

Extent of Resection as the Primary Independent Predictor of Progression- Free Survival in Atypical Intracranial Meningioma: A Retrospective Single-Center Study of 187 Patients

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3 **Study of 187 Patients**

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Abstract

Purpose

Atypical meningiomas (WHO grade 2) show considerable biological heterogeneity and substantial recurrence rates despite surgical treatment, while reliable prognostic markers remain limited. We aimed to identify clinical and radiographic predictors of progression-free survival (PFS) in a large single-center cohort.

Methods

We retrospectively analysed 187 patients with histopathologically confirmed atypical intracranial meningioma (2016–2023), categorised by extent of resection (gross total resection [GTR] vs subtotal resection [STR]) and treatment strategy (surgery alone vs surgery plus radiotherapy). Kaplan–Meier and univariate/multivariate Cox regression were applied to identify predictors of PFS.

Results

GTR was achieved in 168 patients (89.8%) and STR in 19 (10.2%); tumor progression or recurrence occurred in 25 patients (13.4%). On multivariate analysis, extent of resection was the only independent predictor of shortened PFS (adjusted HR 3.09, 95% CI 1.14–8.37; $p = 0.026$). Peritumoral edema showed a consistent, non-significant trend toward shortened PFS (adjusted HR 2.43, 95% CI 0.92–6.37; $p = 0.072$). Age (HR 0.84, 95% CI 0.37–1.92; $p = 0.7$) and radiotherapy (HR 0.99, 95% CI 0.43–2.26; $p > 0.9$) were not significantly associated with PFS. Edema was not associated with the extent of resection or radiotherapy administration.

Conclusion

Extent of resection is the strongest independent predictor of PFS in atypical intracranial meningioma, reaffirming maximal safe resection as the central surgical objective. Peritumoral edema showed a consistent but non-significant trend that warrants confirmation in larger, adequately powered multicenter cohorts.

Keywords: Atypical meningioma, Adjuvant radiotherapy, Extent of resection, Simpson grade, Recurrence

Introduction

Meningiomas are the most common primary intracranial tumors in adults, accounting for approximately 40% of all primary central nervous system neoplasms [1–4]. Although most are biologically benign with favorable outcomes, a relevant subset shows more aggressive behavior with early recurrence and shortened progression-free survival (PFS) [4–6]. Under the 2021 WHO classification, meningiomas are categorized into three grades, with WHO grade 2 lesions representing an intermediate but clinically heterogeneous entity [8–11].

Atypical meningiomas constitute the largest subgroup of WHO grade 2 tumors, defined by increased mitotic activity, brain invasion, or specific atypical histopathological features [4, 12]. Despite advances in microsurgical and adjuvant treatment strategies, recurrence rates remain substantial even after gross total resection (GTR), with progression rates reaching 30–40% at long-term follow-up [12–15], making reliable risk stratification a major clinical challenge.

Extent of resection (EOR) has consistently been identified as one of the most important predictors of tumor control [13–15], and GTR remains the primary surgical objective whenever safely achievable. The role of postoperative radiotherapy remains controversial, particularly after GTR: some studies suggest improved tumor control with adjuvant radiotherapy, while others show no clear survival benefit, resulting in substantial variability in current practice [16–22]. This uncertainty highlights the need for additional prognostic markers capable of identifying biologically aggressive tumors beyond surgical parameters alone.

Increasing attention has been directed toward biological and radiographic features that may reflect aggressive tumor behaviour more accurately than histopathological grading alone. The Ki67 (MIB-1) labeling index has been widely investigated as a marker of proliferative activity and recurrence risk [23–25], and peritumoral edema has emerged as a potentially important radiographic marker of invasive growth and unfavourable outcomes [26, 46], though its clinical relevance in atypical meningioma remains incompletely understood.

The aim of this study was to evaluate clinical and radiographic predictors of PFS in a large single-center cohort of atypical intracranial meningioma, focusing on extent of resection, adjuvant radiotherapy, and preoperative peritumoral edema.

Methods and Materials

Study Design and Patient Selection

This retrospective single-center study included adult patients who underwent surgical treatment for atypical intracranial meningioma at the department of neurosurgery, University Hospital Erlangen Germany between 2016 and 2023. Histopathological grading was based on the original neuropathological reports available at the time of treatment. Given the retrospective design and the 2021 WHO classification revision, no systematic reclassification was performed. All data were anonymised prior to analysis.

Data Collection

Clinical, radiographic, operative, and histopathological data were extracted from the institutional electronic medical records, including patient age (calculated at time of surgery, from date of birth and surgery date), sex, presenting symptoms, neurological deficits, pre- and postoperative Karnofsky Performance Status (KPS), tumor location (supra- vs infratentorial), tumor volume, extent of resection, adjuvant radiotherapy, and histopathological findings. Tumor volume was estimated on preoperative contrast-enhanced MRI using the formula $\text{length} \times \text{width} \times \text{height} / 2$ [28]. Preoperative neurological deficits were defined as motor, sensory, cranial nerve, cognitive, or seizure-related symptoms. Peritumoral edema was assessed on preoperative MRI and categorised dichotomously as present or absent.

Surgical Treatment and Adjuvant Therapy

All patients underwent microsurgical resection, categorised via the Simpson grading system into gross total resection (GTR; Simpson I–II) and subtotal resection (STR; Simpson III–IV) [27]. Postoperative radiotherapy was decided on by an interdisciplinary team considering extent of resection, recurrent disease, radiographic findings, and overall clinical assessment, resulting in the categorization in surgery-alone and surgery-plus-radiotherapy groups.

Follow-Up and Outcome Assessment

Postoperative MRI was performed three months after surgery and at regular intervals thereafter. Progression-free survival (PFS), the primary endpoint, was defined as the interval between surgery and radiological evidence of tumor recurrence or progression, and was analysed according to extent of resection and treatment strategy.

Statistical Analysis

Statistical analysis was performed using RStudio (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were tested for normal distribution (Shapiro–Wilk test), and treatment groups were compared using the Wilcoxon rank-sum test (continuous variables) and Pearson's chi-squared test (categorical variables). Kaplan–Meier analysis with log-rank testing compared PFS between groups. Univariate and multivariate Cox proportional hazards regression, including sex, age, extent of resection, postoperative radiotherapy, primary versus secondary surgery, preoperative KPS, tumor size, and peritumoral edema, identified predictors of PFS; the proportional-hazards assumption was assessed using Schoenfeld residuals. Statistical significance was defined as $p < 0.05$.

Results

Patient Characteristics

A total of 187 patients with histopathologically confirmed atypical intracranial meningioma were included. Median age at surgery was 59 years, and 103 patients (55%) were female. GTR (Simpson I–II) was achieved in 168 patients (89.8%); 19 (10.2%) underwent STR (Simpson III–IV).

Of the overall cohort, 103 patients received surgery alone and 84 additionally underwent postoperative radiotherapy. Median age did not differ significantly between groups (56 vs. 61 years; $p = 0.46$). Secondary surgeries for recurrent/progressive disease were more frequent in the radiotherapy group (29% vs. 11%; $p = 0.003$), as were

neurological deficits, though not significantly (61% vs. 46%; $p = 0.057$). Baseline and postoperative KPS distributions were comparable between groups. Detailed characteristics are summarised in Table 1.

Table 1. Demographic and clinical characteristics of the overall cohort.

Characteristic	Overall N = 187	Surgery Only N = 103	Surgery + Radiation N = 84	p-value
Age ¹	59 (55, 63)	56 (52, 65)	61 (56, 64)	0.5 ²
Sex				0.4 ³
Male	84 (45%)	43 (42%)	41 (49%)	
Female	103 (55%)	60 (58%)	43 (51%)	
Surgery Type				0.003 ³
Primary	152 (81%)	92 (89%)	60 (71%)	
Secondary	35 (19%)	11 (11%)	24 (29%)	
Neurological Deficits				0.057 ³
No Deficit	89 (48%)	56 (54%)	33 (39%)	
Neurological Deficit	98 (52%)	47 (46%)	51 (61%)	
Preoperative KPS				0.2 ³
<80	83 (44%)	51 (50%)	32 (38%)	
≥80	104 (56%)	52 (50%)	52 (62%)	
Postoperative KPS				0.3 ³
<80	89 (48%)	53 (51%)	36 (43%)	
≥80	98 (52%)	50 (49%)	48 (57%)	
Recurrence/Progression	25 (13%)	12 (12%)	13 (15%)	0.6 ³

¹ Median (95% CI, bootstrap)
² Wilcoxon rank-sum test
³ Pearson's chi-squared test

Progression-Free Survival According to Extent of Resection

Patients undergoing subtotal resection showed reduced long-term tumor control compared with GTR. Recurrence/progression occurred in 19 patients (11.3%) after GTR and 6 (31.6%) after STR.

Kaplan–Meier analysis revealed significantly shorter PFS in the STR cohort (log-rank $p = 0.025$; HR 2.76, 95% CI 1.09–6.95); survival curves diverged mainly during longer follow-up, with 8-year PFS of 82.8% after GTR versus 44.3% after STR. These findings are illustrated in Figure 1 and summarised in Table 2.

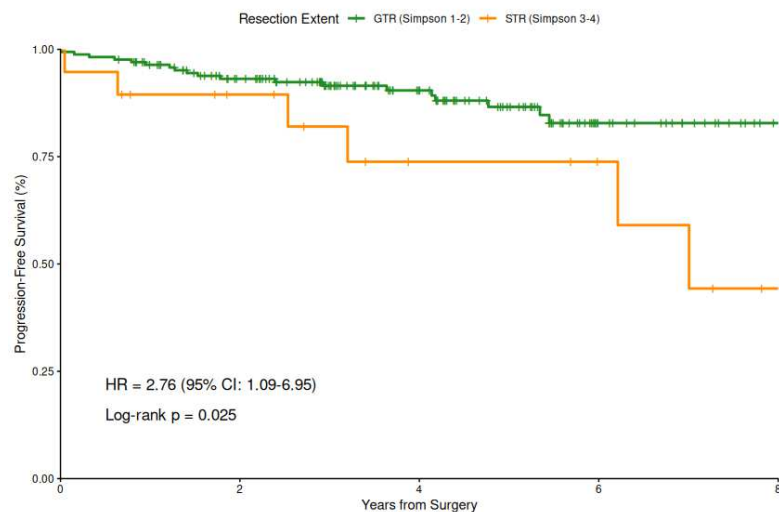


Fig. 1 Kaplan–Meier curves comparing progression-free survival between patients undergoing gross total resection (GTR) versus subtotal resection (STR).

Table 2. Progression-free survival according to extent of resection.

PFS according to Resection Extent		
	GTR (N=168) SIMPSON 1+2	STR (N=19) SIMPSON 3+4
Total Recurrence/Progression	19 (11.3%)	6 (31.6%)
2-Year PFS	93.1%	89.5%
4-Year PFS	90.4%	73.8%
6-Year PFS	82.8%	73.8%
8-Year PFS	82.8%	44.3%
Log-rank p = 0.025 Hazard Ratio = 2.76 (95% CI: 1.09-6.95)		

Progression-Free Survival According to Treatment Strategy

Overall, radiographic progression/recurrence occurred in 25 patients (13.4%): 12 in the surgery-only group and 13 in the surgery-plus-radiotherapy group.

Kaplan–Meier analysis showed no significant PFS difference between groups (log-rank p = 0.72; HR 1.16, 95% CI 0.53–2.54). Estimated 2-, 4-, and 8-year PFS were 89.6%, 88.2%, and 85.3% with surgery alone, versus 96.4%, 89.7%, and 67.2% with surgery plus radiotherapy. Corresponding survival curves are shown in Figure 2 and summarised in supplementary Table 1.

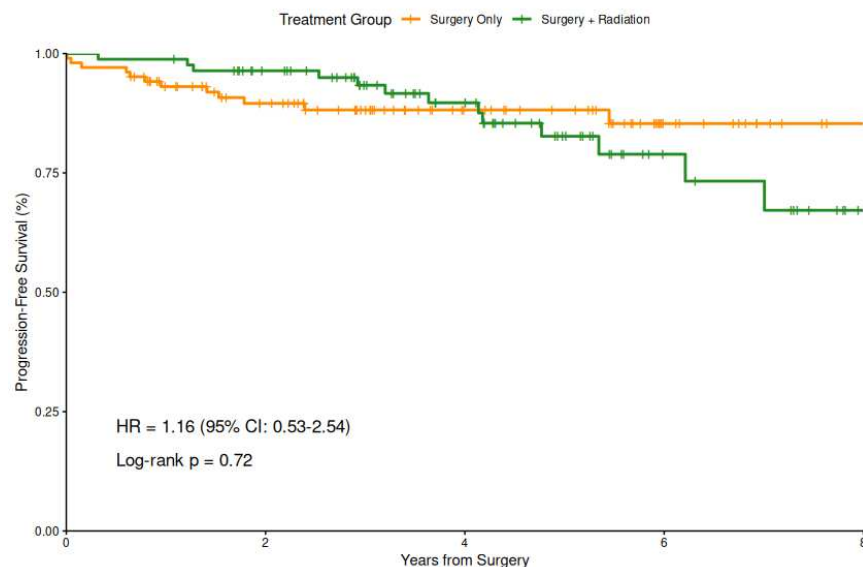


Fig. 2 Kaplan–Meier curves comparing progression-free survival between patients treated with surgery alone versus surgery plus postoperative radiotherapy.

Proliferative Activity and Progression-Free Survival

No significant association between proliferative activity and PFS was observed (HR 1.61, 95% CI 0.60–4.29; $p = 0.37$). Corresponding survival curves are presented in Supplementary Figure 1.

Predictors of Progression-Free Survival

Univariate and multivariate Cox regression analyses identified predictors of PFS. Subtotal resection was associated with reduced PFS in univariate analysis (HR 2.76, 95% CI 1.09–6.95; $p = 0.032$) and remained the only significant independent predictor after multivariate adjustment (adjusted HR 3.09, 95% CI 1.14–8.37; $p = 0.026$).

Peritumoral edema showed a consistent trend toward shortened PFS in univariate (HR 2.35, 95% CI 0.94–5.88; $p = 0.069$) and multivariate analysis (adjusted HR 2.43, 95% CI 0.92–6.37; $p = 0.072$), without reaching significance. Age was not significantly associated with PFS (univariate HR 0.89, 95% CI 0.39–2.02, $p = 0.8$; multivariate HR 0.84, 95% CI 0.37–1.92, $p = 0.7$), nor was postoperative radiotherapy (adjusted HR 0.99, 95% CI 0.43–2.26; $p > 0.9$).

Preoperative KPS was associated with prolonged PFS in univariate analysis (HR 0.41, 95% CI 0.17–0.95; $p = 0.037$) but not after multivariate adjustment (adjusted HR 0.52, 95% CI 0.22–1.26; $p = 0.15$). Sex, tumor size, and primary versus secondary surgery were not significantly associated with PFS. Full analyses are in Table 3.

Table 3. Univariate and multivariate Cox proportional hazards regression analyses of predictors of progression-free survival.

Univariate and Multivariate Cox Regression Analysis for PFS

Characteristic	Univariate		Multivariate	
	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Sex (Female vs. Male)	0.94 (95% CI: 0.43, 2.05)	0.9		
Age (≥ 65 vs. < 65 years)	0.89 (95% CI: 0.39, 2.02)	0.8	0.84 (95% CI: 0.37, 1.92)	0.7
Extent of Resection (STR vs. GTR)	2.76 (95% CI: 1.09, 6.95)	0.032	3.09 (95% CI: 1.14, 8.37)	0.026
Treatment group (Surgery+RT vs. Surgery)	1.16 (95% CI: 0.53, 2.54)	0.7	0.99 (95% CI: 0.43, 2.26)	>0.9
Surgery Type (Secondary vs. Primary)	1.50 (95% CI: 0.62, 3.59)	0.4		
Preoperative KPS (≥ 80 vs. < 80)	0.41 (95% CI: 0.17, 0.95)	0.037	0.52 (95% CI: 0.22, 1.26)	0.15
Tumor Size (≥ 19 cm ³ vs. < 19 cm ³)	1.62 (95% CI: 0.73, 3.57)	0.2		
Peritumoral Edema (Yes vs. No)	2.35 (95% CI: 0.94, 5.88)	0.069	2.43 (95% CI: 0.92, 6.37)	0.072
Abbreviations: CI = Confidence Interval, HR = Hazard Ratio				

The proportional-hazards assumption was violated for radiotherapy ($p = 0.018$) and KPS ($p = 0.030$) in the multivariate model (global $p = 0.063$), so these hazard ratios should be interpreted as time-averaged estimates.

Association Between Peritumoral Edema and Treatment Characteristics

The presence of edema was not significantly associated with extent of resection ($p = 0.4$) or postoperative radiotherapy administration ($p = 0.4$). Among patients with edema, 92% underwent GTR and 48% received radiotherapy, showing no relevant treatment-allocation difference versus patients without edema.

Exploratory Analysis: Resection Extent and Treatment Interaction

Given the independent effect of resection extent, we explored whether radiotherapy's effect on PFS differed between GTR and STR patients. No significant interaction was detected (Cox $p = 0.57$; Firth penalized re-fit $p = 0.47$), but this analysis was substantially underpowered: the STR subgroup contributed only 19 patients and 6 events combined across both arms. A post-hoc calculation indicated that ~200 additional STR patients would be needed to detect the effect size suggested by our estimates ($HR \approx 0.51$) at 80% power — achievable only through multicenter collaboration.

Discussion

In this retrospective study of 187 patients with atypical intracranial meningioma, extent of resection was the only independent predictor of shortened PFS after multivariate adjustment; postoperative radiotherapy and age were not significant. Peritumoral edema showed a consistent, non-significant trend towards a shorter PFS, suggesting a possible but unconfirmed role as a radiographic marker of aggressive biology which should be evaluated in larger cohorts.

Management of atypical meningioma remains challenging given the marked clinical heterogeneity within WHO grade 2 tumors. Although extent of resection is consistently considered one of the most important prognostic factors [13–15, 29–34], recurrence remains substantial even after GTR. In our series, GTR was achieved in nearly 90% of patients, reflecting an aggressive philosophy of maximal safe resection; that recurrence still occurred in a relevant proportion despite this underlines the biological heterogeneity of atypical meningioma beyond surgical classification alone.

Consistent with previous reports, subtotal resection was associated with inferior long-term tumor control compared with GTR [13–15, 29–34], and remained the only significant independent predictor of PFS after multivariate adjustment for age, treatment, KPS, and edema (adjusted HR 3.09, 95% CI 1.14–8.37; $p = 0.026$) — notable given the small STR subgroup ($n=19$) and high GTR proportion (89.8%), both of which would be expected to limit power rather than inflate significance. Retrospective Simpson-grade assessment may nonetheless introduce classification variability. Overall, our data reaffirm maximal safe resection as the primary surgical objective and most robust modifiable predictor of tumor control.

The role of postoperative radiotherapy in WHO grade 2 meningioma remains highly controversial: several studies report improved PFS after adjuvant radiotherapy, particularly following subtotal resection or recurrent disease [18–22, 37, 41], while others show no clear survival advantage [13, 16, 19, 32, 38]. Here, radiotherapy was not significantly associated with prolonged PFS after adjustment for resection extent and clinical variables, but this must be interpreted cautiously: treatment allocation was non-randomised and strongly influenced by recurrent disease, subtotal resection, neurological deficits, and perceived aggressiveness, so the radiotherapy cohort likely represented a biologically higher-risk population. This does not argue against radiotherapy, but underscores the difficulty of identifying who truly benefits from it.

A secondary, hypothesis-generating finding is the consistent trend linking preoperative peritumoral edema to shortened PFS. Although the adjusted hazard ratio approached a nearly two-and-a-half-fold increase in risk, this did not reach significance ($p = 0.072$) and should be interpreted as suggestive rather than confirmatory. The trend was stable across sensitivity analyses, including alternative age modelling and adjustment for calendar year of surgery, arguing against a model-specification artefact. Edema was not associated with resection extent or radiotherapy administration, indicating that even if confirmed, it does not currently influence treatment stratification. Given the modest event count, a larger cohort is needed to determine whether edema independently predicts PFS.

The biological mechanisms underlying peritumoral edema formation likely involves pial invasion, arachnoid disruption, increased vascular permeability, inflammatory signalling, and invasive growth characteristics [26, 46]. Our findings are compatible with edema serving as a readily accessible radiographic biomarker of aggressive disease, though this study alone cannot confirm it; unlike molecular profiling, edema assessment is universally available on routine imaging, making it a practical addition to risk stratification if confirmed in adequately powered future cohorts.

We also examined whether radiotherapy's effect on PFS differed by resection extent, motivated by reports of possible benefit specifically after subtotal resection [18–22, 37, 41]; no significant interaction was detected, but this analysis

was substantially underpowered (Results). Together with the underpowered edema signal above, this represents the clearest opportunity for a future, adequately powered multicenter study focused on the subtotal resection subgroup.

In contrast to prior investigations identifying Ki67 (MIB-1) as a prognostic marker for recurrence [23–25, 30, 41, 42], we found no significant association between proliferative index and PFS. This discrepancy may reflect methodological limitations of retrospective pathology analysis, including inter-observer variability in hotspot selection, and the likelihood that atypical meningioma's biological heterogeneity extends beyond what a single histopathological marker can capture.

These findings also highlight a conceptual limitation of current classification systems: although WHO grading and extent of resection remain central to treatment planning, they incompletely capture the biological diversity of atypical meningioma. Molecular classification advances—methylation profiling, TERT promoter alterations, CDKN2A/B loss—have improved understanding of aggressive biology [9–11] but are not yet universally implemented clinically. Radiographic biomarkers such as peritumoral edema may offer complementary, broadly accessible information for identifying high-risk patients.

Limitations

Several limitations should be acknowledged. First, the retrospective single-center design introduces selection bias, particularly regarding radiotherapy indication. Treatment allocation followed interdisciplinary clinical judgment rather than standardised prospective criteria, likely influenced by recurrent disease, neurological status, resection extent, and perceived biological aggressiveness.

Second, although this is one of the larger single-center series of atypical meningioma, the limited number of progression events may have reduced statistical power and increased overfitting risk; reported hazard ratios should be interpreted cautiously.

Third, follow-up duration varied and some attrition bias cannot be excluded, so long-term recurrence rates may be underestimated, particularly for patients with shorter follow-up.

Fourth, extent of resection was assessed retrospectively from operative reports and postoperative imaging; despite routine Simpson grading, retrospective interpretation may introduce classification variability, particularly without highly standardised documentation.

Fifth, molecular profiling data were not systematically available; recent evidence highlights the importance of TERT promoter mutations, CDKN2A/B loss, and DNA methylation profiles in defining aggressive meningioma subgroups [9–11], this absence limits our ability to correlate edema with underlying tumor biology.

Sixth, the proportional-hazards assumption was violated for postoperative radiotherapy and KPS, indicating their effect may vary over follow-up, so these hazard ratios should be read as time-averaged rather than constant. The exploratory resection-by-treatment interaction and the edema trend were both non-significant but substantially underpowered given

cohort size, and should be regarded as hypothesis-generating pending confirmation in larger, ideally multicenter, cohorts.

Finally, the binary assessment of edema as present/absent simplifies a likely more complex phenomenon; quantitative volumetric analysis and advanced radiographic characterisation were beyond this study's scope but may add prognostic value in future work.

Despite these limitations, this is one of the larger single-center series focusing specifically on PFS in atypical meningioma. Extent of resection was a robust, independent predictor across all analyses, while the edema trend warrants confirmation in larger, adequately powered multicenter cohorts.

Conclusion

In this retrospective cohort of 187 patients with atypical intracranial meningioma, extent of resection was the only independent predictor of shortened PFS after multivariate adjustment (adjusted HR 3.09, 95% CI 1.14–8.37; $p = 0.026$), reaffirming gross total resection as the central surgical objective. Postoperative radiotherapy and patient age were not significantly associated with PFS.

Preoperative peritumoral edema showed a consistent, though non-significant, trend toward shortened PFS that was independent of resection extent and radiotherapy administration. This finding is hypothesis-generating: a post-hoc calculation suggests confirming or refuting an effect of this magnitude within the subtotal resection subgroup would require a multicenter cohort several times larger than the present series. These findings support the view that atypical meningioma is a biologically heterogeneous entity not fully captured by surgical parameters alone, and future prospective multicenter studies — with specific attention to the subtotal resection subgroup — are warranted to confirm whether radiographic biomarkers such as peritumoral edema can meaningfully improve individualised risk stratification.

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374 **Author Contributions**

375 Conceptualization: WM; Methodology: SV and WM; Data acquisition: RC ME, AK, HQ; Data analysis: SV and WM;

376 Writing - original draft preparation: ME; Writing – review and editing: WM and OS; Supervision: WM, OS; IB.

377 **Data Availability**

378 The datasets analysed during the current study are available from the corresponding author on reasonable request.

379 **Ethics Approval**

380 All procedures performed for the purpose of the present study were submitted to the Ethical Committee of the Medical
381 Faculty of the Friedrich-Alexander-University Erlangen-Nürnberg and found to be in accordance with relevant ethical
382 principles, in particular the 1964 Helsinki declaration and its subsequent amendments.

383 **Consent to Participate**

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

385 **Consent to Publish**

386 Not applicable

Supplementary Material

Table 1. Progression-free survival according to treatment strategy (surgery alone vs. surgery plus radiotherapy).

PFS according to Treatment Group		
	Surgery Only (N=103)	Surgery + Radiation (N=84)
Total Recurrence/Progression	12 (11.7%)	13 (15.5%)
2-Year PFS	89.6%	96.4%
4-Year PFS	88.2%	89.7%
6-Year PFS	85.3%	78.9%
8-Year PFS	85.3%	67.2%
Log-rank p = 0.72 Hazard Ratio = 1.16 (95% CI: 0.53-2.54)		

Figure 1. Kaplan–Meier curves of progression-free survival stratified by proliferative activity (Ki-67/MIB-1 labeling index).

