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CLINICAL INVESTIGATION

Pattern of Failure Analysis and Clinical Outcomes in Patients With Grade 2 Meningiomas Following Radiation Therapy

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Purpose: Grade 2 meningiomas often recur after surgery and radiation therapy. However, large, in-depth failure analyses are lacking, limiting the potential to refine radiation therapy. We report a pattern of failure analysis, encompassing treatment and outcome data from over 2 decades.

Methods and Materials: Patients who underwent proton- or photon-based fractionated adjuvant or salvage radiation therapy for a grade 2 meningioma between 2000 and 2023 were included. Subsequently, an in-depth analysis of the failure pattern was conducted.

Results: A total of 105 patients were included, with 36 patients having 46 progressive or recurrent grade 2 meningiomas during the available follow-up. Most patients received 59.4 Gy (interquartile range [IQR] 57.6-59.4) in 33 fractions (62.9%) and underwent proton radiation therapy (61.0%), with a median voxel-based equivalent uniform dose (EUD) of 60.1 Gy (IQR, 57.3-61.3). Most recurrent and progressive tumors were either located in the treatment volume (35/46, 76.1%) or within 2 cm of it (9/46, 19.6%). The median distance to out-of-field failures was 11.9 mm. The EUD (hazard ratio [HR], 0.77, 95% confidence interval [CI], 0.59-0.98), target volume (HR, 1.6; 95% CI, 1.2-2.1), RTOG 0539 risk classification (high vs intermediate, HR, 7.9; 95% CI, 1.5-42.7), male sex (HR, 2.0; 95% CI, 0.9-4.4), treatment indication (salvage vs adjuvant, HR, 2.4; 95% CI, 1.1-5.5), and age at radiation therapy (HR, 1.5; 95% CI, 1.0-2.1) were associated with progression.

Conclusions: This in-depth pattern of failure analysis for grade 2 meningiomas after radiation therapy demonstrated that treatment failures predominantly occur in close spatial relation to the irradiated target volume. Large treatment volumes, macroscopic disease, and a low EUD considerably impact disease control, underscoring the need for further local treatment and targeting refinements.

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Introduction

Meningiomas are the most common primary brain tumors in adults.[1] Although the majority of tumors, ie, grade 1 meningiomas, can be effectively treated by a complete surgical resection, grade 2 and 3 meningiomas often recur after surgery and radiation therapy.[2,3] Although various studies reported short-term local control, tumor progression after adjuvant or salvage radiation therapy is frequent in grade 2 tumors.[4-8] Refinement of local treatment options, such as radiation therapy, requires an understanding of their limitations.[9] The available literature suggests that most local recurrences occur in close spatial relationship to the radiation field.[10-12] However, large, in-depth patterns of failure analyses incorporating voxel-based data are lacking, limiting the potential to refine radiation therapy. Herein, we report the results of a pattern of failure analysis of patients with grade 2 meningiomas treated at a large tertiary center with proton- or photon-based fractionated radiation therapy over a period of more than 2 decades. We apply a voxel-based approach to maximize insights for dosimetric profiling and characterization of recurrences.

Methods and Materials

Data collection and cohort details

Patients treated at the Massachusetts General Hospital who underwent fractionated radiation therapy between January 1, 2000, and November 1, 2023, for a grade 2 meningioma, were screened. Tumor grading followed the fifth edition of the World Health Organization Classification of Tumors of the Central Nervous System.[13] Risk groups were derived based on the RTOG 0539 trial.[6] Patients with a histopathologically confirmed intracranial meningioma diagnosis and with available treatment plans were retrospectively analyzed. All patients were required to have at least 1 clinical and radiographic follow-up. For patients with a confirmed tumor progression or recurrence, respective imaging was mandatory for analysis. Simpson grades I, II, and III were considered gross total resection (GTR), whereas Simpson grades IV and V were defined as subtotal resection (STR).[14] Adjuvant (received radiation therapy after surgery without any intermittent tumor growth) and salvage treatments (received radiation therapy for progressive tumors or recurrence) with proton or photon-based fractionated radiation therapy were assessed. Patients treated with stereotactic radiosurgery and hypofractionated stereotactic radiation therapy, ie, single-fraction dose >2.5 Gy, were excluded. The gross tumor volume typically included the residual or recurrent tumor as well as the resection cavity in the postoperative setting. The clinical target volume was defined at the discretion of the managing physicians, and the respective margin mostly ranged between 3 and 15 mm in the adjuvant setting, with greater expansion along the dura, ie, >15 mm, in selected cases, and smaller margins for salvage treatments.

Pattern of failure analysis and outcomes

Imaging data demonstrating recurrence or tumor progression was overlaid with the initial treatment plan. All observed recurrences were independently confirmed by 2 radiation oncologists and delineated. The dose per voxel was extracted for all patients and analyzed to calculate the dose delivered to the target volume (TV) and recurrent or progressing tumors. Given the differences in planning robustness strategies between photon and proton therapy, the TV refers to the planning target volume for photon treatments and the corresponding treatment volume for proton therapy. All doses were normalized to the standard fraction scheme of 33 fractions. The voxel-based equivalent uniform dose (EUD) was calculated as previously reported.[15] The delineation of structures and export of dose data were done with MIM 7.2.7 (MIM Software Inc.). Freedom from progression, progression-free survival, and overall survival were analyzed as actuarial endpoints. The time of freedom from progression was defined as the period from the first day of radiation therapy to the first available imaging demonstrating unequivocal local or distant tumor progression or recurrence. Progression-free survival was defined as the time from the first day of radiation therapy to tumor progression or death of any cause. Overall survival was calculated from the day of first surgical resection to the date of death, and again from the start of radiation therapy. Patients without recurrence, progression, or death were censored on the day of the last available imaging or last clinical contact for the respective endpoint.

Statistical analysis

The voxel-based EUD calculation was performed with the EUD model parameter "a" set to −10. An Elastic Net with the Cox regression model and either 10-fold cross-validation (for overall survival) or minimization of Bayesian information criterion (for freedom from progression and progression-free survival) was used for variable selection. A finite mixture model with a point mass density and a parametric Weibull survival model was used to estimate the proportion of patients who will never experience disease progression, ie, are considered cured. A multivariable Cox regression analysis was performed using the variables selected by the Elastic Net regression. In addition, a new risk grouping was developed based on these variables. The proportional hazards assumption for each model was tested using a global test based on Schoenfeld residuals. The Kaplan-Meier estimator was used to plot the time-to-event data, with intergroup comparisons being done using the log-rank test and the test for trend. Median follow-up

periods and their 95% confidence intervals (CIs) were estimated using the reversed Kaplan-Meier methodology. Percentages and numbers might not add up due to rounding. The statistical analyses were done using STATA 17 and 18 (StataCorp). The study was approved by the local institutional review board (protocol number: 2024P000907). This study follows the Strengthening the Reporting of Observational Studies in Epidemiology statement.[16]

Results

Patient, tumor, and treatment characteristics

A total of 834 patients with meningioma were treated during the period of interest. After applying all inclusion and exclusion criteria, 105 patients were included in the analysis (54 females and 51 males), with 36 patients having 46 progressive or recurrent grade 2 meningiomas (Fig. 1). The median age at the initial surgery was 54.1 years. Tumors were primarily located around the convexity (41.9%), at the skull base (31.4%), or the falx (25.7%). The resection status of the cohort was balanced, with 51.5% GTR and 48.5% STR cases. This was also the case for the subgroup of patients undergoing adjuvant radiation therapy (GTR 50.9% vs STR 49.1%). Most patients received adjuvant radiation therapy (54.3%), and 81.9% underwent treatment between 2010 and 2023. Forty-eight patients (45.7%) received salvage treatment, with 11 undergoing surgery before radiation therapy. The median prescription dose and TV were 59.4 Gy and 58.0 cm^3, respectively. The median number of fractions and EUD were 33 and 60.1 Gy. Thirteen patients (12.4%) received a boost, most simultaneously integrated (84.6%). The median boost dose, including the regular prescription dose, was 62.7 Gy. All boosts were delivered to gross disease.

Nearly 60% of patients underwent proton radiation therapy. Two patients received a combination of photons and protons. All patients completed their radiation therapy as planned, and no treatments were canceled. Notable differences between patients undergoing proton and photon radiation therapy included TV size (median: 48.9 cm^3 for protons vs 75.9 cm^3 for photons) and tumor location (convexity: 35.9% for protons vs 53.8% for photons; skull base: 39.1% for protons vs 17.9% for photons). No patient underwent positron emission tomography (PET) before radiation therapy to facilitate target delineation. The patient, tumor, and treatment characteristics are summarized in Table 1.

Outcomes and patterns of failure

The median follow-up for the overall survival endpoint was 9.5 years (95% CI, 8.3-10.6) and 7.3 years (95% CI, 6.2-8.8 years) for the progression endpoint and progression-free survival. Thirty-six (34.3%) patients suffered from disease progression. The median time to tumor progression or recurrence for patients with progressive or recurrent disease was 3.9 years (interquartile range [IQR], 1.6-6.3). The 3-, 5-, and 10-year freedom from progression rates were 87.8% (95% CI, 79.5-92.9), 76.7% (95% CI, 66.4-84.3), and 50.9% (95% CI, 37.4-62.9), respectively (File E1). Patients receiving salvage radiation therapy had a shorter time to progression compared to those who underwent adjuvant treatment (Fig. 2A). A total of 46 recurrences have been identified during the available follow-up, with 6 patients experiencing >1 recurrent or progressive lesion at the time of disease progression (range, 2-4). The median recurrence volume was 1.32 cm^3, and the median dose in the recurrence volumes was 57.7 Gy (IQR, 49.6-60.5). Most recurrent and progressive tumors were located within the treatment volume (35/46, 76.1%) and were observed in high-risk patients according to the RTOG 0539 risk classification (34/36, 94.4%)

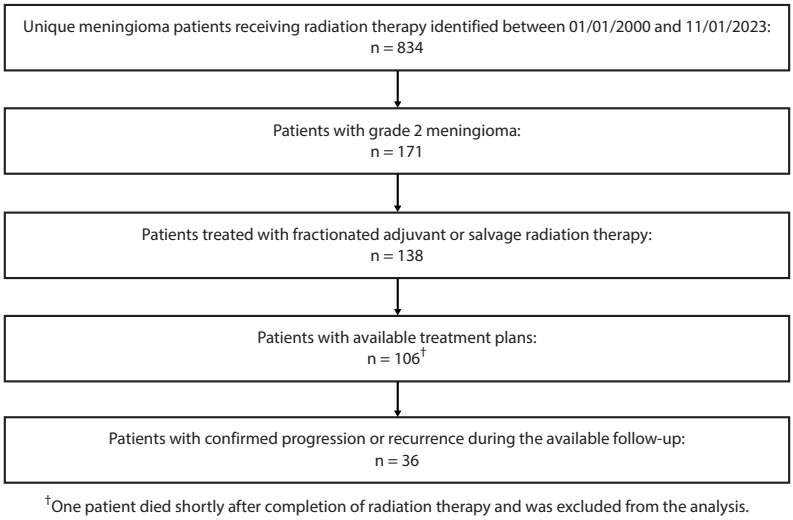

Fig. 1. Flowchart of included patients.

Table 1 Patient, tumor, and treatment characteristics

Sex (number of male (%)/female patients (%))	51 (48.6)/54 (51.4)				
Tumor location	**Convexity**	**Falx**	**Skull base**	**Ventricle**	
Number of tumors (%)	44 (41.9)	27 (25.7)	33 (31.4)	1 (1.0)	
	Median	**Mean (SD)**	**IQR**		
Age at first surgery (y)	54.1	55.0 (14.7)	46.4-64.6		
Age at radiation therapy (y)	58.6	56.8 (14.3)	49.2-65.7		
Time from surgery to radiation therapy (y)	0.46	1.79 (3.08)	0.25-1.83		
Simpson grade at first resection	**I**	**II**	**III**	**IV**	**V**
Number of patients (%)*	26 (25.2)	21 (20.4)	6 (5.8)	49 (47.6)	1 (1.0)
Radiation therapy indication	**Salvage**	**Adjuvant**			
Number of patients (%)	48 (45.7)	57 (54.3)			
Surgery before salvage radiation therapy	**Yes**	**No**			
Number of patients (%)	11 (22.9)	37 (77.1)			
Resection status before salvage radiation therapy	**Gross total resection**	**Subtotal resection**			
Number of patients (%)	8 (72.7)	3 (27.3)			
RTOG 0539 risk groups	**Intermediate-risk**	**High-risk**			
Number of patients (%)	29 (27.6)	76 (72.4)			
Radiation therapy modality	**Photon**	**Proton**	**Photon and proton**		
Number of patients (%)	39 (37.1)	64 (61.0)	2 (1.9)		
	Median	**Mean (SD)**	**IQR**		
Prescription dose (Gy)	59.4	57.9 (3.6)	57.6-59.4		
Equivalent uniform dose (EUD) normalized to 33 fractions (Gy)	60.1	57.2 (10.6)	57.3-61.3		
Single-fraction dose (Gy)	1.8	1.8 (0.1)	1.8-1.8		
Number of fractions	33	32 (2.9)	33-33		
Target volume (cm^3)	58.0	75.3 (65.0)	30.1-92.1		
Radiation therapy boost	**Yes**	**No**			
Number of patients (%)	13 (12.4)	92 (87.6)			
Type of radiation therapy boost	**Sequential**	**Simultaneous**			
Number of patients (%)	2 (15.4)	11 (84.6)			
Use of SSTR-PET for target delineation	**Yes**	**No**			
Number of patients (%)	0 (0.0)	105 (100.0)			
	Median	**Mean (SD)**	**IQR**		
Radiation therapy boost doses† (Gy)	62.7	61.9 (6.3)	60.1-66.0		
Recurrence volume (cm^3)	1.32	5.51 (9.54)	0.86-5.25		
Dose in the recurrence volume (Gy)	57.7	49.4 (18.5)	49.6-60.5		
EUD in the recurrence volume (Gy)	51.4	37.0 (25.8)	7.6-60.2		
EUD in the out-of-field failure volume (Gy)	28.3	31.4 (25.8)	1.8-58.6		
EUD in the in-field failure volume (Gy)	60.7	59.6 (3.9)	60.2-61.5		
EUD in the recurrence volume for patients with gross disease prior to radiation therapy (Gy)	59.4	55.7 (12.9)	56.7-61.3		
EUD in the recurrence volume for patients without gross disease prior to radiation therapy (Gy)	60.5	59.9 (2.4)	58.9-61.3		

Abbreviations: EUD = equivalent uniform dose; SD = standard deviation, SSTR-PET = somatostatin receptor positron emission tomography; IQR: interquartile range.

* Missing data for 2 patients.

† Including the prescription dose.

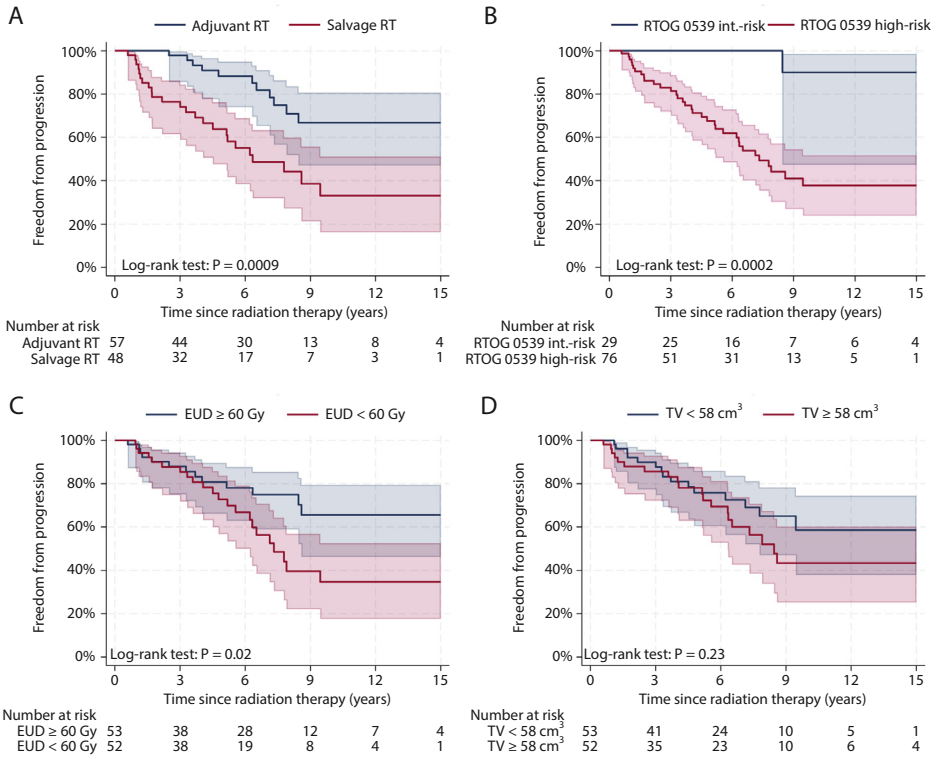

Fig. 2. Freedom from progression. (A) adjuvant versus salvage radiation therapy (RT), (B) RTOG intermediate- (int.) versus high-risk, (C) equivalent uniform dose (EUD) ≥ 60 Gy versus < 60 Gy, and (D) target volume (TV) ≥ 58 cm^3 versus < 58 cm^3.

(Fig. 2B). The median distance between the TV and recurrences for patients without treatment failure within the TV was 11.9 mm (range, 3.3-70.1). Three failures were within 1 cm of the TV (6.5%), and 9 were within 2 cm of the TV (19.6%). Two distant failures, ie, a distance of >2 cm from the TV, were observed (4.3%). Qualitatively, progressive tumors and recurrences were predominantly located inside or at the border of the resection cavity. No osseous failures were identified. In summary, 95.7% of all recurrent or progressing tumors were either within the TV or in close spatial relationship to it.

Regression analyses and risk groups

Seventeen treatment and patient variables were included in the Elastic Net analysis. Specifically, age at surgery, age at radiation therapy, interval between surgery and radiation therapy, year of surgery, year of radiation therapy, Simpson grade, TV, sex, extent of resection (GTR vs STR), RTOG 0539 risk classification (high vs intermediate), tumor location, radiation modality, treatment indication (adjuvant vs salvage), prescribed dose, boost dose, dose per fraction, and EUD. Of those 17, 6 were identified as significantly associated with freedom from progression and progression-free survival by the Elastic Net algorithm. Specifically, in the order of importance in the prediction model, ie, standardized absolute values of coefficients, they were RTOG 0539 risk classification (high vs intermediate, hazard ratio [HR], 7.9; 95% CI, 1.5-42.7), TV (HR, 1.6; 95% CI, 1.2-2.1), EUD (HR, 0.77; 95% CI, 0.59-0.98), treatment indication (salvage vs adjuvant, HR, 2.4; 95% CI, 1.1-5.5), age at radiation therapy (HR, 1.5; 95% CI, 1.0-2.1), and sex (male vs female, HR, 2.0; 95% CI, 0.9-4.4) (Fig. 2, File E2).

The 6 variables selected by the Elastic Net analysis were used to define risk groups. The continuous variables, TV, EUD, and age at radiation therapy, were dichotomized at their median values of 58 cm^3, 60 Gy (rounded to the nearest full Gy), and 59 years (rounded to the nearest year), respectively. According to penalized relative HRs obtained from Elastic Net analysis, TVs larger than 58 cm^3, EUDs lower than 60 Gy, age older than 59 years, RTOG 0539 high-risk classification, salvage radiation therapy, and male sex are associated with a higher risk of progression. Assuming all 6 binary risk factors are additive, a composite risk score was calculated, ranging from 0 risk factors to a maximum of 6. Because there was only 1 case with no risk factors and only 2 cases with all 6 risk factors, the 5 risk groups were defined as follows: low-risk with zero to 1 risk factors, medium-low-risk with 2 risk factors, medium-high-risk with 3 risk factors, high-risk with 4 risk factors, and very-high-risk with 5 or 6 risk factors. The Kaplan-Meier plot of freedom from progression stratified by the 5 risk groups is shown in Figure 3. Looking at the crude rates, there are no progressions among the 11 low-risk cases, whereas in the very-high-risk group, 75% (12 of 16) of patients experienced progression.

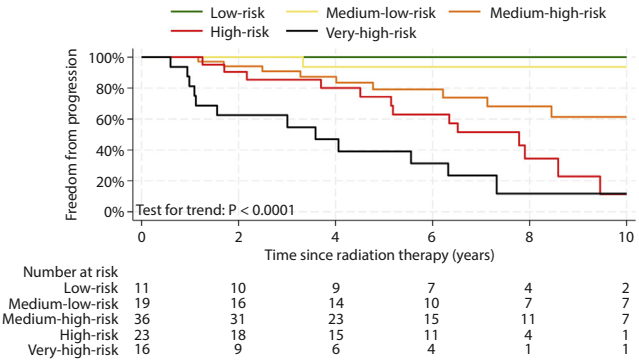

Fig. 3. Risk stratification according to RTOG 0539 risk classification, target volume, equivalent uniform dose, treatment indication (salvage versus adjuvant), age at radiation therapy (RT), and sex.

Survival and long-term disease control

Eighteen deaths were observed during the available follow-up. The survival rates at 3-, 5-, and 10 years since initial surgery were 98.0%, 94.6%, and 79.6%, respectively (File E3). The corresponding survival rates since the start of radiation therapy were 95.8%, 91.0%, and 78.1% (File E4). Elastic Net analysis revealed disease progression (as a time-varying variable) (HR, 14.1; 95% CI, 4.8-41.5) and male sex (HR, 3.7; 95% CI, 1.1-13.2) as variables associated with shorter survival (Fig. 4, File E2). The age at surgery or the resection status was not associated with overall survival. The 3-, 5-, and 10-year progression-free survival rates were 85.9%, 75.4%, and 51.4%, respectively (File E5). A few patients have had very long follow-up periods without progression, ie, >15 years. Therefore, we investigated whether some patients are durably controlled and will never experience progression. We employed a finite mixture model with a point mass density and a parametric Weibull survival model, using the set of variables obtained from the Elastic Net analysis. The estimate shows that 12% (95% CI, 2.4-44.7) of the patient cohort can be considered durably controlled (P = .03). The proportional hazard assumption was fulfilled for all models.

Discussion

Radiation therapy is a central treatment modality for grade 2 meningiomas.[2,3,17] Although numerous retrospective studies and a limited number of prospective trials have demonstrated its efficacy, long-term tumor control remains unsatisfactory.[8] Therefore, its further refinement is essential to improving outcomes. Pattern of failure analyses of various tumor entities and radiation techniques can yield significant insights, creating the potential to refine radiation therapy.

To compare our findings with the available evidence, we performed a nonsystematic review using PubMed to collect studies primarily reporting on the pattern of failure and outcomes of high-grade meningiomas (Table 2). Despite the epidemiologic relevance of meningiomas, it is notable that there is a lack of large and detailed pattern of failure analyses for meningiomas after radiation therapy, especially for grade 2 tumors (Table 2).[4-6,10-12,18-23] This is aggravated by the heterogeneity of analyzed cohorts and treatments and varying definitions of failure patterns (Table 2).[24] The literature search identified 12 other studies reporting data on the pattern of failure for meningiomas. The 12 studies we identified included nearly 650 patients, with around 520 having grade

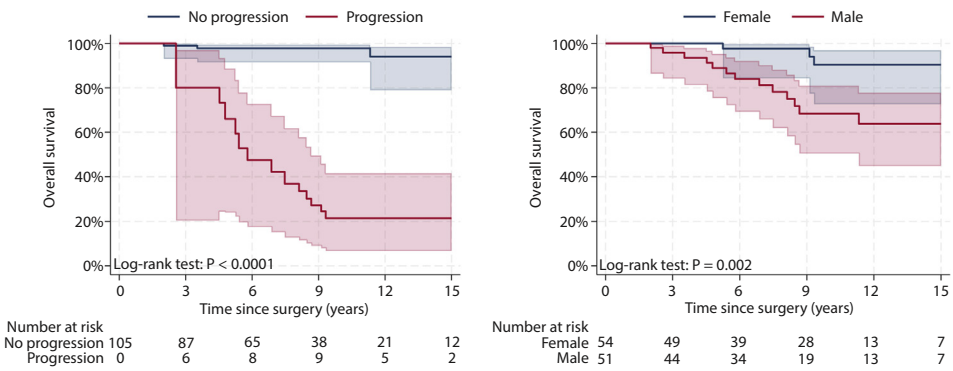

Fig. 4. Overall survival. (A) No disease progression versus disease progression; (B) female versus male.

Table 2 Overview of the pattern of failure studies for high-grade meningiomas

Author/Study	Year	Study type	Number of patients	Tumor grading	Resection status	Radiation modality	Dose	Outcomes	Pattern of failure
Chan et al [18]	2012	Prospective phase 1/2 trial	6	4 grade 2, 2 grade 3	3 STR, 3 recurrent grade 2 tumors	Bimodal (photon, proton)	GTV: 68.4 Gy (RBE) (grade 2) 72.0 Gy (RBE) (grade 3) CTV*: 61.2 Gy (RBE) (high risk) 54.0 Gy (RBE) (low risk), single-fraction dose: 1.8 Gy (RBE)	1 treatment failure (16.7%), 5 out of 6 tumors (83.3%) controlled after a median follow-up of 145 mo, Median overall survival: 133 mo, 2 patients with grade 3 disease died	1 in-field failure (100%)
Weber et al, EORTC 22042-26042[4]	2018	Prospective phase 2 trial	56	56 grade 2	56 GTR	Photon	Median: 60.0 Gy Median single-fraction dose: 2.0 Gy	8 treatment failures (14.2%), 3-y progression-free survival: 88.7% 3-y overall survival: 98.2%	6 in-field failures (75.0%), 2 in-field and out-of-field failures (25.0%)
Rogers et al, RTOG 0539 (intermediate-risk arm)[5]	2018	Prospective phase 2 trial	52†	36 grade 2, 16 grade 1	32 GTR, 5 STR‡	Photon	54.0 Gy, single-fraction dose: 1.8 Gy	4 treatment failures (7.6%), 3-y progression-free survival: 93.8% 3-y overall survival: 96.0%	3 local failures (75.0%)§
Rogers et al, RTOG 0539 (high-risk arm)[6]	2019	Prospective phase 2 trial	53‖	19 grade 2, 22 grade 3¶	25 GTR, 16 STR¶	Photon	60.0 Gy, single-fraction dose: 2.0 Gy	19 treatment failures (35.8%), 3-y progression-free survival: 58.8% 3-y overall survival: 78.6%	13 in-field failures (92.9%), 1 in-field and marginal failure (7.1%)#
Deng et al, MARCIE[19]	2023	Prospective phase 2 trial	33	33 grade 2	33 STR	Bimodal (photon, carbon ion)	50.0 Gy, single-fraction dose: 2.0 Gy, 18 Gy (RBE) carbon ion boost, single-fraction dose: 3.0 Gy	10 treatment failures (30.3%) 3-y progression-free survival: 80.3% 3-y overall survival: 89.8%	8 in-field failures (80.0%), 2 out-of-field failures (20.0%)
Adeberg et al[20]	2012	Retrospective cohort study	85	62 grade 2, 23 grade 3	50 STR, 35 GTR	Mixed (photon, photon and carbon ions)	Photon Median: 59.4 Gy Photon and carbon ion: 50.4 Gy, 18 Gy (RBE) carbon ion boost, single-fraction dose: 3.0 Gy	Number of treatment failures not explicitly reported, 2-y progression-free survival (grade 2/3): 95%/63% 5-y overall survival (grade 2/3): 81%/53%	85% in-field failures, 7% marginal failures, 7% out-of-field failures
Press et al[11]	2014	Retrospective cohort study	46	46 grade 2	20 STR, 19 GTR**	Photon	Median: 59.4 Gy	8 treatment failures (17.4%), 6 with available imaging	5 in-field failures (83.3%), 1 in-field and marginal failure (16.7%)
Lee et al[12]	2019	Retrospective cohort study	98	73 grade 2, 25 grade 3	64 GTR, 34 STR	Not explicitly mentioned	45 patients with surgery alone, 53 patients with adjuvant radiation therapy, median: 59.4 Gy, single-fraction dose: 1.8 Gy	33 treatment failures (33.7%), 3-y progression-free survival after adjuvant radiation therapy: 73.7% 3-y overall survival after adjuvant radiation therapy: 83.3%	28 local failures (84.8%), 4 out-of-field failures (12.1%), 1 local and out-of-field failure (3.0%)††

(*Continued*)

Table 2 (*Continued*)

Author/Study	Year	Study type	Number of patients	Tumor grading	Resection status	Radiation modality	Dose	Outcomes	Pattern of failure
Hoffmann et al[21]	2021	Retrospective cohort study	31	31 grade 2	11 STR, 17 GTR[‡‡]	Not explicitly mentioned	Mostly between 57.6 and 60.0 Gy, single-fraction doses 1.8 or 2.0 Gy	8 treatment failures (25.8%), 5-y local control: 67.9%	5 in-field failures (62.5%), 3 out-of-field and in-field failures (37.5%)
Susko et al[10]	2021	Retrospective cohort study	51	8 grade 1, 30 grade 2, 13 grade 3	29 STR, 22 GTR	Not explicitly mentioned	Not reported	27 treatment failures (52.9%)	16 failures in resection cavity (72.7%), 11 failures along dura margins (50%), 2 failures along surgical tracts (9.1%), 2 intraparenchymal failures (9.1%)[§§]
Obiri-Yeboah et al[22]	2023	Retrospective cohort study	22	22 grade 2	10 STR, 12 GTR	No radiation therapy	No radiation therapy	22 treatment failures (100%)	19 central failures (39.6%), 21 marginal failures (43.8%), 8 remote failures (16.7%)[§§]
Zeng et al[23]	2024	Retrospective cohort study	118	111 grade 2, 7 grade 3	35 STR, 83 GTR	Photon	Standard dose cohort: 50-64 Gy Dose escalation cohort: 66-70 Gy	Number of treatment failures not explicitly reported 3-y progression-free survival: 78.9% (dose escalation), 57.2% (standard dose) 3-y overall survival: 91.2% (dose escalation), 84.8% (standard dose)	100% in-field failures
This study	2025	Retrospective cohort study	105	105 grade 2	50 STR, 53 GTR[‖‖]	Mixed (photon, proton, photon and proton)	Median: 59.4 Gy Median single-fraction dose: 1.8 Gy	36 patients with treatment failure (34.3%), 46 lesions 3-y progression-free survival: 85.9% 3-y overall survival: 98.0%	35 in-field failures (76.1%), 3 failures within 1 cm of the target volume (6.5%), 9 within 2 cm of the target volume (19.6%), 2 distant failures, ie, >2 cm distance to the target volume (4.3%)

Abbreviations: GTR = gross total resection; STR = subtotal resection; y = year; mo = month.

[*] See reference for the definition of high- and low-risk CTV.

[†] Forty-eight patients evaluable for primary endpoint (3-year progression-free survival).

[‡] Thirteen recurrent tumors diagnosed by imaging only. All patients were required to have a documented history of a grade 1 tumor. Two cases with an unknown extent of resection.

[§] One newly diagnosed tumor without details on the pattern of failure.

[‖] Fifty-one patients evaluable for the primary endpoint, ie, 3-year progression-free survival.

[¶] Twelve recurrent tumors diagnosed by imaging only. All patients were required to have a documented history of a grade 2 or 3 tumor.

[#] Fourteen tumor progressions per central review within 3 years. No data on treatment failures after 3 years were provided.

[**] Seven definitive treatments.

[††] Local failure was defined when the shortest distance between the tumor bed and recurrence was shorter than 2 cm.

[‡‡] Three cases with an unknown extent of resection.

[§§] Multiple categories for each recurrence were counted if they met more than 1 pattern of failure category.

[‖‖] Missing data for 2 patients.

2 meningiomas. Five studies were prospective trials, whereas 7 retrospective studies were identified. The sample sizes of the studies ranged from 6 to 118, whereas several included and analyzed patients who did not receive radiation therapy. Doses ranging from 54 to 59.4 Gy were most commonly applied for patients undergoing radiation therapy. During the available follow-up of the reviewed trials and studies, more than 140 treatment failures were observed. Most of them occurred locally, with reported ranges mostly between 80% and 100%. Actual distant failures were rarely observed.

While most patterns of failure analyses apply a qualitative approach to describe failure patterns, our analysis used a voxel-based approach, incorporating data from the 105 treatment plans for investigation, making it the most comprehensive study to date. Our results confirm that grade 2 meningiomas recur locally with overwhelming frequency. The TV covered 35 out of 46 identified recurrences and progressive tumors, indicating that the targeting is mostly adequate. However, 3 and 9 treatment failures occurred within 1 and 2 cm of the TV, respectively, which suggests that in a smaller subgroup of patients, tumor cells were either not treated with a sufficient radiation dose or were not identifiable with the conventional imaging, such as computed tomography and magnetic resonance imaging, used for target delineation at the time of treatment planning. In summary, over 95% of observed treatment failures occurred within the TV or a 2-cm distance. Therefore, improving target identification and individualizing treatment margins are paramount in radiation oncology. A promising avenue for this approach is PET, which uses radiolabeled ligands that bind to somatostatin receptors, which are overexpressed in most meningiomas.[9,25,26] Various studies have highlighted the notable benefits of PET in assessing the extent and spatial configuration of meningiomas, also allowing for the identification of meningioma tissue not visible on conventional imaging, ie, computed tomography and magnetic resonance imaging.[25] While the resection status in meningiomas is primarily rated using the Simpson grading, assessment of residual tumor near the skull base or in tumors with osseous invasion can be particularly challenging.[14] Even in the setting of recurrence, before salvage radiation therapy, PET might help to localize recurrent tumors more precisely, especially facilitating the differentiation between postoperative changes and tumors.[26,27] Despite the potential advantages of PET guidance, a lack of prospective trials investigating its utility and directly comparing it to conventional imaging-based target delineation remains.[9] However, early prospective observational data on the use of PET guidance in meningioma management are promising.[28,29]

While accurate targeting is the foundation for a successful local treatment, such as radiation therapy, the results of our pattern of failure analysis highlight the critical role of dose, particularly EUD, in achieving disease control (Fig. 2, File E2). Most reviewed studies in the field had a more qualitative approach in their analysis (Table 2). Reporting was mainly restricted to the prescription dose, with the lack of quantitative data, such as the voxel-based analysis and EUD, we are reporting. However, as many intracranial meningiomas, such as skull base ones, grow adjacent to critical organs at risk, like the brainstem and optic apparatus, an ideal coverage of the TV with high doses may not always be feasible or desirable. This issue is aggravated by larger tumors, given that our analysis suggested an increased risk of progression with larger TV, which can be considered as a surrogate for tumor size in the preoperative setting and before salvage radiation therapy. To use our quantitative data, we created an additional and easy-to-use risk stratification based on the RTOG 0539 risk classification, TV, EUD, treatment indication, age at radiation therapy, and sex (Fig. 3). The risk stratification can help counsel patients and identify those at the highest risk for early recurrence.

While PET guidance may help refine target delineation, dose escalation has been of growing interest to improve disease control in grade 2 and 3 meningiomas.[9,30] This is particularly relevant in the context of macroscopic disease. Our analysis highlighted the poor prognosis in patients with residual and macroscopic disease, as highlighted by the predominant failure of patients in the RTOG 0539 high-risk group (Fig. 1). Therefore, focal dose escalation to gross disease is a promising avenue to reduce local treatment failures. Stereotactic radiosurgery, proton therapy, or carbon ion boosts are potential options to achieve this.[18,19,23] While dose escalation is likely one part of the equation, the intrinsic biological aggressiveness of meningiomas must also be taken into account. Recent advances in molecular neuropathology have provided critical insights into the behavior of meningiomas.[31] Copy number variants, DNA methylation patterns, and genetic drivers of aggressiveness, such as CDKN2A/B deletions and TERT promoter mutations, can improve the risk stratification of meningiomas beyond a histopathological assessment alone.[31,32] A recent study developed and highlighted the utility of a 34-gene expression risk score in predicting outcomes and response to radiation therapy.[33] According to the study results, the postoperative management of patients could have been refined in nearly 30% of cases. Incorporating the molecular and genetic profiles of the tumor into radiation therapy treatment planning, including dose prescription, EUD, margins, and fractionation, yields considerable potential to individualize patient care and improve outcomes for patients while reducing over- and undertreatment. Given the lack of prospective studies and trials and the absence of high-quality evidence, further research is warranted.

This study has several limitations that need to be acknowledged. Its retrospective design is an inherent limitation, as data collection was not standardized. While the generalizability of the investigated cohort is relatively high, including adjuvant and salvage treatments, various extents of resection, and photon and proton radiation therapy, the subgroups and number of recurrences may be too small to detect potential outcome differences

between subgroups. Moreover, the potential for future recurrences must be acknowledged due to different follow-up periods. Additionally, the assessment and reporting of treatment-related toxicity are beyond the scope of this work. Dose intensification and prioritization of target coverage, particularly in large tumors, may increase the risk of toxicity, which must be acknowledged. A balanced discussion of the potential risks and benefits of such an approach with the patient is critical. Furthermore, some of the reported HRs are relatively large. It is important to note that these ratios should be interpreted with caution, as some of the analyzed subgroups have a limited sample size. Finally, treatment paradigms, radiation techniques, and target delineation have evolved throughout the analyzed treatment period and have not been standardized, necessitating prospective and standardized studies. Therefore, post hoc analyses of NRG BN-003 and EORTC 1308/ROAM on the pattern of failure are highly encouraged and could provide valuable insights into the potential refinement of radiation therapy for grade 2 meningiomas.

Conclusion

This in-depth pattern of failure analysis for grade 2 meningiomas after fractionated radiation therapy demonstrates and confirms that treatment failures predominantly occur in close spatial relation to the irradiated TV. Distant failures were rare, highlighting the need for further therapy refinements to prevent treatment failure. Factors such as the indication for radiation therapy, ie, adjuvant versus salvage, EUD, TV, and macroscopic disease, are strongly associated with outcomes and should be considered during patient counseling and treatment planning. Further research is warranted to improve long-term tumor control after radiation therapy. Targeted dose escalation to gross disease and PET guidance represent promising avenues for this approach. Future pattern of failure analyses should include detailed treatment plan data and quantitative dose distributions to maximize insights.

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