Meningiomas account for 13 to 19% of all primary intracranial tumors.26,50,57 The incidence of meningioma in the general population varies from 2.3 cases per 100,000 when detected while the patient is alive to 5.5 per 100,000 if postmortem data are included.29,54 The majority of meningiomas (91%) are benign,49 but this does not preclude recurrence: there is a recurrence rate of between 11.5% and 29% within 7 to 20 years of surgical resection.4,39 Any of the benign histological subtypes demonstrating atypical features 27 are more likely to recur, 53 as are papillary 31 and malignant meningiomas. The incidence of atypical and malignant (including papillary) meningiomas has been reported to be 0.9 to 10.6%, with an average of 2.8%.49 There is a 50% recurrence rate of atypical meningiomas at 10 years, and for malignant meningiomas, recurrence rates of 33%, 66%, and 100% have been found at 5, 10, and 15 years, respectively.52

Atypia and malignancy aside, the most important factor in predicting meningioma recurrence is completeness of resection: 10-year recurrence rates vary from 10% for tumors determined macroscopically to be totally excised (including dural attachment and any abnormal bone) to 100% for tumors that have simply been debulked.52 The site is considered relevant because the least accessible tumors and those intimately related to vital structures are less likely to be totally resected.10 The histological subtype of benign meningiomas is not related to risk of recurrence.33

The higher incidence of meningiomas in women (female/male preponderance 2:1),48 the observation that in women these tumors may enlarge and become symptomatic during hormonal flux, particularly during pregnancy 40 and in the luteal phase of the menstrual cycle,5 and the observation of a nonrandom association between meningioma and carcinoma of the breast51 indicate that female hormones play a role in the growth of meningiomas. Although estrogen receptor levels in these tumors are variable and usually undetectable, PRs are found in most meningiomas (50–88%).7,9,16,17,19,20,22 The PRs are functional and therefore may play an important role in meningioma growth.13,41 In recent studies investigators have found associations between PR status and factors related to meningioma growth/recurrence.13,41 In the Ki-67 assay,56 absence of PRs has been shown to be associated with a high cellular proliferative index, high mitotic index,21 and high tumor grade/nonbenign tumors.8,17,21 Hsu, et al.21 have recently demonstrated that absence of PRs, high mitotic index, and higher tumor grade are significant factors for shorter disease-free intervals following surgery. There is little information in the literature regarding the prognostic

Long-term follow up of progesterone receptor status in benign meningioma: a prognostic indicator of recurrence?


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Object. A long-term prospective analysis of patients with benign meningioma was undertaken to determine whether progesterone receptor (PR) status of the excised tumor has any influence on recurrence.

Methods. Between 1983 and 1985, a total of 62 meningiomas in 53 patients (age range 19–79 years, mean age 55.6 years) were studied for clinical, histological, and pathological characteristics, including hormone receptor status and DNA features. Progesterone receptor status was quantified by cryostat section assay, and then factors affecting recurrence were analyzed. During 1997 all case records were reviewed to determine whether tumor had recurred in any patient, and PR status was correlated with tumor recurrence.

Of the 62 tumors, 60 were benign, and of the benign tumors 29 (48%) were PR positive. Patients harboring 14 of the 60 benign tumors were lost to follow up. Of the 46 tumors included in the final analysis, 13 were recurrent (all within 5 years) and 33 were nonrecurrent. Of the 33 nonrecurrent tumors, 14 had not recurred 5 to 10 years postresection and 19 had not recurred after more than 10 years. Chi-square analysis of the results did not show an association between recurrence and histological subtype, or tumor site but did show an association between recurrence and PR negativity (p = 0.013).

Conclusions. The results indicate that benign meningiomas that are PR positive are less likely to recur, a finding that has prognostic and therapeutic implications.

Key Words • benign meningioma • progesterone receptor • tumor recurrence

Abbreviations used in this paper: PR = progesterone receptor; RU-486 = Mifepristone.
significance of PR status and meningioma recurrence in benign tumors only, which is the group in which most recurrences will manifest. Between 1983 and 1985, meningiomas treated in our department were studied in detail. Clinical, histological, and various pathological characteristics were assessed, including hormone receptor status and DNA features. On the basis of these studies we thought that hormone receptor status and cellular proliferative index might be involved in the biological progression of the tumors. We therefore proposed a prospective analysis of factors affecting recurrence.

**Clinical Material and Methods**

Between 1983 and 1985, a total of 53 patients harboring 62 tumors presented to the Royal Hallamshire Hospital, Sheffield and underwent surgery for meningioma. The patients came from a reporting area with a population of 2.2 million relevant to our unit. Thirty-seven patients (70%) were women and 16 (30%) were men, with an age range of 19 to 79 years (mean 55.6 years). Age, sex, and clinical presentation were recorded. The site of origin of each tumor was identified on radiological studies and confirmed at the time of surgery. Complete excision correlated to Simpson Grade I and incomplete to Simpson Grades II to V. The histological subtype of each tumor was confirmed to the World Health Organization classification (1979), and at the time of analysis (1997) the subtype was also related to the patient’s sex, extent of resection and show that benign meningiomas that were PR positive more than 10 years (19 tumors) were reported. Between 1983 and 1985, 14 (30%) occurred in men, of which five (36%) were PR positive, and 32 (70%) occurred in women, of which 21 (51%) were PR positive. Fourteen of these tumors were not included in the final analysis. Of the 46 tumors included in the final analysis, 14 (30%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive.

**Results**

Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive. Sixty benign neoplasms were studied, of which 29 (48%) were PR positive. Nineteen tumors (32%) occurred in men, of which eight (42%) were PR positive, and 41 (68%) occurred in women, of which 21 (51%) were PR positive.
compared with the 46 lesions studied. We have assumed therefore that the exclusion criteria have not introduced any bias into the final analysis.

Discussion

In this study we demonstrate the previously observed lack of association between PR status and sex, but do not show an association between patient’s sex and tumor recurrence as has been reported by others. This can perhaps be explained by the fact that in our study we only investigated recurrences of benign meningiomas and that the sample included only a few young men (< 40 years old; seven individuals). Regarding sex and recurrence, the previously demonstrated association is between young men and atypical/malignant meningiomas.

We did not find a significant association between tumor site and recurrence, although there was a trend for basal tumors to recur, in keeping with previous studies. Our results did not show a significant difference for recurrence rate and extent of resection, although there was a trend for basal tumors to recur. The majority of the incomplete resection group were classified as Simpson Grade II, which is the 10-year recurrence rate being 15%. The 10-year recurrence rate for Simpson Grade I resections (total resection with dural attachment) is 10%. Because most of the tumors in our study were either completely or significantly resected, this may explain our findings. No association was shown between tumor resection and a benign histological subtype, which agrees with previous reports.

Although we have shown that PR-positive meningiomas were less likely to recur, review of the quantitative data (Fig. 1) reveals that at PR levels of less than 10 fmol/mg of cytosol protein (the level at which appreciable levels of PR were accepted: “PR positive”), the sensitivity and specificity of the PR levels as a predictor of recurrence is only 85% and 45%, respectively. Our results indicate that PR negativity is associated with an increased risk of recurrence of benign meningiomas. Previous investigators have shown an increased rate of recurrence in association with PR negativity, high mitotic rate, and higher tumor grade and others have demonstrated that PR negativity is associated with a high cellular proliferative index, high mitotic index, and nonbenign tumors. Also, the presence of PRs has been shown to result in a more favorable prognosis in patients with breast cancer.

The mechanism by which PR positivity carries a more favorable prognosis remains unclear. In all series in which the relationship between PR status and recurrence has been investigated, recurrences have been shown in the PR-positive group, which indicates that other factors are involved. In several series, the presence of other hormone receptors in meningioma tissue has been identified, including androgen, glucocorticoid, somatostatin, and dopamine, although none has been associated with recurrence. Growth factors shown to stimulate meningioma include platelet-derived growth factor, insulin-like growth factor–I and –II (also shown to be associated with anaplasia in meningioma), epidermal growth factor, and fibroblast growth factor. Although the mechanism of action of growth factors has not been elucidated, intracellular calcium appears to be part of the signal transduction mechanism. Voltage-dependent calcium channel blocking agents have been shown to cause a dose–response decrease in meningioma cell growth in vitro.

The mechanism by which PR positivity results in a more favorable prognosis may be mediated by angiogenesis inhibition. Angiogenesis is known to play an impor-
tant role in tumorigenicity. Plasminogen activator inhibitor Type 1, which is present in proliferating blood vessels, is more strongly expressed in malignant meningiomas than in benign meningiomas. The authors of a recent study have shown that the activity of thrombospondin-1, an inhibitor of angiogenesis, is enhanced by progesterone and suppressed by the antiprogesterone agent RU-486; the release of thrombospondin-1 in the human endometrium is regulated by progesterone.

The observation of functional PRs in meningioma has led to several studies investigating hormone manipulation and antiprogesterone agents as possible therapeutic agents. Both in vitro and in vivo studies have been conducted in which differing efficacies of antiprogesterone agents were shown. For example, RU-486 has been shown to reduce meningioma growth in vitro (malignant meningioma cell culture) and in vivo (malignant meningioma transplanted into nude mice). This beneficial effect has not been consistent when RU-486 has been used to treat meningiomas in humans; however, in one study control of tumor growth has been demonstrated in six of 10 patients who had shown recent evidence of such growth. In three of those six, consistent tumor shrinkage was observed. A study has also been conducted in humans to investigate the efficacy of gestrinone, a synthetic antiprogesterone agent, in controlling growth of known active tumors; there were beneficial results for some patients.

It seems paradoxical that antiprogesterone agents should be beneficial in controlling growth/recurrence of meningiomas when it has been demonstrated that increased growth/recurrence is associated with PR negativity. Matsuda, et al. confirmed the antitumor effect of RU-486 and a newer potent antiprogesterone, onapristone, on meningiomas, both in vitro and in vivo, and the antitumor effect occurred regardless of the tumor’s PR status, indicating that the antitumor effect is manifested via the PRs and/or another receptor.

Conclusions

In previous studies an association has been demonstrated between PR status and high mitotic index, tumor grade, and recurrence. In this study we demonstrate that PR negativity is associated with recurrence of benign meningiomas. There is now substantive evidence of the importance of PR status with regard to meningioma recurrence. However, PR status alone is not specific enough to rationalize expending clinical resources for follow up or to aid accurate prognosis. The wide availability of monoclonal antibodies to the PR will facilitate further research in this field. The relationship of PR status and other hormone receptors/growth factors to meningioma recurrence merits further study and may have important prognostic and therapeutic implications.

References

Long-term follow up of PR status in benign meningioma


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