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ORIGINAL ARTICLE - TUMOR - MENINGIOMA

Clinical, radiological, and histopathological predictors for long-term prognosis after surgery for atypical meningiomas

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Abstract

Background Despite considerable rates of recurrence and mortality in atypical meningiomas, reliable predictors for estimating postoperative long-term prognosis remain elusive.

Methods Clinical, histopathological, and radiological variables from 138 patients, including 64 females and 74 males (46% and 54%, median age 62 years), who underwent surgery for intracranial atypical meningioma were retrospectively analyzed. Associations between variables and recurrence and mortality were investigated using uni- and multivariate analyses.

Results Gross total (GTR) and subtotal resection (STR) was achieved in 81% and 19% of cases, respectively. Within a median follow-up of 62 months, recurrence occurred in 52 (38%) and mortality in 22 (16%) cases. In patients who did not receive adjuvant irradiation, recurrence rates were higher after STR than after GTR (32% vs 63%, $p = 0.025$). In univariate analyses, only intratumoral calcifications on preoperative MRI ($p = 0.012$) and the presence of brain invasion in the absence of other histological grading criteria ($p = 0.010$) were correlated with longer progression-free intervals (PFI). In multivariate analyses, patient age was positively (HR 1.03, 95%CI 1.04–1.05; $p = 0.018$) and the presence of brain invasion as the only grading criterion (HR 0.37, 95%CI 0.19–0.74; $p = 0.005$) was negatively related with progression, while rising age at the time of surgery (HR 1.07, 95%CI 1.03–1.12; $p = 0.001$) was prognostic for mortality.

Conclusions PFI was longer in brain invasive but otherwise histological benign meningiomas and in tumors displaying calcifications on preoperative MRI. Advancing patient age and lower Karnofsky Performance Score were associated with higher overall mortality.

Keywords Atypical · Meningioma · Mortality · Prognosis · Recurrence · Surgery

This article is part of the Topical Collection on *Tumor - Meningioma*

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Introduction

Atypical meningiomas account for approximately 20% of all intracranial meningiomas and are characterized by distinct histopathological criteria and an increased risk of postoperative recurrence as compared with grade I lesions [30]. Concurrent with the inclusion of brain invasion as a grading criterion for atypia in the WHO Classification of Central Nervous System Tumours [30], the proportion of meningiomas characterized by atypical histology has increased over the past decade, e.g., from 7 to 11% in an own series [37]. However, although correlated with higher recurrence in several studies, the prognostic value of brain invasion in meningiomas is increasingly discussed and even contradicted in some series [5].

Despite the controversies associated with atypical meningioma, maximum safe resection remains the main goal during surgical treatment of atypical meningiomas [13].

Moreover, adjuvant irradiation was shown to increase local tumor control rates in some studies [2, 8, 9, 11, 36] and is therefore currently recommended after subtotal resection, after GTR of tumors with high proliferative activity, and following microsurgery for recurrent lesions [13]. However, the benefits of adjuvant irradiation for atypical meningiomas remain to be established prospectively [9, 12, 16, 27–29], and multiple trials designed to shed light on that issue are currently ongoing [19, 33, 34].

Regarding their aggressive biological behavior, several further studies attempted to identify additional risk factors for both progression and mortality in atypical meningiomas. Although genetic and epigenetic alterations such as loss of histone H3K27 trimethylation or hTERT promoter mutations were shown as strong predictors for progression [4, 14, 20], molecular investigations are usually not integrated in routine neuropathological analyses in meningiomas and are therefore mostly not available in daily clinical practice. In addition, several retrospective studies investigated correlations between clinical or histopathological variables and prognosis but with mostly inconclusive results [8, 9, 12, 23, 27, 28, 36, 41, 43]. Moreover, while found to be correlated with progression or high-grade histology in meningiomas in general [18, 25, 26], the prognostic value of distinct characteristics on preoperative MRI in atypical meningiomas is largely unexplored [9, 28, 43].

In this series, we therefore aimed to investigate associations between clinical, radiological, and histopathological variables available in a daily clinical routine with both progression and mortality after surgery in a large series of atypical meningiomas.

Methods and materials

Medical, histopathological, and radiological data from all patients who underwent surgery for intracranial meningiomas in our department (Department of Neurosurgery, University Hospital Münster, Germany) between 1991 and 2018 were reviewed according to previous descriptions [1, 6, 7, 17, 37, 39]. Briefly, histopathological diagnosis and grading were neuropathologically reviewed according to the current 2016 WHO criteria in all cases [30]. Hence, brain invasion was diagnosed in cases of "irregular, tongue-like protrusions of tumor cells infiltrating underlying parenchyma, without an intervening layer of leptomeninges" on hematoxylin & eosin and Elastica van Gieson-stained slides, and was considered as a standalone grading criterion for atypia. Further histological features such as increased mitotic count, increased cellularity, small cells with a high nuclear to cytoplasmatic ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of spontaneous or geographic necrosis were registered and labeled as "other criteria" hereinafter when sufficient for grading according to the WHO classification.

Medical data included patients' sex and age at the time of surgery, the preoperative Karnofsky Performance Score (KPS), indication for surgery (primary or recurrent meningioma), and the grade of resection according to the Simpson classification system [38], and were extracted from medical records and operative reports. After the maximum safe tumor resection or reduction, adjuvant irradiation was recommended for recurrent or sub-totally removed lesions depending on patients' morbidities and contraindications. Initial routine postoperative gadolinium-enhanced magnet resonance imaging (MRI) was performed three months after surgery, repeated semi-annually and, after five years of event-free survival, in annual intervals [13]. Contrast-enhanced CT-scans were performed for surveillance in cases with contraindications to MRI. Imaging was analyzed for recurrence by at least one neurosurgeon and one neuroradiologist, and tumor recurrence was diagnosed in case of any tumor growth beyond MRI- or CT-depending measurement range [6, 7, 39]. Data about mortality and progression were updated by standardized questionnaires which were sent to the primary caretakers.

Radiological data included several variables previously reported to be associated with prognosis or high-grade histology in meningiomas in general [1, 17, 21, 24–26] and was analyzed by two radiologists (PBS and AA) blinded to any histopathological or clinical information. Figure 1 gives illustrative examples of some of the analyzed radiological variables. Tumor location was classified as "convexity," "falcine/parasagittal," "skull base," "posterior fossa," and "intraventricular." Both tumor and edema volumes (V_T and V_E) were calculated using the established formula for a spheroid $V = 4/3 \times \pi \times r1 \times r2 \times r3$, where r is the tumor radius at the site of its largest extension in axial ($r1$), coronal ($r2$), and sagittal ($r3$) planes [1, 17]. The arachnoid layer was evaluated on T2-weighted imaging and was classified as intact in case of a sharp tumor border and/or evidence of cerebrospinal fluid at the brain/meningioma surface. The contrast enhancement of the tumor and the capsule was evaluated on gadolinium-enhanced T1-weighted and classified as absent or present and hetero- or homogeneous, respectively. The tumor shape was labeled irregular in case of any mushroom-like, lobulated growth. Both the intensity of the tumor and the presence of intratumoral calcifications were evaluated on T2-weighted images and classified as hyper-, iso-, or hypo-intense, as compared with the gray matter, and present or absent, respectively. Data collection and scientific use were approved by the local ethics committee (Münster 2018-061-f-S).

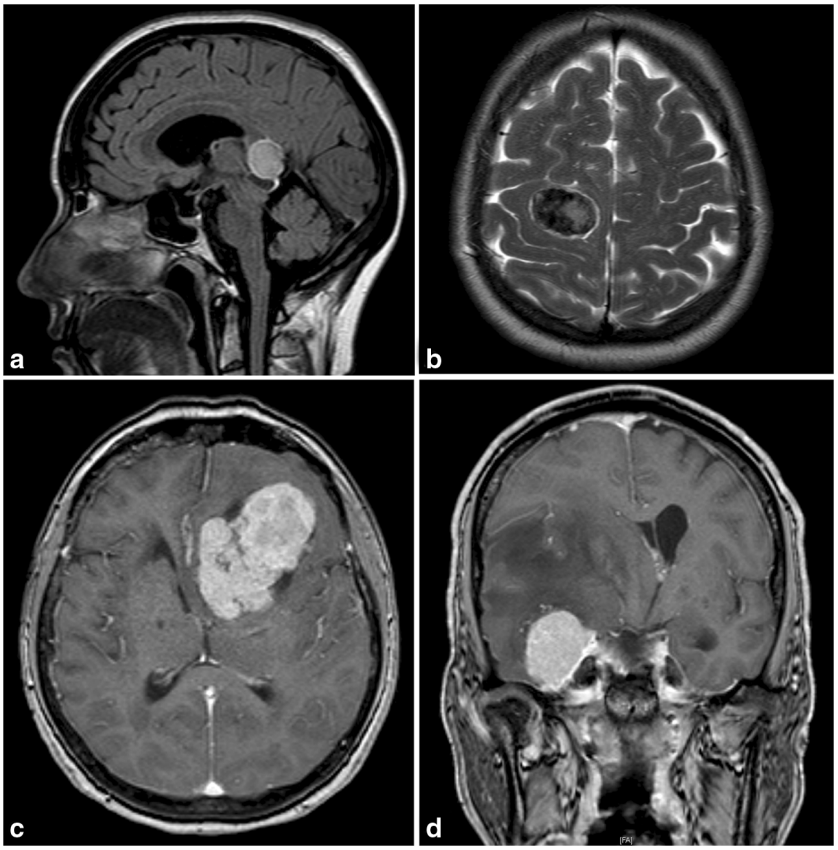

Fig. 1 Illustrative examples of the analyzed MRI criteria. **a** Sagittal T1-weighted imaging showing a meningioma near the pineal gland with distinct capsular contrast enhancement. **b** Axial T2-weighted MRI delineates both intratumoral calcifications as well as a CSF cleft between a convexity meningioma and the adjacent brain parenchyma. **c** Heterogeneous contrast enhancement and an irregular tumor shape with mushroom-like growth in axial, T1-weighted imaging. **d** Homogeneous contrast enhancement and a distinct peritumoral edema of a sphenoid ridge meningioma in coronal T1-weighted imaging

Statistical analyses

Data are described by standard statistics including median and range for continuous and absolute and relative frequencies for categorical variables. Continuous and categorical variables were compared by Mann-Whitney *U* and Fisher's exact test, respectively, while the time-to-event variables were compared by the Kaplan-Meier method and log-rank tests. The progression-free interval (PFI) was defined as the duration between the index surgery and the date of tumor progression or, in case of an event-free course, the date of the last follow-up examination. Overall survival (OS) was defined as the interval between index surgery and date of all-cause death. For dichotomous analyses, the Simpson grade I and II resections were classified as gross total resection (GTR), while the Simpson grade ≥ III surgeries were labeled as subtotal resection (STR). Multivariate analyses for tumor recurrence and mortality were performed using the Mantel-Cox test and backward Wald logistic regression, and characterized by hazard ratios (HR), 95% confidence intervals (CI), and the Wald test *p* values. Cox regression models included patients' age and sex (female = reference (ref)), tumor location (classified as convexity/parasagittal (ref) vs others), extent of resection (GTR (ref) vs STR), and clinical and histological variables found to significantly correlate with prognosis in univariate analyses. All calculations were performed using a commercial statistic software (IBM SPSS Statistics, Version 25, Ehningen, IBM, Germany). All reported *p* values are two-sided and considered statistically significant when < 0.05.

Results

Using the above-described approach, 1098 patients who underwent surgery for intracranial meningiomas during the inclusion period were identified. Among those, histopathological grading according to the 2016 WHO Classification of Central Nervous System Tumours [30] revealed grade II histology in 138 patients (13%), who were subjected to subsequent analyses. Diagnosis of atypia was based exclusively on the presence of brain invasion on the microscopic slides in 48 patients (35%, labeled hereinafter as "otherwise benign"), on the detection of other grading criteria in 75 patients (54%), and on a combination of both in 15 individuals (11%). Samples included 136 primary (99%) and two secondary (1%) atypical meningiomas, in which neuropathological evaluation following the initial surgery had previously revealed WHO grade I histology. In the 18 patients who underwent surgery for recurrent atypical meningioma, previous treatment included singular or

Table 1 Clinical, histopathological, and radiological characteristics. While histopathological and clinical data were available in the vast majority of cases, the availability of MRI imaging was reduced especially in patients who underwent surgery in the initial years of the inclusion period

Variable	Data available (*n*%)	*N* (*n*%)
Age (median; range)	138 (100%)	62 years (10–86 years)
Sex	138 (100%)	
Male		74 (54%)
Female		64 (46%)
Karnofsky Performance Score (KPS)	136 (99%)	80 (± 10)
Initial diagnosis	138 (100%)	120 (87%)
Recurrence		18 (13%)
Primary atypical meningioma	138 (100%)	136 (99%)
Secondary atypical meningioma		2 (1%)
Simpson grade	127 (92%)	
I		46 (36%)
II		57 (45%)
III		15 (12%)
IV		8 (6%)
V		1 (1%)
Gross total		103 (81%)
Subtotal		24 (19%)
Tumor location	138 (100%)	
Convexity		69 (50%)
Falx		23 (17%)
Skull base		40 (29%)
Posterior fossa		4 (3%)
Intraventricular		2 (1%)
Grading criteria	138 (100%)	
Brain invasion only		48 (35%)
Other criteria only		75 (54%)
Both brain invasion and other criteria		15 (11%)
Chordoid meningiomas		3 (2%)
Clear cell meningiomas		1 (< 1%)
Tumor volume (median; range)	62 (45%)	20.5 ccm (1.0–172.9 ccm)
Edema volume (median; range)	58 (42%)	15.6 ccm (0–739.3 ccm)
Capsular enhancement	49 (36%)	
Present		15 (31%)
Contrast enhancement	57 (41%)	
Heterogeneous		35 (61%)
Tumor shape	55 (40%)	
Irregular		30 (55%)
Intensity on T2-weighted MRI	57 (41%)	
Isointense		3 (5%)
Hypo-intense		36 (63%)
Hyper-intense		18 (32%)
Arachnoid layer on T2-weighted MRI	53 (38%)	
Disrupted		32 (60%)
Calcification	54 (39%)	
Present		13 (24%)

repeated surgery alone in 13 cases (72%) and surgery and additional irradiation in three cases (17%), while previous treatment could not be determined in two patients (11%). For this study, none of the patients was registered multiple times. Table 1 summarizes baseline clinical, histopathological, and radiological characteristics. Adjuvant irradiation

was administered in only 14 patients (11%) including both stereotactic radiosurgery ($N = 2$) and external beam radiation therapy (EBRT, $N = 12$). Median preoperative tumor volumes in patients with and without adjuvant irradiation did not differ significantly ($p = 0.250$). Irradiation was performed for five of 21 sub-totally and eight of 96 gross totally resected meningiomas, respectively (24% vs 8%, $p = 0.041$), and in 11 of 103 initially diagnosed and in three of 13 recurrent lesions (10% vs 23%, $p = 0.156$). Median dose for EBRT was 59.4Gy applied in 1.8–2.0Gy fractions. No routine adjuvant chemotherapy was administered. Within a median follow-up of 68 months (0–307), mortality occurred in 22 individuals (16%). Recurrence was observed in 52 patients (38%) after a median PFI of 25 (5–186) months. During the clinical course, additional irradiation, Somatostatin receptor-targeted radionuclide therapy (DOTATE/ DOTATOC), and everolimus/Hydroxyurea were administered for tumor recurrence in 24 (20%), 8 (6%), and one cases (< 1%), respectively.

Correlation of clinical variables with prognosis

Recurrence occurred in 22 female and in 30 male patients (35% vs 42%; $p = 0.478$) with a similar PFI ($p = 0.663$). Similarly, age at the time of surgery was not associated with recurrence ($p = 0.873$). GTR was achieved in 89% ($N = 55$ of 62) of the convexity, in 64% ($N = 14$ of 22) of the falcine, in 79% ($N = 30$ of 38) of the skull base, in all posterior fossa ($N = 3$), and in one of two intraventricular tumors (50%, $p = 0.057$). Among all patients, thirty-six of 99 gross totally and 13 of 24 sub-totally resected tumors recurred (36 vs 54%, $p = 0.162$), and the median PFI did not significantly differ between patients after gross or subtotal resection ($p = 0.233$; Fig. 2a). Correspondingly, no correlation between the extent of resection according to the Simpson classification and tumor recurrence ($p = 0.189$) or the PFI ($p = 0.683$) was detected. However, in subgroup analyses of patients who did not receive adjuvant irradiation, recurrence was observed in 27 of 85 gross totally but in 10 of 16 sub-totally resected meningiomas (32% vs 63%, $p = 0.025$). Forty-three of 116 patients who underwent surgery for primary diagnosed high-grade meningioma and nine of 18 patients who operated on recurrence developed subsequent tumor relapse (37% vs 50%, $p = 0.310$). KPS at the time of surgery was not correlated with the development of tumor recurrence ($p = 0.267$). Remarkably, recurrence was observed in 69% and 36% in patients with and without adjuvant irradiation, respectively ($N = 9$ of 13 vs 39 of 110, $p = 0.032$). Correspondingly, the median PFI was 116 months in irradiation naïve but 21 months in postoperatively irradiated patients ($p = 0.001$, Fig. 2b). As apparently illogical, further subgroup and multivariate analyses were performed. Hence, adjuvant radiation therapy was associated with an *increased* risk of recurrence after GTR (HR 4.34, 95%CI 1.65–11.40; $p = 0.003$) but not after STR (HR 1.67, 95%CI 0.40–6.99; $p = 0.484$). Rates of recurrence did not significantly differ among patients with surgery for primary diagnosed meningioma with and without adjuvant irradiation (60%, $N = 6$ of 10 vs 35%, $N = 35$ of 100; $p = 0.170$). Similarly, in multivariate analyses of the entire cohort, no correlation between adjuvant irradiation and recurrence was found (see details below).

As expected, the rising age at the time of surgery was positively correlated with mortality ($p = 0.031$). However, no other correlations between mortality and patients' sex ($p = 0.817$), the Simpson grade ($p = 0.588$), the dichotomized extent of resection ($p = 0.547$), or the preoperative KPS ($p = 0.817$) were found. Moreover, rates of mortality were similar comparing individuals who underwent surgery for primary ($N = 20$ of 120, 17%) and recurrent meningioma ($N = 2$ of 18, 11%; $p = 0.738$). No associations between administration of adjuvant irradiation and mortality ($p = 0.462$) or OS ($p = 0.58$) were found.

Correlation of radiological variables with prognosis

In univariate analyses, no correlations between recurrence and tumor location ($p = 0.515$), intensity on T2-weighted imaging ($p = 0.674$), absence of the arachnoid layer ($p = 1.00$), heterogeneous ($p = 1.00$) or capsular contrast enhancement ($p = 0.552$), an irregular tumor shape ($p = 0.103$), the presence of intratumoral calcifications ($p = 0.122$), the tumor volume ($p = 0.340$), and peritumoral edema volume ($p = 0.897$) on preoperative MRI were found. However, the median PFI in tumors lacking calcification was 31 (16–46) months but was not reached in non-calcified lesions at the time of diagnosis ($p = 0.012$; Fig. 2c). No statistically significant associations between mortality and tumor location ($p = 0.311$), intensity on T2-weighted imaging ($p = 0.195$), absence of the arachnoid layer ($p = 0.143$), heterogeneous ($p = 0.389$), or capsular contrast enhancement ($p = 0.079$), intratumoral calcifications ($p = 1.00$), an irregular tumor shape ($p = 0.100$), the tumor volume ($p = 0.614$), and peritumoral edema volume ($p = 0.730$) on preoperative MRI were detected.

Correlation of histopathological variables with prognosis

Grading criteria significantly correlated with the development of recurrence. Hence, recurrence was observed in 24% ($N = 11$) of brain invasive but otherwise histologically benign but in 47% of non-invasive atypical meningiomas ($N = 35$) and in 43% ($N = 6$) of tumors displaying both brain invasion *and* other grading criteria ($p = 0.037$). Correspondingly, the median PFI differed significantly between the three groups ($p = 0.010$; Fig. 2d). Both of the two secondary but 38% of the primary atypical meningiomas relapsed. Although one of

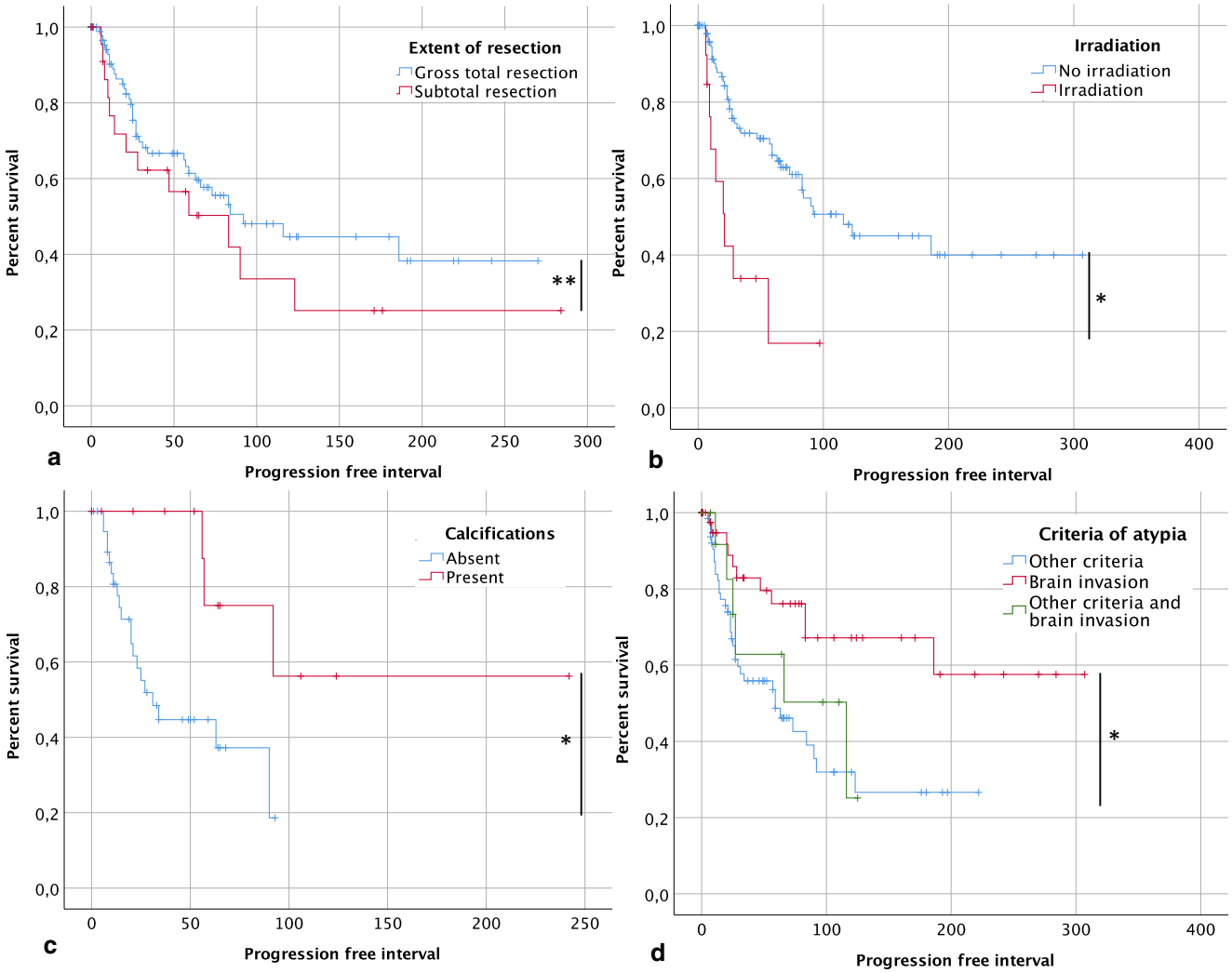

Fig. 2 Selected Kaplan-Meier plots of PFI atypical meningiomas. In cumulative analyses, median PFI was 92 (10–144) months after GTR and 83 (24–142) months after STR ($p = 0.233$, log-rank test, **a**) and recurrence rates were similar comparing both groups ($p = 0.162$). In contrast, the median PFI after surgery and adjuvant irradiation (21 months, range 9–33) was shorter than after surgery alone (116 months, range 73–159; $p = 0.001$, log-rank test, **b**). However, the plots also reveal the low number of patients and events in the irradiation group. The median PFI in patients with calcified tumors on preoperative MRI was 31 (16–46) months, while the median was not reached at the time of analyses in non-calcified tumors ($p = 0.012$, log-rank test, **c**). Moreover, histopathological grading criteria significantly correlated with prognosis. Hence, the median PFI in tumors harboring grading criteria other than brain invasion was 59 (19–99) months and was shorter than in brain invasive but otherwise histologically benign lesions (median not reached) or tumors displaying both brain invasion and other grading criteria (116 months, range 25–207 months; $p = 0.010$, log-rank test, **d**). *Statistically significant. **Not statistically significant. Progression-free intervals in months

three chordoid and the clear cell meningioma recurred, no mortality occurred in this group. Similarly, no correlation was found between the histopathological grading criteria and mortality ($p = 0.414$) or OS ($p = 0.141$).

Multivariate analyses

In multivariate analyses, increasing age at the time of surgery (HR 1.03, 95%CI 1.04–1.15; $p = 0.018$) and grading solely based on the presence of brain invasion (HR 0.37, 95%CI 0.19–0.74; $p = 0.005$) were correlated with tumor recurrence. No further associations between any of the analyzed variables and recurrence were found. Increasing age at the time of surgery (HR 1.07, 95%CI 1.03–1.12; $p = 0.001$) was the only predictor of mortality (Table 2). Due to the low number of events in patients with available preoperative MRI, the imaging data were not included in the multivariate analyses (also see limitations of the study).

Separate multivariate analyses of 72 patients with a follow-up of at least five years (52%) confirmed the presence of brain invasion as the only grading criterion to be independently associated with lower recurrence rates (HR 0.38, 85%CI 0.17–0.87; $p = 0.022$) and an increasing age

Table 2 Results of the multivariate analyses for predictors of progression-free and overall survival. All *p* values are from the backward Wald regression analyses and written in bold if statistically significant. Due to the low number of available data, imaging characteristics except tumor location were not included in the multivariate model

	Progression-free interval			Overall survival		
Variable	Hazard ratio	95%CI	*p* value	Hazard ratio	95%CI	*p* value
Age (in years)	1.03	1.04–1.05	0.018*	1.07	1.03–1.12	0.001*
Gender (female vs male)	1.00	0.56–1.79	0.992**	0.75	0.31–1.79	0.515**
Karnofsky Performance Score (< 80 vs ≥ 80)	1.02	0.44–2.34	0.967**	1.47	0.46–4.69	0.517**
Tumor location (convexity/falx vs others)	1.09	0.54–2.20	0.802**	1.29	0.43–3.88	0.645**
Extent of resection (GTR vs STR)	1.67	0.88–3.19	0.119**	1.52	0.52–4.40	0.442**
Grading criteria						
Other than brain invasion		ref			ref	
Brain invasion	0.37	0.19–0.74	0.005*	0.39	0.13–1.18	0.095**
Both	0.60	0.23–1.53	0.283**	1.05	0.29–3.79	0.945**

at the time of surgery to be related with higher mortality (HR 1.06, 95%CI 1.00–1.12; $p = 0.044$). *statistically significant; **not statistically significant

Discussion

Correlation of clinical variables with progression

With few exceptions [36, 41], patient's sex was not correlated with progression or mortality in neither this nor most of the previously published series [9, 11, 12, 15, 22, 23, 27, 28, 40, 43]. In contrast, correlations between patients' age and recurrence remain controversial [9, 11, 12, 15, 22, 23, 27, 28, 36, 43]. In our study, age at the time of surgery was identified as a slight risk factor for relapse in multivariate tests. As the extent of resection was included in the multivariate regression model, it is unlikely that this observation is biased by a more retentive surgical treatment in elderly patients. As similar rates of both mortality and local tumor control after microsurgery for meningiomas in elderly patients were reported [6], this finding further contradicts a more retentive surgical strategy in these patients. In contrast to previous studies [23, 28], rates of recurrence in our series were similar after surgery for initially diagnosed and recurrent meningiomas. Anticipating a more aggressive biological behavior of recurrent lesions, this finding appears to be illogical and might be caused by method-depending bias. In fact, 23% of patients with recurrent but 10% of the individuals with primary diagnosed atypical meningiomas received adjuvant irradiation. In line with results from most previous studies [11, 15], no correlations between the KPS and recurrence were found.

In contrast to other studies [3, 8–11, 23, 27, 28, 35, 36, 42, 43], a less radical surgery in our series was not *generally* associated with increased rates of recurrence but only in subgroup analyses of patients who did not receive adjuvant irradiation. On the other hand, both STR (HR 2.26, 95%CI 1.47–3.49; $p < 0.001$) and an increasing Simpson grade ($p < 0.001$) were highly correlated with recurrence when analyzing patients who underwent surgery for intracranial grade I meningiomas from the same database ($N = 871$, data not shown). Hence, these data further suggest both a maximum safe tumor resection and, moreover, the administration of adjuvant irradiation after subtotal resection.

In contrast, drawing conclusions about the effects of adjuvant irradiation on tumor control from further analyses in our series was hardly possible. In fact, rates of adjuvant irradiation were considerably lower as compared with other studies, reporting postoperative irradiation therapy in about 20–60% [9, 11, 12, 36]. As the longitudinal analyses of the same database showed rates of adjuvant irradiation increased by almost tenfold between 1991 and 2018 [37], the observation is presumably caused by the long inclusion period. Hence, these findings strongly suggest bias in terms of selective prescription of adjuvant irradiation, e.g., for surgically complicated cases. While we found, e.g., higher rates of adjuvant irradiation in patients treated for recurrent than for primary diagnosed tumors, we were unable to detect further confounders such as the tumor volume or the extent of resection. However, the multivariate analyses adjusted for the extent of resection and tumor volume revealed no correlation between adjuvant irradiation and recurrence. Thus, while surely not implicating a higher risk of recurrence due to postoperative radiation therapy, our results further indicate the necessity of prospective clinical trials, such as [19, 33, 34], to receive evidence about the effects of adjuvant irradiation on local tumor control in atypical meningiomas.

Correlation of histological variables with progression

In contrast to the descriptions in the current WHO classification of brain tumors, the PFI of patients with brain invasive but

otherwise histologically benign tumors in our series was distinctly longer as compared with patients with meningiomas displaying further characteristics of atypia. Hence, these results confirm findings from subgroup analyses previously published from our group [39] as well as observations from other authors, and contribute to the discussion about the prognostic value of brain invasion in meningiomas [5, 11, 22, 23, 32, 36, 42]. Discordant findings might also result from bias caused by non-standardized neurosurgical sampling and neuropathological analyses [5] and need to be further elucidated. However, the question rises if the addition of further histological markers of malignancy and proliferation, such as the Ki-67/MIB1 labeling index [11], might help to estimate the patients' prognosis more precisely and should be therefore added to routine neuropathological analyses. Both lesions that underwent a secondary malignant transformation from benign into atypical meningioma between initial and index surgery recurred. Although this low number does not allow statistical analyses, these findings are in line with the results from previously published studies and raise the question about different biological behavior of de-novo and secondary high-grade meningiomas [10, 23, 31]. Due to the low number of patients, no further comparison of the prognosis of chordoid or clear cell meningioma with "classical" atypical lesions was performed.

Correlation of radiological variables with progression

Only a few studies reported associations of tumor recurrence in atypical meningiomas with distinct locations such as parafalcine [8] or skull base [22] positions, with partially inconclusive results, while corresponding associations were lacking in the majority of studies [11, 12, 15, 23, 40, 43]. Similarly, the prognostic value of either peritumoral brain edema or the tumor volume for prediction of prognosis remains controversial and largely unexplored [8, 23, 43]. Remarkably, although well investigated in meningiomas in general, associations of prognosis with other MRI characteristics, such as calcifications, heterogeneous, or capsular contrast enhancement [18, 25, 26], have not been separately analyzed in atypical meningiomas yet. In 2016, Nanda et al. reported the absence of "certain" MRI findings, e.g., cyst formation or edema, to be associated with better prognosis in patients with atypical meningiomas. However, detailed and separate analyses of these variables were not provided. Similar to findings in meningiomas in general [18], calcification was slightly correlated with a longer PFI in our series of atypical lesions, hence indicating regression and slow growth rates. However, it is remarkable that MRI characteristics correlated with aggressive biological behavior in meningiomas in general, such as an irregular shape or an inhomogeneous or capsular contrast enhancement [18, 26], are not correlated with recurrence in atypical lesions.

Correlation of clinical, histological, and radiological variables with mortality

As compared with predictors for recurrence, associations of clinical, histological, or radiological variables with mortality have been distinctly less investigated yet. In our study, none of the analyzed histological or radiological features was correlated with survival. As expected, among the clinical variables, only a rising age at the time of surgery was found to independently predict mortality, hence indicating both tumor-related and unrelated preoperative morbidity. In fact, similar observations were reported previously [12, 23, 41, 42]. Further studies found other variables such as a female gender, STR, tumor location, peritumoral edema, adjuvant irradiation or malignant transformation of the meningioma to be associated with mortality, however, with partially inconclusive results [10–12, 23, 41, 42].

Limitations of the study

The authors are aware of some limitations of the study. Although providing analyses in a large cohort with sufficient follow-up, our study suffers the limitations of its retrospective nature. Although follow-up imaging was critically reviewed by a team of at least one neurosurgeon and one radiologist, progression was not defined in a standardized manner, e.g., according to the response evaluation criteria in solid tumors (RECIST). Due to the long inclusion period, the determination of the causes of death was limited so only all-cause mortality was registered and datasets were more complete in more recently operated patients. However, multivariate analyses of patients with follow-up data of at least five years basically confirmed results retrieved in analyses of the entire cohort. Information on tumor recurrence do not allow conclusions regarding quality of life and postoperative morbidity. Moreover, changes of surgical practice during the long inclusion period [37] might have influenced our results but could not be considered in statistical analyses. Although clinical and histopathological data could be completely obtained in the vast majority of patients, preoperative imaging was not available in a considerable portion of patients mostly operated in the initial years of the inclusion period and was therefore not included into multivariate analyses. Finally, the portion of patients who received adjuvant irradiation in our series was too low to draw conclusions about the effects on tumor recurrence or to be included into further subgroup or multivariate analyses.

In conclusion, reliable clinical predictors for both progression and mortality in patients with atypical meningiomas are sparse. Both gross total resection and, in some cases, adjuvant irradiation might improve local tumor control rates [13]. The impact of brain invasion on prognosis is increasingly challenged. Hence, our findings further delineate the difficulty of

an individual estimation of prognosis in patients with atypical meningiomas but raise a question about the inclusion of molecular variables in future routine neuropathological analyses.

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Compliance with ethical standards

Conflict of interest Author BB received funding from the "Codman Stipendium zur Förderung der kranialen Neurochirurgie" of the Deutsche Gesellschaft für Neurochirurgie." BB and all other authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Data collection and scientific use were approved by the local ethics committee (Münster 2018-061-f-S).

Informed consent Informed consent was obtained from all participants included in the study.

References

1. Adeli A, Hess K, Mawrin C, Streckert EMS, Stummer W, Paulus W, Kemmling A, Holling M, Heindel W, Schmidt R, Spille DC, Sporns PB, Brokinkel B (2018) Prediction of brain invasion in patients with meningiomas using preoperative magnetic resonance imaging. Oncotarget 9:35974–35982
2. Aghi MK, Carter BS, Cosgrove GR, Ojemann RG, Amin-Hanjani S, Martuza RL, Curry WT Jr, Barker FG II (2009) Long-term recurrence rates of atypical meningiomas after gross total resection with or without postoperative adjuvant radiation. Neurosurgery 64: 56–60 **discussion 60**
3. Aizer AA, Arvold ND, Catalano P, Claus EB, Golby AJ, Johnson MD, Al-Mefty O, Wen PY, Reardon DA, Lee EQ, Nayak L, Rinne ML, Beroukhim R, Weiss SE, Ramkissoon SH, Abedalthagafi M, Santagata S, Dunn IF, Alexander BM (2014) Adjuvant radiation therapy, local recurrence, and the need for salvage therapy in atypical meningioma. Neuro-Oncology 16:1547–1553
4. Biczok A, Kraus T, Suchorska B, Terpolilli NA, Thorsteinsdottir J, Giese A, Tonn JC, Schichor C (2018) TERT promoter mutation is associated with worse prognosis in WHO grade II and III meningiomas. J Neuro-Oncol. https://doi.org/10.1007/s11060-018-2912-7
5. Brokinkel B, Hess K, Mawrin C (2017) Brain invasion in meningiomas-clinical considerations and impact of neuropathological evaluation: a systematic review. Neuro-Oncology 19:1298–1307
6. Brokinkel B, Holling M, Spille DC, Hess K, Sauerland C, Bleimuller C, Paulus W, Wolfer J, Stummer W (2017) Surgery for meningioma in the elderly and long-term survival: comparison with an age- and sex-matched general population and with younger patients. J Neurosurg 126:1201–1211
7. Brokinkel B, Stummer W, Sporns P (2018) Simpson grade IV resections of skull base meningiomas: does the postoperative tumor volume impact progression? J Neuro-Oncol 137(1):219–221
8. Budohoski KP, Clerkin J, Millward CP, O'Halloran PJ, Waqar M, Looby S, Young AMH, Guilfoyle MR, Fitzroll D, Devadass A, Allinson K, Farrell M, Javadpour M, Jenkinson MD, Santarius T, Kirollos RW (2018) Predictors of early progression of surgically treated atypical meningiomas. Acta Neurochir 160:1813–1822
9. Champeaux C, Dunn L (2016) World Health Organization grade II meningioma: a 10-year retrospective study for recurrence and prognostic factor assessment. World Neurosurg 89:180–186
10. Champeaux C, Wilson E, Shieff C, Khan AA, Thorne L (2016) WHO grade II meningioma: a retrospective study for outcome and prognostic factor assessment. J Neuro-Oncol 129:337–345
11. Chen WC, Magill ST, Wu A, Vasudevan HN, Morin O, Aghi MK, Theodosopoulos PV, Perry A, McDermott MW, Sneed PK, Braunstein SE, Raleigh DR (2018) Histopathological features predictive of local control of atypical meningioma after surgery and adjuvant radiotherapy. J Neurosurg. https://doi.org/10.3171/2017.9.JNS171609
12. Endo T, Narisawa A, Ali HS, Murakami K, Watanabe T, Watanabe M, Jokura H, Endo H, Fujimura M, Sonoda Y, Tominaga T (2016) A study of prognostic factors in 45 cases of atypical meningioma. Acta Neurochir 158:1661–1667
13. Goldbrunner R, Minniti G, Preusser M, Jenkinson MD, Sallabanda K, Houdart E, von Deimling A, Stavrinou P, Lefranc F, Lund-Johansen M, Moyal EC, Brandsma D, Henriksson R, Soffietti R, Weller M (2016) EANO guidelines for the diagnosis and treatment of meningiomas. Lancet Oncol 17:e383–e391
14. Goutagny S, Nault JC, Mallet M, Henin D, Rossi JZ, Kalamarides M (2014) High incidence of activating TERT promoter mutations in meningiomas undergoing malignant progression. Brain Pathol 24: 184–189
15. Hammouche S, Clark S, Wong AH, Eldridge P, Farah JO (2014) Long-term survival analysis of atypical meningiomas: survival rates, prognostic factors, operative and radiotherapy treatment. Acta Neurochir 156:1475–1481
16. Hasan S, Young M, Albert T, Shah AH, Okoye C, Bregy A, Lo SS, Ishkanian F, Komotar RJ (2015) The role of adjuvant radiotherapy after gross total resection of atypical meningiomas. World Neurosurg 83:808–815
17. Hess K, Spille DC, Adeli A, Sporns PB, Brokinkel C, Grauer O, Mawrin C, Stummer W, Paulus W, Brokinkel B (2018) Brain invasion and the risk of seizures in patients with meningioma. J Neurosurg. https://doi.org/10.3171/2017.11.JNS172265
18. Huang RY, Bi WL, Griffith B, Kaufmann TJ, la Fougere C, Schmidt NO, Tonn JC, Vogelbaum MA, Wen PY, Aldape K, Nassiri F, Zadeh G, Dunn IF, International Consortium on M (2019) Imaging and diagnostic advances for intracranial meningiomas. Neuro-Oncology 21:i44–i61
19. Jenkinson MD, Javadpour M, Haylock BJ, Young B, Gillard H, Vinten J, Bulbeck H, Das K, Farrell M, Looby S, Hickey H, Preusser M, Mallucci CL, Hughes D, Gamble C, Weber DC (2015) The ROAM/EORTC-1308 trial: radiation versus observation following surgical resection of atypical meningioma: study protocol for a randomised controlled trial. Trials 16:519
20. Katz LM, Hielscher T, Liechty B, Silverman J, Zagzag D, Sen R, Wu P, Golfinos JG, Reuss D, Neidert MC, Wirsching HG, Baumgarten P, Herold-Mende C, Wick W, Harter PN, Weller M, von Deimling A, Snuderl M, Sen C, Sahm F (2018) Loss of histone H3K27me3 identifies a subset of meningiomas with increased risk of recurrence. Acta Neuropathol 135:955–963
21. Kawahara Y, Nakada M, Hayashi Y, Kai Y, Hayashi Y, Uchiyama N, Nakamura H, Kuratsu J, Hamada J (2012) Prediction of high-grade meningioma by preoperative MRI assessment. J Neuro-Oncol 108:147–152
22. Klinger DR, Flores BC, Lewis JJ, Hatanpaa K, Choe K, Mickey B, Barnett S (2015) Atypical meningiomas: recurrence, reoperation, and radiotherapy. World Neurosurg 84:839–845
23. Li H, Zhang YS, Zhang GB, Zhang GJ, Wang B, Li D, Wu Z, Zhang JT (2019) Treatment protocol, long-term follow-up, and

predictors of mortality in 302 cases of atypical meningioma. World Neurosurg 122:e1275–e1284
24. Li H, Zhao M, Jiao Y, Ge P, Li Z, Ma J, Wang S, Cao Y, Zhao J (2016) Prediction of high-grade pediatric meningiomas: magnetic resonance imaging features based on T1-weighted, T2-weighted, and contrast-enhanced T1-weighted images. World Neurosurg 91: 89–95
25. Lin BJ, Chou KN, Kao HW, Lin C, Tsai WC, Feng SW, Lee MS, Hueng DY (2014) Correlation between magnetic resonance imaging grading and pathological grading in meningioma. J Neurosurg 121:1201–1208
26. Liu Y, Chotai S, Chen M, Jin S, Qi ST, Pan J (2015) Preoperative radiologic classification of convexity meningioma to predict the survival and aggressive meningioma behavior. PLoS One 10: e0118908
27. Masalha W, Heiland DH, Franco P, Delev D, Haaker JG, Schnell O, Scheiwe C, Grauvogel J (2018) Atypical meningioma: progression-free survival in 161 cases treated at our institution with surgery versus surgery and radiotherapy. J Neuro-Oncol 136:147–154
28. Nanda A, Bir SC, Konar S, Maiti T, Kalakoti P, Jacobsohn JA, Guthikonda B (2016) Outcome of resection of WHO grade II meningioma and correlation of pathological and radiological predictive factors for recurrence. J Clin Neurosci 31:112–121
29. Pereira BJA, de Almeida AN, Paiva WS, Teixeira MJ, Marie SKN (2018) Impact of radiotherapy in atypical meningioma recurrence: literature review. Neurosurg Rev. https://doi.org/10.1007/s10143-018-0959-8
30. Perry A, Louis DN, von Deimling A, Sahm F, Rushing EJ, Mawrin C, Claus EB, Loeffler J, Sadetzki S (2016) Meningiomas. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Ellison DW, Figarella-Branger D, Perry A, Reifenberger G, von Deimlig A (eds) WHO classification of tumors of the central nervous system. International Agency on Cancer Research, Lyon, pp 232–245
31. Peyre M, Gauchotte G, Giry M, Froehlich S, Pallud J, Graillon T, Bielle F, Cazals-Hatem D, Varlet P, Figarella-Branger D, Loiseau H, Kalamarides M (2018) De novo and secondary anaplastic meningiomas: a study of clinical and histomolecular prognostic factors. Neuro-Oncology 20:1113–1121
32. Phonwijit L, Khawprapa C, Sitthinamsuwan B (2017) Progression-free survival and factors associated with postoperative recurrence in 126 patients with atypical intracranial meningioma. World Neurosurg 107:698–705
33. Rogers L (2017) Observation or radiation therapy in treating patients with newly diagnosed grade II meningioma that has been completely removed by surgery (NCT03180268). https://clinicaltrials.gov/ct2/show/NCT03180268. Accessed 6 March 2019
34. Rogers L, Zhang P, Vogelbaum MA, Perry A, Ashby LS, Modi JM, Alleman AM, Galvin J, Brachman D, Jenrette JM, De Groot J, Bovi JA, Werner-Wasik M, Knisely JPS, Mehta MP (2018) Intermediate-risk meningioma: initial outcomes from NRG oncology RTOG 0539. J Neurosurg 129:35–47
35. Rydzewski NR, Lesniak MS, Chandler JP, Kalapurakal JA, Pollom E, Tate MC, Bloch O, Kruser T, Dalal P, Sachdev S (2018) Gross total resection and adjuvant radiotherapy most significant predictors of improved survival in patients with atypical meningioma. Cancer 124:734–742
36. Shakir SI, Souhami L, Petrecca K, Mansure JJ, Singh K, Panet-Raymond V, Shenouda G, Al-Odaini AA, Abdulkarim B, Guiot MC (2018) Prognostic factors for progression in atypical meningioma. J Neurosurg 129:1240–1248
37. Sicking J, Voss KM, Spille DC, Schipmann S, Holling M, Paulus W, Hess K, Steinbicker AU, Stummer W, Grauer O, Wolfer J, Brokinkel B (2018) The evolution of cranial meningioma surgery-a single-center 25-year experience. Acta Neurochir 160:1801–1812
38. Simpson D (1957) The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 20:22–39
39. Spille DC, Hess K, Sauerland C, Sanai N, Stummer W, Paulus W, Brokinkel B (2016) Brain invasion in meningiomas: incidence and correlations with clinical variables and prognosis. World Neurosurg 93:346–354
40. Sun SQ, Kim AH, Cai C, Murphy RK, DeWees T, Sylvester P, Dacey RG, Grubb RL, Rich KM, Zipfel GJ, Dowling JL, Leuthardt EC, Leonard JR, Evans J, Simpson JR, Robinson CG, Perrin RJ, Huang J, Chicoine MR (2014) Management of atypical cranial meningiomas, part 1: predictors of recurrence and the role of adjuvant radiation after gross total resection. Neurosurgery 75:347–354 **discussion 354-345; quiz 355**
41. Wang C, Kaprealian TB, Suh JH, Kubicky CD, Ciporen JN, Chen Y, Jaboin JJ (2017) Overall survival benefit associated with adjuvant radiotherapy in WHO grade II meningioma. Neuro-Oncology 19:1263–1270
42. Yoon H, Mehta MP, Perumal K, Helenowski IB, Chappell RJ, Akture E, Lin Y, Marymont MA, Sejpal S, Parsa A, Chandler JR, Bendok BR, Rosenow J, Salamat S, Kumthekar P, Raizer JK, Baskaya MK (2015) Atypical meningioma: randomized trials are required to resolve contradictory retrospective results regarding the role of adjuvant radiotherapy. J Cancer Res Ther 11:59–66
43. Zhi M, Girvigian MR, Miller MJ, Chen JC, Schumacher AJ, Rahimian J, Lodin K (2019) Long-term outcomes of newly diagnosed resected atypical meningiomas and the role of adjuvant radiotherapy. World Neurosurg 122:e1153–e1161