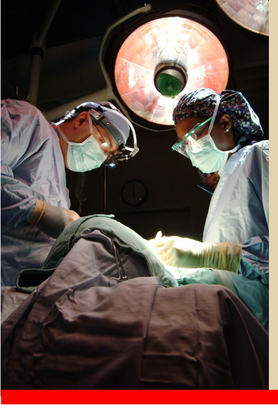

Impact of Salvage Surgery and Re-irradiation for Radiation Failed Recurrent Skull Base Meningiomas

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Introduction and objective:

Long-term follow up of meningiomas has demonstrated recurrence rates of up to 60% after 15 years. There is limited data available to guide the management of recurrent and previously radiated skull base meningiomas and challenges related to salvage surgery, re-irradiation and lack of clear systemic therapy strategies remain. In this study, we analyzed data from our experience with recurrent and previously radiated meningiomas to assess the impact of salvage surgery and re-irradiation on PFS.

Methods:

A retrospective cohort study of 48 patients with recurrent and previously radiated meningiomas who were treated between 1995 and 2021 was conducted. Data were extracted from medical records and include clinical, radiologic, and pathologic reports. Patients were clustered according to WHO grades. We analyzed the complications related to re-irradiation and salvage surgery and the impact of different treatment modalities on PFS using Cox proportional hazard ratios.

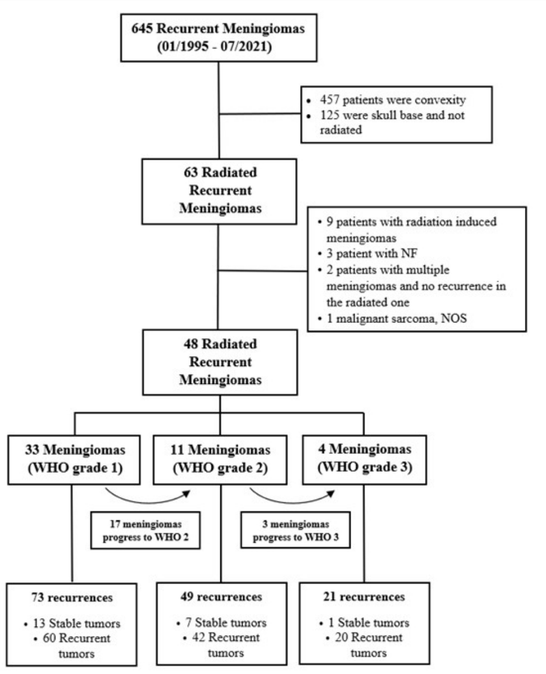

Figure 1. Diagram outlining patient selection

Results:

• Patient Demographics and number of recurrences

Forty-eight patients (33 WHO grade 1; 11 WHO grade 2; and 4 WHO grade 3) were treated for 143 recurrences after their first radiation treatment. Although patients with higher grade meningiomas seem to have lower KPS at recurrence, there was no significant association between KPS and recurrence rate (X^2 [1, N = 143] =3.52, *p=.06*). The overall survival rate was 56.2% after a mean follow-up period of 12.4±7.6 years, with 21 patients with stable disease and 6 patients in hospice. Twenty patients from our cohort (41.6%) had histologic progression (Figure 1 and Table 1).

Table 1. Treatment Outcomes

OUTCOMES	TOTAL	WHO 1	WHO 2	WHO3
All recurrences (n=143)				
Disease status	**143 (100%)**	**73 (51%)**	**49 (34.2%)**	**21 (14.8%)**
• **Stable disease**	21 (14.6%)	13 (9.1%)	7 (4.9%)	1 (0.7%)
• **Disease Recurrence**	122 (85.4%)	60 (42%)	42 (29.4%)	20 (14%)
Mean follow up (months, mean/range)	**32.1 (1-210)**	**47.6 (1-210)**	**19 (1-60)**	**8.9 (1-30)**
• **Stable disease**	35.8 (2-204)	51 (2-204)	18.8 (4-35)	8 (8)
• **Disease Recurrence**	31.5 (1-210)	47.8 (1-210)	19 (1-60)	8.9 (1-30)
All patients (n=48)				
Life Status in Last Contact	**48 (100%)**	**33 (68.7%)**	**11 (22.9%)**	**4 (8.4%)**
• **Alive**	27 (56.2%)	20 (41.6%)	3 (6.3%)	-
• **Dead**	21 (43.7%)	13 (27.1%)	8 (16.6%)	4 (8.4%)

• Treatment offered to recurrences

Surgery alone (SX) was the most frequent treatment offered for recurrences in WHO grade 1 and WHO grade 2 patients (37% and 19.8%, respectively). Patients with GTR had a median time to recurrence of 123, 15 and 6 months for WHO grade 1, WHO grade 2 and WHO grade 3, respectively. Surgical procedures had a complication rate of 23.8% (20/84), and this rate increased over time: 10% (1/10), 18.4% (7/38), 100% (1/1), 39.3% (11/28) and 100% (1/1) for first, second, third, fourth and fifth surgeries, respectively.

Re-irradiation therapy was administered for seventy-three recurrences. Re-irradiation was used along the course of the disease one, two and three time in 32 (66.7%), 13 (27%) and 3 patients (6.3%). Among them, 38 (52%) patients received EBRT, and 35 (48%) patients received SRS, with different doses.

• Analysis of Factors Associated with PFS

Upon conducting univariate log-rank and Cox proportional hazards analysis, we identified those variables that correlated with higher recurrence rate. Among demographics variables, the 3-year PFS was 43.5%, 24.5% and 0%, for WHO grade 1, WHO grade 2 and WHO grade 3, respectively (Figure 2, A).

Furthermore, age ≥60 years-old was associated with increased progression (HR 1.68; 95% CI, 1.15-2.44; p=.0025) (Figure 2, B). As seen in Table 2, patients with WHO grade 1 meningiomas who underwent a STR had a 3.4-fold increase of disease progression compared to patients where GTR was achieved (HR 3.38; 95% CI, 1.268-9.03; p=.0189) (Figure 2, D). For WHO grade 2 and 3 patients however, EOR was not associated with differences in PFS (Figure 3, B and D).

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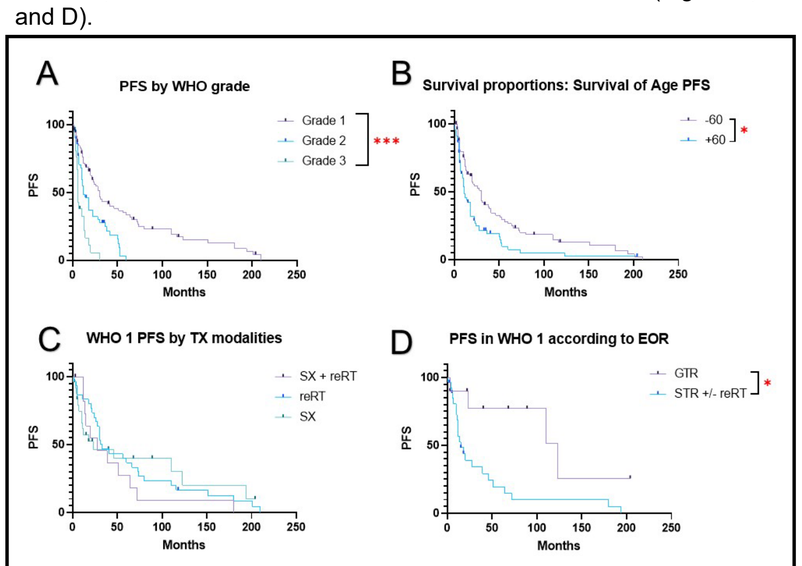

Figure 2. A: Progression-free survival (PFS) according to WHO grades, asterisk indicates a statistically significant difference *(p=<.0001)*. **B:** PFS according to age, asterisk indicates a statistically significant difference *(p=.0025)*. **C:** PFS of WHO grade 1 radiated meningiomas by different treatment modalities *(p=.162),* SX (surgery), reRT (re-irradiation). **D:** PFS of WHO grade 1 radiated meningiomas by extent of resection (EOR) *(p=.0087)*.

When looking at the impact of re-irradiation, WHO grade 3 patients who were re-irradiated were significantly less likely to progress over the course of the study (HR 0.27; 95% CI, 0.078-0.975; *p=.0028*) (Figure 3, C). Furthermore, adjuvant re-irradiation of subtotally or totally resected WHO grade 2 meningioma patients decreased the likelihood of disease progression over the course of the study (HR 0.316; 95% CI, 0.1304-0.7682; *p=.0029* for STR+RT and HR 0.259; 95% CI, 0.099-0.6747; *p=.0048* for GTR+RT). (Figure 3, A). Repeat radiation was not found to be associated with improved PFS in WHO grade 1 meningioma patients (Table 2).

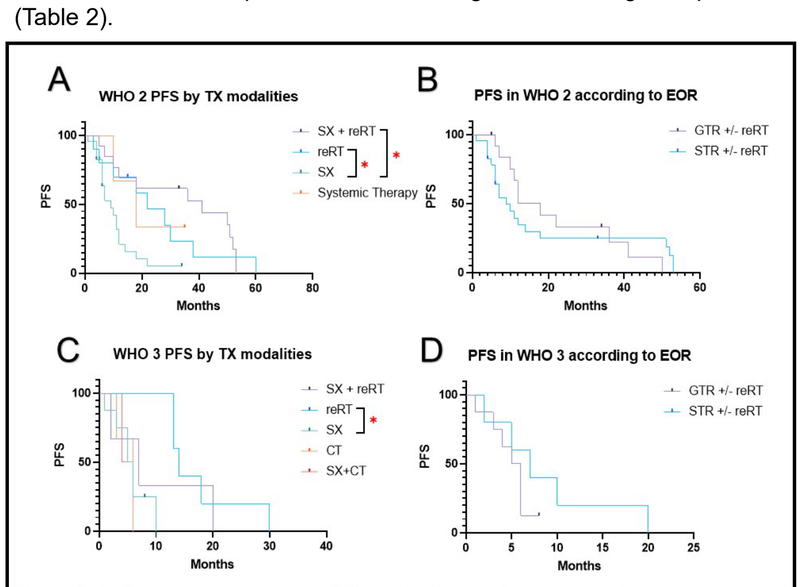

Figure 3. A: Progression-free survival (PFS) of WHO grade 2 radiated meningiomas by different treatment modalities, asterisk indicates a statistically significant difference (reRT alone vs SX alone; *p=.0238* and reRT+SX vs SX alone; *p=.0008*). **B:** PFS of WHO grade 2 radiated meningiomas by extent of resection (EOR) (*p=.139*). **C:** PFS of WHO grade 3 radiated meningiomas by different treatment modalities, asterisk indicates a statistically significant difference (*p=.0028*). **D:** PFS of WHO grade 3 radiated meningiomas by EOR *(p=.299*).

Discussion:

To our knowledge, this is the largest reported cohort of post-radiation recurrent skull base meningiomas summarizing the impact of salvage surgery and repeat radiation on tumor control rates. The management of post-radiation recurrence is not clear, but the decision should consider the WHO grading, along with the multidisciplinary treatments available.

For WHO 1 meningiomas, despite the challenges associated with previous radiation, we found a clear benefit of GTR over STR alone or combined with RT. The impact of EOR on outcomes for WHO grade 2 meningiomas remains unclear and is even less effective in malignant meningiomas. One hypothesis to explain the lack of correlation between EOR and PFS could be the more aggressive behavior and a higher proliferative index labeling in tumors that recur versus tumors that don't recur[1]. Furthermore, previous radiation might be a risk factor to increase the aggressiveness of the tumor[2].

This study also helps elucidate the potential role of re-irradiation with recurrent skull base meningiomas. In our cohort, there were no associated improvements in PFS with re-irradiation of grade 1 meningiomas. Conversely, the role of radiation seems to be more important for WHO 2 and WHO 3 meningiomas. Indeed, we found an improvement in PFS for re-irradiated WHO grade 2 meningiomas, but this finding is opposed to other authors[3]. Nevertheless, it is important to highlight that our patient cohort consisted exclusively of skull base meningiomas, which have a different genomic signature than convexity meningiomas and have different biological and clinical behavior[4]. Although survival and tumor control are poor in WHO grade 3 meningiomas, there is a consensus on the beneficial effect of radiation, irrespective of the EOR[5], and in our cohort of anaplastic meningiomas, re-irradiation provided a PFS benefit when compared with surgery alone, demonstrating that salvage RT still has a survival impact in already radiated recurrences. Among demographic variables, age over 60 and KPS ≤ 70 were predictors of unfavorable results that have been seen in other studies[6]. To resume, we propose the following treatment algorithm according to our results and the literature reported (Figure 4).

Table 2. Univariate Analysis of prognostic factors affecting PFS

UNIVARIATE ANALYSIS		HR	CI (95%)	Median PFS (months)	P-Value
Patient demographics					
Age	<60 years-old	Ref	Ref	30	-
	≥60 years-old	**1.68**	**1.156-2.443**	**11**	**0.0025**
KPS	KPS 90-100	Ref	Ref	26	-
	KPS 60-80	**2.61**	**1.510-4.50**	**7**	**<0.0001**
Gender	Female	Ref	Ref	15	-
	Male	1.288	0.8564-1.938	20	0.971
Tumor features					
Location	AF/MF/PF/Combined	-	-	-	0.2535
Form	Globoid	Ref	Ref	12	-
	En-Plaque	1.001	0.7012-1.429	20	0.1968
WHO grade	WHO 1	Ref	Ref	30	-
	WHO 2	**1.972**	**1.269-3.067**	**12**	**0.0002**
	WHO 3	**3.563**	**1.628-7.798**	**6**	**<0.0001**
KI-67	KI-67 0-9%	Ref	Ref	51	-
	KI-67 10-19%	**2.285**	**1.249-4.178**	**12**	**0.003**
	KI-67 ≥20%	**3.426**	**1.771-6.628**	**6**	**<0.0001**
Treatment Related Variables					
Type of reRT	SRS	Ref	Ref	28	-
	EBRT	0.8507	0.5280-1.371	36	0.483
Treatment Modality WHO I	SX	Ref	Ref	23	
	SX + reRT	-	-	28	0.162
	reRT	-	-	32	
	Systemic Therapy	-	-	14.5	
Treatment Modality WHO II	SX	Ref	Ref	9	-
	SX + reRT	**0.365**	**0.175-0.757**	**41**	**0.0008**
	reRT	**0.457**	**0.218-0.959**	**22**	**0.0238**
	Systemic Therapy[1]	-	-	18	-
Treatment Modality WHO III	SX	Ref	Ref	5.5	-
	SX + reRT	0.653	0.184-2.32	7	0.468
	reRT	**0.276**	**0.078-0.975**	**14**	**0.0028**
EOR in WHO I	GTR	Ref	Ref	123	-
	STR +/- reRT	**0.2760**	**0.1272-0.5987**	**15**	**0.0087**
EOR in WHO II	GTR +/- reRT[2]	Ref	Ref	15	-
	STR +/- reRT[3]	0.8919	0.4321-1.841	9	0.139
EOR in WHO III	GTR +/- reRT	Ref	Ref	5.5	-
	STR +/- reRT	1.649	0.5297-5.132	7	0.299

[1]Only 3 patients, unpowered for statistical purposes
[2] GTR + reRT = RR 0.259, 95% CI 0.099-0.6747, *p=.0048,* Median PFS=27 months
[3] STR + reRT= RR 0.316, 95% CI 0.1304-0.7682, p=*.0029,* Median PFS=52 months
Bold letters indicate statistical significance

Conclusion:

We presented a retrospective analysis with the largest cohort of radiated and recurrent skull base meningiomas. According to our results, achieving GTR is the best option for recurrent WHO grade 1 meningiomas, radiation is the best option for WHO grade 3 meningiomas, and radiation appears to provide a benefit in subtotally resected WHO grade 2 meningiomas. Reoperation for recurrent skull base meningiomas is associated with a higher complication rate. Further prospective studies are needed to validate our results.

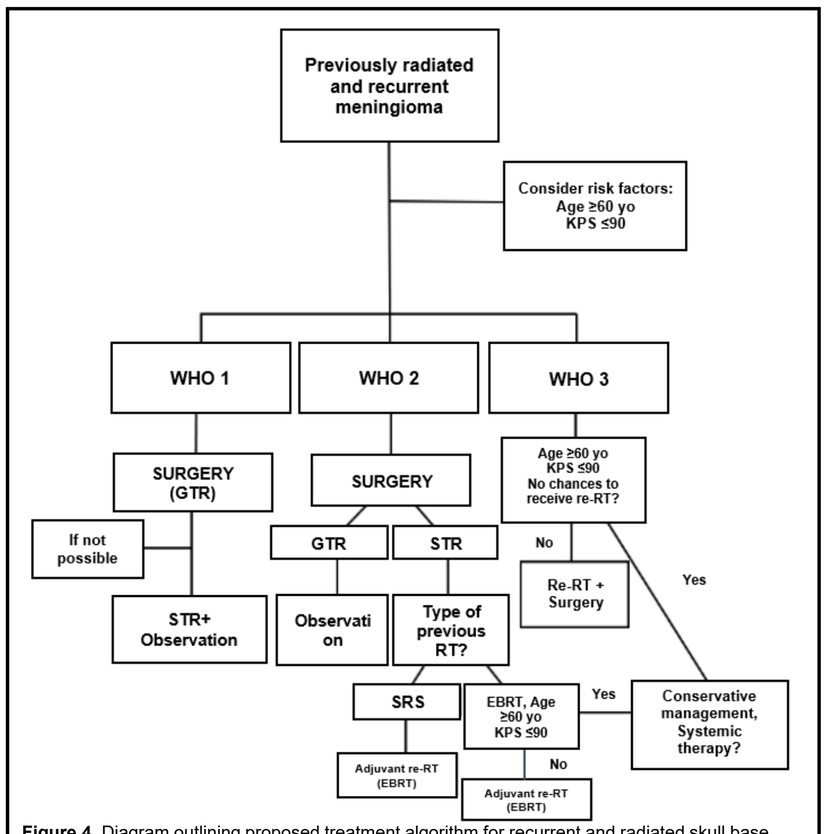

Figure 4. Diagram outlining proposed treatment algorithm for recurrent and radiated skull base meningiomas

Conflict of Interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations:

HR, Hazard ratio; PFS, progression free survival; EOR, extent of resection; GTR, gross total resection; STR, subtotal resection.

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