findings in the literature.

It is well established that meningiomas are found predominantly in women.8,14,15,24,28,44,62,73,81,86 It was seen in both women and men, but was statistically significant for women. The ER-positive group had an increase in the distribution of recurrent lesions compared with de novo ones, but because of the small number of patients, the numbers were not statistically significant. Hence, the presence of PRs is predominant for de novo tumors, with a de novo/recurrent tumor ratio of 5.2:1. In the receptor-negative group the de novo/recurrent tumor ratio was 1.4:1, and in the ER-positive group it was 2:1. This finding differs somewhat from the results of the study conducted by Rubinstein and colleagues.82 In that study the rate of PRs was 82% in patients who had undergone initial excision of the tumor, whereas the rate was 92% in patients with recurrent tumor. Of 13 recurrent tumors in their study, seven were also positive for ER. An association between
### TABLE 4

Chromosome changes in different receptor status groups*

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Total</th>
<th>Agr Men</th>
<th>Rec Cases</th>
<th>DN Cases</th>
<th>Monosomy</th>
<th>Total</th>
<th>Agr Men</th>
<th>Rec Cases</th>
<th>DN Cases</th>
<th>Monosomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103</td>
<td>13</td>
<td>19</td>
<td>84</td>
<td>37</td>
<td>12</td>
<td>16</td>
<td>21</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>PR-Only (Group 1) Receptor-Negative (Group 2) ER-Positive (Group 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Agr Men = aggressive meningioma (WHO Grade II or III); DN = de novo; Rec = recurrent tumor at time of treatment; Total = total no. of cases.

† Statistical significance between indicated groups (p = 0.000093).
‡ Statistical significance between indicated groups (p = 0.000017).
§ Statistical significance between indicated groups (p = 0.000113).
|| Statistical significance between indicated groups (p = 0.001289).
|a| Statistical significance between indicated groups (p = 0.005076).
|b| Statistical significance between indicated groups (p = 0.008331).
|c| Statistical significance between indicated groups (p = 0.008056).
|d| Statistical significance between indicated groups (p = 0.008331).
|e| Statistical significance between indicated groups (p = 0.008331).
|f| Statistical significance between indicated groups (p = 0.008331).
|g| Statistical significance between indicated groups (p = 0.008331).
|h| Statistical significance between indicated groups (p = 0.008331).
|i| Statistical significance between indicated groups (p = 0.008331).
|j| Statistical significance between indicated groups (p = 0.008331).
|k| Statistical significance between indicated groups (p = 0.008331).
|l| Statistical significance between indicated groups (p = 0.008331).
|m| Statistical significance between indicated groups (p = 0.008331).
|n| Statistical significance between indicated groups (p = 0.008331).
|o| Statistical significance between indicated groups (p = 0.008331).
|p| Statistical significance between indicated groups (p = 0.008331).
|q| Statistical significance between indicated groups (p = 0.008331).
|r| Statistical significance between indicated groups (p = 0.008331).
|s| Statistical significance between indicated groups (p = 0.008331).
|t| Statistical significance between indicated groups (p = 0.008331).
|u| Statistical significance between indicated groups (p = 0.008331).
|v| Statistical significance between indicated groups (p = 0.008331).
|w| Statistical significance between indicated groups (p = 0.008331).
|x| Statistical significance between indicated groups (p = 0.008331).
|y| Statistical significance between indicated groups (p = 0.008331).
|z| Statistical significance between indicated groups (p = 0.008331).

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* S. Pravdenkova, et al.
J. Neurosurg. / Volume 105 / August, 2006
Sex receptors as prognostic indicators in meningiomas

recurrence and PR-negative status has been documented. Rubinstein and associates found ERs in tumors in 26% of patients who were undergoing initial excision and in 54% of patients with recurrent lesions. These data correlate with our findings of a tendency for increased numbers of recurrent lesions in the ER-positive group.

Relation of PRs and ERs to the Pathological Grade of the Tumor

Meningiomas have been found to be atypical in 1.8 to 19% of cases and malignant meningiomas in approximately 0.9 to 18.5% of cases in different studies. In our study we have shown that WHO Grades II and III tumors were significantly more numerous in the receptor-negative group and the ER-positive group in comparison with the PR-positive group. These lesions represented 10% of cases in the PR-positive group, 31% of cases in the receptor-negative group, and 33% of cases in the ER-positive group. The increased proportion of men in the receptor-negative group does not account for these findings. Men are known to harbor higher-grade meningiomas more frequently than women (32% compared with 12%). In our study, however, the number of meningiomas with aggressive pathological behavior (Grades II and III lesions) was significantly higher in the receptor-negative group, especially among the women (p < 0.0034), with a trend in the men in comparison with the PR-positive group. In the ER-positive group, the number of Grade II or Grade III meningiomas found in men was statistically higher than that in the PR-positive group (p < 0.0374).

According to the literature, the PR-positive status occurs more frequently in benign meningiomas than in malignant tumors. Meningiomas with atypical features have been reported to be PR-negative, but Hsu and colleagues found that 40% of malignant meningiomas contained PR-positive nuclei albeit with a lower mean PR score. Estrogen receptors were present in 7.1% of benign, 7.4% of atypical, and 13.3% of malignant tumors in the study conducted by Hsu and associates. Anaplastic meningiomas were consistently negative for ER markers in the study by Taddei and colleagues.

In our study, the recurrence rate tended to increase overall from Group 1 to Group 3; it was 19% in the PR-positive group, 39% in the receptor-negative group, and 39% in the ER-positive group. Recurrence from a totally resected tumor (with no residual lesion seen on postoperative MR images) was significantly lower in the PR-positive group in comparison with both receptor-negative and ER-positive tumors.

Proliferation Indices and Sex Steroids

To predict the biological and clinical behavior of a meningioma remains difficult. Proliferative labeling indices such as PCNA and Ki67 (MIB-1) are widely applied but strictly associated with cell proliferation. The labeling index has been shown to increase generally with an increasing histological tumor grade or with recurrent meningiomas. A high labeling index and a high tumor grade have also been found to be significant risk factors for recurrence. A negative correlation between PR and the mitotic index was observed clinically and in an experimental study, but no correlation was found between ER and mitotic indices.

We saw a statistically significant higher PCNA index overall in tumors in the receptor-negative group compared with the PR-positive group. The Ki67 index was statistically significantly higher for women in the receptor-negative group compared with those in the PR-positive group. Significantly increased PCNA and Ki67 indices were seen in the ER-positive group compared with the PR-positive group. Despite the small number of patients in the ER-positive group, there was a significantly increased PCNA index for men, compared with the PR-positive group, and an increased Ki67 index for women, compared with the PR-positive and receptor-negative groups. The PCNA and Ki67 are completely different proteins. The antigen identified by the monoclonal antibody Ki67 is expressed during the active phase of the cell cycle but is absent in the G0, resting phase. Expression of the Ki67 protein is an absolute requirement for progression through the cell division cycle. The gene for coding this protein is located on 14q25-qter. Either PCNA or cyclin is essential for cellular DNA synthesis. An elevated expression of PCNA has been documented in the nucleus during the late G1 phase immediately before the onset of DNA synthesis. It becomes maximal during the S phase and declines during the G2 and M phases. Its gene is located at 20p12. One study has documented a constant expression of PCNA in all breast carcinomas with a heterogeneous pattern, whereas the immunoreactivity for Ki67 appeared to be less represented and focal so that a linear relationship between PCNA and Ki67 immunostaining was absent.

Increased levels of proliferative indices in the receptor-negative and ER-positive groups indicate that the PR status may be closely related to the growth potential of the meningioma. Proliferating meningioma tumor cells do not express PR, and PR levels appear to decrease rapidly in vitro in cell cultures.

Chromosome Alterations in Meningiomas and the Possible Relation to Sex Steroids

The PR gene is located on 11q22-q23. Progesterone receptors activate the transcription from PR-containing promoters. The gene for expressing ERs is located on chromosome 6q24-q26 (6q25.1). In our study we found no dramatic changes in chromosome 11 or chromosome 6 in any of the groups. In the literature, there is no correlation between the loss of ER expression and the loss of 6q24-q26, or between the loss of chromosome 11q22-q23, where the PR gene is located, and the expression of the PR in patients with breast cancer.

Cytogenetic studies show that meningiomas are relatively heterogeneous and that they display complex karyotypes in 87 to 95% of aggressive tumors and in 60 to 68% of benign tumors. Some investigators have documented the accumulation of genomic abnormalities from benign to atypical and anaplastic meningiomas with an increased number and frequency of involved chromosomes. The current model of malignant progression is an increasing number of genetic mutations or a mutation affecting a number of genes with an oncogenic potential, regardless of whether they are oncogenes or tumor suppressor genes.
In our study, a statistically significant accumulation of cytogenetic abnormalities was seen from the PR-positive group to the receptor-negative and ER-positive groups. Abnormal karyotypes were seen in 50, 84, and 86% of cases in the PR-positive, receptor-negative, and ER-positive groups, respectively.

The most frequent chromosome abnormality detected in patients with meningioma is the entire loss of chromosome 22 or deletion of its long arm (22q). The loss of genetic material on chromosome 22 is an early step in the development of meningiomas. Monosomy 22 as a sole abnormality has been reported in 6 cases in a study of meningiomas and meningiomas that are positive for both ERs and PRs. Authors also separated genes with different expressions related to the WHO grade of meningiomas. These genes include ear-2, the junB protooncogene located on 19p13.2, and calreticulin located on chromosome 19p13.3–p13.2. The calreticulins inhibit angiogenesis and tumor growth (Burkitt lymphomas in nude mice). Ear-2 is associated with hormonal gene regulation and can repress estrogen-stimulated transcriptional activity of the human oxytocin gene promoter. Ear-2 is upregulated in meningiomas; junB, which encodes transcription factors and transcriptional coregulators, is downregulated in WHO Grades II and III meningiomas, and Ear is bound directly to JunB.

SULT2B1 is mapped to human chromosome band 19q13.3 and sulfotransferase catalyzes the sulfation of dehydroepiandrosterone, which is known to be a precursor to numerous steroid sex hormones including estrogen and testosterone.

Receptor Regulation. Actions of PRs to regulate the activity of ligand-dependent transcription may be depend on coactivator and/or corepressor proteins. Carroll and colleagues studied different expressions of the steroid receptor coactivators SRC-1, AIB1, and TIF2 in meningiomas. These authors hypothesized that the relative expression of coactivators in meningiomas may contribute to the heterogeneity of hormonal responses. Coactivators SRC-1 and TIF2 correlate with the presence of PRs and are expressed in 100% (SRC-1) and 92% (TIF2) of PR-positive tumors. No significant relationship was observed between AIB1 and PR status. All meningiomas (six cases) in a study of Carroll, et al., that stained positively for both PR and ER stained positively for AIB1, which is an important component of the estrogen-response pathway.

Regulation of the expression of PRs in meningiomas with an absence of ERs remains unknown. Two isoforms of PR have been identified, PR-A and PR-B, and they are expressed in meningiomas. The PR-A and PR-B isoforms regulate different subsets of genes in breast cancer cells. Tumors that express PR-B grow to twice the size of those that express PR-A in ovariecctomized mice supplemented with estradiol but lacking progesterone. A significant inverse correlation between PR-A and Ki67, was found in meningiomas. Estrogen primarily regulates the PR-B promoter, whereas progestin regulates both PR isoforms in breast cancer cells (for a review see the paper by Graham and Clarke). The PR-B isoform tends to be a stronger activator of target genes, but PR-A can act as a dominant repressor of PR-B. Interaction with progesterone may be modulated via alteration in the ratio of PR-A to PR-B expression, and higher PR-A expression may result in reduced progestin responsiveness. The PR-A isoform has been shown to diminish the response of ERs to their ligands (for a review see the paper by Graham and Clarke). Further study of the expression of PR isoforms in meningiomas that display a positive reaction only for PR and meningiomas that are positive for both ERs and PRs is necessary to increase our understanding of the biology and clinical behavior of meningiomas with differing receptor statuses. This is indicated because the data from the ER-positive group with PRs were quite different from data in the PR-positive group.
Sex receptors as prognostic indicators in meningiomas

Conclusions

Our analysis emphasizes that the expression of PRs alone in a meningioma is a favorable sign for the clinical and biological behavior of the tumor. An absence of both PRs and ERs or the presence of ERs with or without PR receptors separated the tumors into three different types according to increases in the numbers of tumors with aggressive histopathological characteristics as well as qualitative and quantitative accumulations of abnormal karyotypes, especially in de novo tumors and in tumors in women. The fact that a higher proportion of de novo tumors involved chromosomes 14 and 22 in receptor-negative and ER-positive tumors raises the potential for aggressive clinical behavior, progression, and recurrence after total microsurgical resection. The receptor status should be included in any classification of the grade of a meningioma, especially for women. Furthermore, it should be noted that the initial receptor status might change in any progression or recurrence of the tumor.

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Manuscript received May 20, 2005.
Accepted in final form January 20, 2006.
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