Brain Invasion in Meningiomas: Incidence and Correlations with Clinical Variables and Prognosis

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■ OBJECTIVE: **In meningioma, correlation of brain invasion with prognosis and clinical variables remains controversial.**

■ METHODS: **Correlation of brain invasion with clinical and histopathologic variables was investigated in 467 patients with primary intracranial meningioma.**

■ RESULTS: **Diffuse ($n = 3$; 10%), clusterlike ($n = 11$; 34%) or fingerlike ($n = 18$; 56%) invasion was detected in 32 patients (7%). Brain invasion was more common in males than in females (13% vs. 5%; odds ratio, 2.75; 95% confidence interval, 1.29–5.89; $P = 0.009$) and pattern of invasion differed between genders ($P = 0.037$). Brain invasion was absent in 401 benign meningiomas and present in 48% of 60 atypical ($n = 29$) and 50% of 6 anaplastic ($n = 3$) meningiomas ($P < 0.001$) but was independent of tumor location and extent of resection. Progression occurred in 11% and was more frequent (31% vs. 15%; $P = 0.036$) in invasive than in noninvasive tumors, but only after gross total resection and in univariate analyses, and independent of invasion pattern. In atypical meningiomas, frequency of adjuvant irradiation was similar comparing invasive and noninvasive tumors and grading solely based on brain invasion ($n = 20$; 33%), other World Health Organization (WHO) criteria ($n = 31$; 52%) or a combination of both ($n = 9$; 15%). Risk of recurrence was lower (hazard ratio, 0.258, 95% confidence interval, 0.09–0.734; $P = 0.011$) when grading exclusively based on brain invasion than when further WHO criteria were in addition present and the progression-free interval among the first was similar to benign tumors.**

■ CONCLUSIONS: **Brain invasion and its patterns are correlated to gender. In contrast to the current WHO classification, invasion was associated with recurrence only after gross total resection and not independent of further histopathologic criteria of atypia.**

INTRODUCTION

Grading of benign, atypical, or anaplastic meningiomas exclusively depends on histopathologic criteria associated with worse prognosis in terms of tumor recurrence and survival. As found to correlate with worse prognosis by Perry et al.,[1] brain invasion, in this context, was only recommended to consider diagnosis of atypical meningioma in the 2000 and 2007 World Health Organization (WHO) Classifications of Central Nervous System Tumors,[2,3] without listing it as a stand-alone grading criterion. Although its prognostic impact remains controversial and genetic alterations characteristic for high-grade meningiomas have not been shown in brain-invasive but otherwise histologic benign tumors,[4-6] the recently published 2016 WHO classification of brain tumors explicitly lists brain invasion as a criterion of atypia.[7] However, only a few studies have reported

Key words
- Brain invasion
- Gender
- Meningioma
- Prognosis

Abbreviations and Acronyms
GTR: Gross total resection
HR: Hazard ratio
MRI: Magnetic resonance imaging
n.r.: Not reached
OS: Overall survival
PFI: Progression-free interval
REF: Reference
STR: Subtotal resection
WHO: World Health Organization

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varying correlations of brain invasion with either mortality or progression on small subgroups of, for example, anaplastic or irradiated atypical meningiomas.[8-11] Moreover, correlations with clinical variables[10] and studies of different invasion subtypes are even more uncommonly reported.[12-14] Thus, we aimed to investigate the frequency of brain invasion in a large series of meningiomas diagnosed between 1994 and 2009 and its correlation with clinical variables and outcomes.

METHODS

Clinical Data

Medical reports were reviewed for all patients who underwent surgery for histopathologically diagnosed intracranial meningioma in our department (Department of Neurosurgery, University Hospital Münster, Germany) between May 1994 and April 2009. This period was chosen to enable a sufficient long-term follow-up of at least 5 years between surgery and date of data collection. Clinical data were collected from medical and operative reports in the local computer-based data documentation system and included age at the time of surgery, sex, tumor location, extent of surgical tumor resection according to Simpson classification system,[15] and administration of postoperative radiation therapy. For statistical analyses, tumor location was classified into falx cerebri/parasagittal, convexity, intraventricular, and skull base. After maximum safely achievable tumor resection/reduction, adjuvant radiation therapy was recommended for all grade III and subtotally resected atypical meningiomas as well as for benign lesions after simple surgical decompression. No chemotherapy was administered. First, routine postoperative gadolinium-enhanced magnetic resonance imaging (MRI) was performed at 3 and 6 months after surgery, as is standard in our institution. Unless no tumor progression was reported, patients with grade I and high-grade meningiomas usually received annual and semiannual radiologic and clinical controls, respectively. Contrast-enhanced computed tomography was performed in case of any contraindications against MRI. Follow-up in terms of overall survival (OS) and progression-free interval (PFI) was updated using a standardized questionnaire, which was sent to the primary caretakers in each case. Progression was diagnosed in case of radiologically confirmed tumor regrowth with or without subsequent therapy. PFI and OS were calculated from the date of initial surgery to the date of tumor progression or death, respectively. In case of an event-free follow-up, PFI and OS were calculated from date of surgery to the date of last patient contact.

Histopathologic Analyses

For this analysis, histopathologic subtype and WHO grade were neuropathologically reviewed and diagnosed for all 498 intracranial meningiomas at the Institute of Neuropathology, University Hospital Münster, Germany, according to the 2007/2016 WHO criteria.[3,7] Thus, all meningiomas were considered atypical/grade II in case of microscopically detected brain invasion. Further criteria of atypia included increased mitotic count[3] or 3 or more of the following histologic features: increased cellularity, small cells with a high nuclear/cytoplasmatic ratio, prominent nucleoli, uninterrupted patternless or sheetlike growth, and foci of spontaneous or geographic necrosis. Brain invasion was exclusively microscopically evaluated on hematoxylin-eosin– and van Gieson-Elastica–stained slides and diagnosed in case of presence of tumor tissue within the adjacent brain without a separating connective tissue layer.[16] Presence of neural tissue was not mandatory for the evaluation of brain-invasive growth. Thus, in case of no detectable neural tissue on the analyzed slices, brain invasion was diagnosed as absent. For further characterization, brain invasion was classified into 1) diffuse (single cells spreading into the brain parenchyma), 2) nests/clusters of tumor cell, and 3) fingerlike tumor expansion into the adjacent brain (**Figure 1**), similar to previous descriptions.[12-14] For subgroup analyses and concise description, brain-invasive grade II tumors without further histopathologic criteria of atypia are labeled otherwise benign meningiomas.

Statistical Analyses

Statistical analyses were performed using commercial statistic software (IBM SPSS Statistics version 22 [IBM, Ehningen, Germany]). Data were described by standard statistics in terms of absolute and relative frequencies for categorical variables and median and range for continuous variables. Univariate analyses were performed to compare categorical (Fisher exact test) and continuous variables (Mann-Whitney U test). OS and PFI were estimated by Kaplan-Meier analyses and compared by log-rank tests. Multivariate analyses were performed for prognostic (OS, PFI, recurrence, and mortality) and nonprognostic variables using Cox proportional hazards models and backward Wald logistic regression analyses, respectively, including the following variables (REF = reference): brain invasion (absent [REF] vs. present), age, sex (male [REF] vs. female), tumor location (classified into convexity [REF], skull base, falx/parasagittal, intraventricular), and grade of resection (classified into Simpson grade I and II [REF, gross total resection (GTR)] vs. III and IV, subtotal resection [STR]). Because brain invasion was per se considered as a criterion of atypia, as is standard in our institution, WHO grade was omitted from multivariate analyses unless otherwise described (if classified into grade I [REF] vs. grade II vs. III). The results are described with hazard ratios (HRs) or odds ratios, 95% confidence intervals (CIs), and P values based on Cox proportional hazards models and backward Wald logistic regression analyses, respectively. All P values reported are 2-sided and considered significant if < 0.05 throughout the whole analyses. Data collection and scientific use were approved by the local ethics committee (Münster 2007-420-f-S) and permitted by the patients in each case.

RESULTS

Our analysis yielded 467 patients (94%), including 331 women (71%) and 136 men (29%) with a median age of 57 years (range, 7–85 years), who underwent surgery for newly diagnosed meningioma in our institution. Tumor location was determined in all patients and was stratified as follows: falx cerebri/parasagittal ($n = 66$; 14%), convexity ($n = 173$; 37%), intraventricular ($n = 7$; 2%), and skull base ($n = 221$; 47%). Among 436 patients with available data (93%), Simpson grade I, II, III, and IV resection was achieved in 161 (37%), 177 (41%), 81 (18%), and 17 surgeries (4%), respectively, and no simple decompression (grade V) was performed. Thus, 338 patients (78%) underwent GTR, whereas 98

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