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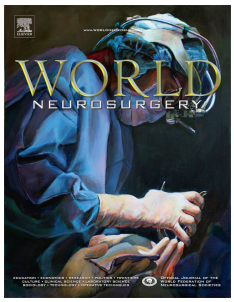

Radiotherapy for WHO grade 1 and 2 Intracranial Meningiomas – A Retrospective Analysis of Efficacy

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Structured Abstract

Purpose: To evaluate the efficacy of radiotherapy (RT) for WHO grade 1 and 2 intracranial meningiomas, focusing on the impact of post-surgical tumor volume on treatment outcomes.

Methods: Adult patients (≥18 years) with WHO grade 1 or 2 intracranial meningiomas who received RT between January 1, 2019, and April 1, 2022, were identified. Exclusion criteria encompassed known extracranial tumors, preoperative radio- or chemotherapy, and insufficient RT modality data. Patients were treated according to the international guidelines. Tumor recurrence was identified on MRI with a follow-up period until April 2024. Kaplan-Meier estimates for progression-free survival (PFS) calculations and Cox proportional hazard models were performed to evaluate the impact of tumor volume and other covariates on PFS.

Results: Among 113 patients with intracranial meningiomas who received RT, 103 met the inclusion criteria. Of these, 84.5% received photon-based and 15.5% proton-based treatment. The cohort was predominantly female (72.8%) with a mean age of 59 years. The 2-year and 5-year PFS rates were 95.6% and 90% for grade 1 tumors, respectively, and 83.3% for grade 2 tumors. Tumors >21 cm^3 post-surgical pre-RT had a significantly higher risk of progression (HR = 4.35, p = 0.006).

Conclusions: Tumor volume was identified as a key prognostic factor for PFS in WHO grade 1 and 2 intracranial meningiomas treated with RT. A critical post-surgical volume threshold of 21 cm^3 significantly influences 2-year and 5-year PFS rates, with patients exceeding this threshold experiencing a 335% increase in risk of progression.

Introduction:

Meningiomas account for approximately one third of all CNS tumors in adults [1,2]. They are believed to arise from arachnoid cap cells of the leptomeninges comprising pia and arachnoid mater lining the brain and spinal cord. In Scandinavia the incidence for females is 4.9/100,000 and 1.5/100,000 for males [3]. The development of meningiomas is multifactorial, and the only well-established known environmental risk factor is prior ionizing radiation [4-8]. Familiar syndromes as e.g. neurofibromatosis type 2 is a predisposing factor for meningioma development; this is however rare and is mostly observed in the younger population [4,9,10].

Meningiomas are classified into grade 1, 2 and 3 according to the World Health Organization (WHO) grading system [11]. The frequency is 80%, 18% and 2% respectively [4,5]. Histological transformation to a higher grade is possible but extremely rare. In fact, recent studies show that only 0.12% of WHO grade 1 meningiomas undergo a malignant transformation per patient-year follow-up [12]. Dedifferentiation after radiotherapy (RT) is a matter of debate as studies have shown opposing results exhibiting both higher and lower risk of atypical or malignant transformation [12-17].

Incidental findings of meningiomas on computed tomography (CT) and magnetic resonance (MR) imaging are the most common presentation at diagnosis. For asymptomatic patients with meningiomas of smaller volume (diameter < 2.5 cm), a pragmatic wait-and-watch approach with serial MR imaging is often preferred [18,19, 33]. In the adverse events of symptomatic patients, patients with larger tumors (diameter ≥ 4 cm) or rapid growth, maximal safe surgery is recommended [16,20,21]. Adjuvant treatment is usually not recommended in cases with surgically treated WHO grade 1 meningiomas due to the low recurrence rate [22,23]. In meningiomas with a higher WHO grade where a higher risk of recurrence is observed, adjuvant RT is often the choice of treatment subsequent to surgery [16,24,25].

Different RT modalities for adjuvant treatment for meningiomas include photon- and proton-based therapies. While advancements in photon therapy techniques have improved dose conformity around tumors, proton RT may reduce dose to normal tissue, potentially lowering the risk of long-term cognitive side effects [26-29,30].

The efficacy of RT to treat WHO grade 1 and 2 intracranial meningiomas is relatively good with reported 5-year progression-free survival (PFS) ranging from 77-86% and 48-83% respectively [4,31-33]. In this retrospective study, we aimed to analyze our institution's results for patients with WHO 1 and 2 meningioma treated with RT within a 12-year period. In addition, we sought to identify an optimal meningioma cutoff volume. The primary endpoint was PFS.

Methods:

Study population

Data was extracted from the regional electronic patient journal system (EPJ-SYD, COSMIC archive). We identified relevant patients with ICD-10 codes including D32.0 (intracranial meningioma) procedure code BWGC4A (intensity modulated radiation therapy) or AFV01X3 (proton therapy).

The inclusion criteria were: Adult patients (>18 years at time of RT), with MR imaging and/or histology confirmed WHO grade 1 or 2 intracranial meningiomas who received RT between January 1, 2010 and April 1, 2022. The exclusion criteria were known extracranial tumors, preoperative radio- or chemotherapy and lack of information regarding RT modality.

Patients were classified based on the applicable WHO classification of CNS tumors corresponding to the time of diagnosis: WHO 2007, WHO 2016, or WHO 2021. WHO Grade 2 meningiomas were defined by histopathological criteria that included mitotic index (≥4 mitoses per 10 HPF), brain invasion, or the presence of three or more atypical features (e.g., hypercellularity, high nuclear-to-cytoplasmic ratio, prominent nucleoli, sheeting architecture, or necrosis). Brain invasion was considered a stand-alone criterion in the WHO 2016 and 2021 classifications.

Each record was reviewed and for patients included, the following data points were extracted. Patient demographics and baseline characteristics: age, sex, pre-radiation Eastern Cooperative Oncology Group (ECOG) performance status (PS), age and date at diagnosis, primary surgery, RT progression and death. Moreover, pre-radiation tumor volume, tumor localization, type of surgical treatment, histology and WHO grade, radiation dose and fractions and tumor progression based on MR imaging were registered.

Follow-up

All meningioma patients in Denmark are routinely followed for 10 years with MRI regardless of resection grade. For WHO grade 1 meningiomas follow-up MRI are done 3-6 months, 1, 3, 5, 7 and 10 years after surgery. For WHO grade 2 meningiomas it is done 3-6 months, 9 months, 15 months, 2, 3, 5, 7 and 10 years after surgery. For WHO grade 3 meningiomas MRI is done every 3rd month. The minimum slice thickness on the follow-up MRI was 3 mm max.

During follow-up visits, side effects were recorded and categorized for both photon- and proton-therapy groups (Table 4). Effects were classified into specific categories including hypopituitarism, inflammation, neurological effects, dizziness, nausea, headache, fatigue, and skin rash.

Radiotherapy regimens

All meningioma cases treated with RT in the Region of Southern Denmark from 2010–2022 were included in the analysis. This included patients initially treated with gross total resection but with later recurrent disease in a surgical unfavorable location (e.g., cavernosus sinus). It also included patients with subtotal resection having either adjuvant RT or patients who during post-operative follow-up had progression in a surgical unfavorable location thus receiving salvage RT. In the context of this study, we defined adjuvant therapy as RT administered within three months following the latest surgical intervention. Conversely, salvage therapy refers to RT initiated more than three months after the latest surgical intervention.

WHO grade 1 meningiomas were typically treated with radiation in cases of growth of remnants in the cavernous sinus, non-occluding remnants in the superior sagittal sinus, intraorbital meningiomas, and petroclival meningioma remnants, aligning with our institution's practice for managing complex or residual disease.

The delineation of target volumes was performed in accordance with international guidelines and remained consistent throughout the study period. Gross Tumor Volume (GTV) was defined as the meningioma or meningioma remnants, including pathological enhancement of the dura (e.g., dural tails), bone changes in cases of bone invasion, and the resection cavity. The Clinical Target Volume (CTV) was defined as CTV = GTV for WHO Grade 1 meningiomas. For WHO Grade 2 meningiomas, the CTV included the GTV with a concentric margin of 10 mm in all directions, adjusted for anatomical structures, and reduced to 5 mm toward the brain parenchyma. All delineations were performed by a radiologist.

Patients receiving photon-based RT were treated in the Department of Oncology at Odense University Hospital, whereas patients receiving proton-based RT, were treated at the Danish Centre for Particle Therapy (DCPT) which opened in 2019. Patients' treatment regimen was decided in accordance with the national guidelines where a dosimetric advantage based on comparative radiotherapy plans were evaluated ([34]). Regardless of treatment facility, all patients with intracranial meningioma WHO grade 1 received 54 Gy in 30 fractions, whereas patients with WHO grade 2 received 59.4 Gy in 33 fractions ([34]).

Tumor volume determination

Pre-radiation tumor volumes were determined using the Brainlab® neuronavigation platform by semiautomatic segmentation. The latest pre-radiation T1-weighted contrast enhanced images were uploaded in the Brainlab® system. Tumor volume was calculated using the independent, modular software application, SmartBrush, which enabled 3D outlining, followed by visual inspection and volume extraction.

Statistical analysis

All analyses were performed using Python (3.11.7) including the lifelines library for survival analysis and matplotlib for data visualization. PFS was defined as date of initiated radiotherapy to the date of registered progression on MR imaging or date of latest follow-up (18.04.2024). Progression was defined as more than 2 mm growth in length, width and/or height on follow-up MR imaging compared to the most recent pre-radiation MR imaging. PFS was calculated in months and analyzed using Kaplan-Meier estimates. Kaplan-Meier survival curves were generated for WHO grade 1 and 2 tumors and for tumor volume groups, with censoring events represented by progression or recurrence. Survival functions were compared using the log-rank test to assess differences between groups.

An iterative method utilizing the log-rank test was employed to determine the optimal cutoff for tumor volume across 100 equally spaced points within the volume range. Patients were categorized into Low (≤ 21.013 cm^3) and High (> 21.013 cm^3) groups based on this cutoff. Cox proportional hazards models were fitted to evaluate the impact of tumor volume and other covariates on PFS. Model 1 included tumor volume and ECOG PS score; Model 2 considered tumor volume alone; Model 3 incorporated tumor volume, ECOG PS score, age at radiation, sex, and WHO grade. Using the cutoff value, new Kaplan-Meier curves were generated, and 2- and 5-year PFS was calculated. The groups were compared using a log-rank test.

Ethics

This study was approved by the local ethics committee under the Region of Southern Denmark (Journal nr. 22/28919) and the Danish Data Protection Agency (Journal nr. 22/29549).

Results:

Study population

A total of 113 patients underwent RT, and 103 met the inclusion criteria. In the same period 702 meningioma patients were managed by surgery alone in our institution. Among the RT treated patients 84.5% received photon-based RT, while 15.5% were treated with proton-based RT. There was a predominance of females compared to males consistent across both stable disease (SD) and progressive disease (PD) groups (Table 1). In the group with SD mean age at diagnosis was 59 years compared to 64 years in the group with PD. Mean age at time of RT was also higher in the group with PD (69 years) compared to the group with SD (62 years) (Table 1). ECOG PS before initiation of RT was in the majority of cases 1 or 2 reflecting good functional status prior to treatment. The mean duration from date of diagnosis to RT was approximately 64.35 months. Mean follow-up time was 61.35 months with 14 recorded events.

Surgical Treatment

A total of 27 patients (26.2%) underwent total resection as their primary surgical intervention, while 56 (54.4%) patients had subtotal resection. Two patients (1.9%) received a biopsy alone and 18 patients (17.5%) did not undergo any surgical procedure. A total of 51 patients (49.5%) underwent a single surgical procedure, whereas 24 patients (33%) underwent multiple surgeries. Notably, four patients (3.9%) had surgery after radiation (Table 1).

Tumor Characteristics

Overall, the mean pre-radiation post-surgical tumor volume was 22.7 (range 1.2-142.4 cm^3), with SD group having a lower mean tumor volume compared to PD group (Table 1). Notably, 60.2%. of patients had tumors measuring less than 10 cm^3.

WHO grade 1 tumors represented the majority of cases while only 12% of patients had WHO grade 2 meningiomas. No instances of WHO grade 3 tumors were identified in the study.

WHO grade and PFS

PFS analysis revealed that the overall 2-year PFS was 95.6% and 83.3% for patients with WHO grade 1 and 2 meningiomas respectively. At the 5-year mark, was 90% for patients with WHO 1 meningiomas while patients with WHO 2 meningiomas maintained a PFS rate of 83.3%. There was no statistically significant difference between the two groups (p=0.20). In total, 17 patients (16.5%) experienced progression after RT (Table 1). In the group with PD after RT, 47.1% progressed within the first two years and 76.5% within five years. Analysis by WHO grade revealed that patients with grade 1 meningiomas had a 5% risk of progression at two years, increasing to 13% at five years, as shown in Figure 1. In contrast, grade 2 meningiomas exhibited a consistent risk of progression at both time points.

Tumor Volume and PFS

The optimal cutoff for pre-radiation post-surgical tumor volume was identified at 21 cm^3. Patients with tumor volumes exceeding this threshold experienced a markedly higher risk of progression, with a hazard ratio (HR) of 4.35 (95% CI: [1.52, 12.44], p = 0.006).

Further analysis revealed that for every 1 cm^3 increase in tumor volume, the hazard of progression increased by approximately 2.89% (HR = 1.029, p <0.001). The robustness of this association was further evaluated by incremental hazard ratios calculated for various volume increases, represented in Table 3. Cox proportional hazards analysis evaluating the effect of tumor volume and WHO grade (Model 3) revealed no statistically significant variables.

The analysis of hazard progression revealed a clear, exponential relationship between tumor volume and the risk of progression in meningiomas (Figure 3). Utilizing the identified cutoff, patients were stratified into two groups: High (>21 cm^3) and Low (≤21 cm^3). The event rates illustrated this disparity, with the High Group (19 patients) experiencing 7 events (a 36.8% event rate), compared to the Low Group (84 patients) with only 7 events (8.3% event rate).

The impact of tumor volume on PFS was significant. The 2-year PFS for low and high-volume groups was 96.4% and 84.2% respectively, decreasing to 93.8% and 71.2% at 5 years. The concordance index of 0.7228 suggested good predictive accuracy for PFS outcomes based on tumor volume.

Side effects

Fatigue was the most prevalent side effect for both photon (20.6%) and proton (31.3%) therapy groups (Table 4). Notably, 62.5% of proton therapy patients reported no side effects, compared to 27.5% in the photon group. Hypopituitarism were exclusively observed in photon therapy patients.

Discussion:

This retrospective study underscores the efficacy of RT in treating patients with WHO grade 1 and 2 intracranial meningiomas. The findings demonstrate that RT is an effective treatment option for the majority of patients, particularly highlighting the significant impact of post-surgical pre-radiation tumor volume on PFS. Notably, 83.5% of patients remained progression-free within 5 years after RT, underscoring its durability in disease control.

Our findings reveal a pivotal cutoff tumor volume of 21 cm^3, serving as a significant independent prognostic factor for PFS. The 2-year PFS in the low volume (<21 cm^3) group and high volume (>21 cm^3) group was 96.4% and 84.2% respectively. Remarkably, at the 5-year mark however, PFS decreased to 93.8% in low volume group and as much as 71.2% in the high tumor volume group. Moreover, patients face a substantially increased risk of disease progression, with a HR of 4.35 (95% CI: [1.52, 12.44], p = 0.006), underscoring the importance of pre-radiation residual tumor volume after primary surgical resection. Supporting our findings, several studies highlight the correlation between larger tumor volumes and poorer outcomes in meningioma patients. For instance, Hwang *et al.* emphasize that increased tumor size is associated with higher recurrence rates, while Chen *et al.* demonstrates a significant rise in progression risk correlated with larger volumes [17,35]. Additionally, Moraes and Chung discuss various cutoff values for tumor volume, affirming that our threshold aligns with existing literature [36]. Based on that we find it reasonable to suggest that surgical tumor volume reduction to less than 21 cm^3 before initiating RT should be done if possible. If not possible our data still suggests that tumor reduction should be performed to a maximal safe extent before RT as for every 1 cm^3 increase in tumor volume, the hazard of progression increased by approximately 3%.

Contrarily, our analysis did not demonstrate statistically significant differences in PFS between WHO grade 1 and 2 meningiomas. This finding diverges from existing literature that often highlights a clear distinction in outcomes based on histological grading. Meningiomas classified as WHO grade 2 typically exhibit higher cellularity, increased mitotic activity, and atypical cellular features compared to WHO grade 1 meningiomas [4, 21, 31, 37-41]. For example, Fahlstrom *et al*. (2023) noted that grade 2 meningiomas typically exhibit higher recurrence rates compared to grade 1 tumors [5]. Our results, however, suggest that tumor volume may play a more pivotal role in determining PFS than histological classification alone, indicating a potential need to reassess the weight given to grading in clinical decision-making. On the other side, the absence of significant differences between the two grades could also be attributed to the predominance of WHO grade 1 meningiomas in our cohort, limiting our ability to draw robust conclusions regarding meningiomas WHO grade 2.

While our findings align with previous studies stating poorer outcomes in meningiomas with larger tumor volumes, some studies present with contrasting perspectives on tumor volume's impact on prognosis. Specifically, Vagnoni (2022), Nakasu (2020) and Corniola *et al*. (2020) suggest that tumor volume alone does not fully dictate the prognosis of meningiomas, highlighting the potential for smaller tumors to exhibit aggressive behavior or undergo malignant transformation[12-14]. The discrepancies with our study may arise from differences in study design and population characteristics. Our cohort focused on WHO grade 1 and 2 treated with RT, differing from the broader range of tumor grades and treatment modalities studied by Vagnoni *et al.* and Nakasu *et al.* For instance, Vagnoni *et al.* concentrated on atypical and anaplastic meningiomas, which may behave differently than lower-grade tumors. Additionally, demographic factors such as age also play a role; our mean age was approximately 59 years, while Nakasu *et al*. included younger patients who may respond differently to treatment, and while larger tumors are generally associated with worse prognosis, some smaller tumors may exhibit aggressive characteristics leading to unexpected progression. Nakasu *et al.*'s systematic review indicated that malignant transformations can occur even in smaller tumors, suggesting that factors beyond size, such as histological features, may significantly influence prognosis [13]. Finally, although this is a single center study, the public healthcare system in Denmark ensures that patients are followed and treated at the same university hospital except in the rare occasions where they move to a different catchment area.

Moreover, our analysis demonstrated an exponential relationship between tumor volume and risk of progression, as depicted in Figure 3. For every cubic centimeter increase in tumor volume, there was an approximate 2.89% increase in the hazard of progression (HR = 1.029, p = 0.000697). This finding is consistent with prior studies that have reported similar exponential associations between tumor size and risk of recurrence or progression in other malignancies [2,7,12].

While patients received different RT modalities (proton- and photon-based), this study refrains from directly comparing them for several reasons. Firstly, proton therapy was only first introduced in Denmark in 2020, resulting in a limited follow-up period for patients treated with this modality; thus, the lack of observed recurrences may not reflect treatment efficacy but rather this short duration. Additionally, patients receiving proton therapy in our cohort

were generally younger and did not have rapidly progressing tumors, complicating direct comparisons between treatment groups.

While our study focused on tumor volume and PFS, long-term toxicities associated with RT are important considerations. We refrained from directly comparing photon and proton therapies due to the short follow-up for proton-treated patients. Since side effects like hypopituitarism often emerge years after RT, it is too early to assess long-term endocrine effects in this group. Although our data suggested a potentially favorable toxicity profile for proton therapy, current evidence does not conclusively show that it causes fewer permanent side effects in CNS patients compared to photon therapy. Some patients even report more post-treatment pain with proton therapy. The absence of randomized trials further limits definitive comparisons. Furthermore, long-term studies with randomized designs are needed to clarify these differences.

Although we identified a notable correlation between larger tumor volumes and worse outcomes, the lack of statistically significant differences in PFS across tumor grades invites further exploration. Further investigations should aim to validate our findings across larger cohorts and consider additional factors such as molecular characteristics and treatment response variations. Furthermore, exploring biological mechanisms underlying tumor behavior, especially in smaller tumors exhibiting aggressive features, could enhance our understanding of meningioma progression. Longitudinal studies assessing the impact of different radiation modalities on tumor behavior and patient outcomes will also be crucial in refining treatment strategies for meningioma patients.

Strengths and Limitations

Strengths

This study has several strengths that enhance the validity of the findings. Firstly, the retrospective design includes a substantial sample size of 103 patients, which provides a solid foundation for analyzing the data. Additionally, the longitudinal follow-up period with a mean follow-up time of 61.35 months allows for a thorough assessment of PFS, contributing to our understanding of long-term outcomes. The study also employs detailed tumor volume assessments using segmentation, adding precision to the analysis.

Limitations

Several limitations should be acknowledged. The retrospective design may introduce biases related to data collection and patient selection, potentially affecting generalizability. The exclusion criteria may limit applicability; patients with known extracranial tumors were excluded, which could affect the relevance of the results to a broader population. Additionally, reliance on an institutional database may result in selection bias, as patients treated at a single institution may not represent the wider population of meningioma patients. However, it's worth noting that the treatment approach in Denmark closely aligns with international guidelines, which may enhance the external validity of our findings. Nonetheless, caution should be exercised when extrapolating these results to populations with significantly different treatment protocols.

In addition, the large discrepancy in population size between WHO grade 1 and 2 meningiomas (88% vs 11%) could limit the study's ability to provide comprehensive insights into prognosis and treatment outcomes, particularly for the less common and more aggressive WHO grade 2 tumors. Furthermore, the discrepancy among the patient population between the tumor volume groups with a predominance of smaller tumors (60.2%) may limit the generalizability of findings to patient with larger tumors and affect overall prognosis outcomes. A more balanced patient population to allow for a robust analysis of the relationship between tumor volume and clinical outcomes would be beneficial in the future.

Furthermore, while the Cox proportional hazards analysis did not yield statistically significant results for tumor volume and WHO grade, a subtle negative trend was observed with increasing grade. This observation, though not reaching statistical significance, may be attributed to the limited sample size, particularly in higher grade meningiomas, potentially constraining the statistical power to detect grade-specific effects.

Conclusion:

This study highlights the significant impact of post-surgical tumor volume on PFS in patients with WHO grade 1 and 2 intracranial meningiomas treated with RT. We identified a critical post-surgical pre-radiation tumor volume threshold of 21 cm^3, for patients with smaller tumors showing significantly better 2-year and 5-year PFS rates compared to those with larger tumors.

Our findings emphasize the importance of surgical tumor volume reduction, if possible, to less than 21 cm^3 before initiating RT. Despite the lack of statistically significant differences in PFS between WHO grade 1 and 2 meningiomas, our results suggest that tumor volume may play a more crucial role than histological grading alone, indicating a potential need to reassess the emphasis on grading in treatment planning.

The observed exponential relationship between tumor volume and progression risk highlights the complexity of meningioma behavior and underscores the importance of personalized treatment strategies. Future research should validate these findings in larger cohorts and explore additional factors such as molecular characteristics and treatment response variations.

Tables

	Overall, n (%)	**Stable disease (SD), n (%)**	**Progressive disease (PD), n (%)**
Patients included	103 (100)	86 (83.5)	17 (16.5)
Gender, n (%)			
Male	28 (27.2)	23 (26.7)	5 (29.4)
Female	75 (72.8)	63 (73.3)	12 (70.6)
Age at diagnosis in years, mean (range)	58.6 (15.4-86.8)	57.4 (15.4-79.5)	64.41 (31.3-86.9)
Age at radiation start in years, mean (range)	63.9 (20.9-89.6)	62.7 (20.9-89.6)	69.7 (39.9-87.7)
Surgery, n (%)			
Biopsy	2 (1.9)	1 (1.6)	1 (5.9)
Subtotal resection	56 (54.4)	46 (53.5)	10 (58.8)
Total resection	27 (26.2)	23 (36.7)	4 (23.5)
No surgery	18 (17.5)	16 (18.6)	2 (11.8)
No. surgeries, n (%)			
Single	51 (49.5)	42 (48.8)	9 (52.9)
Multiple	34 (33.0)	27 (31.4)	7 (41.2)
None	18 (17.5)	16 (18.6)	2 (11.8)
Surgery after radiation, n (%)	4 (3.9)	0 (0.0)	4 (23.5)
Pre-radiation tumor-size in cm^3, mean (range)	22.7 (0.0-142.4)	21.4 (0.0-142.4)	29.8 (0.0-121.7)
Pre-radiation ECOG[1] score, n (%)			
0	3 (2.9)	2 (2.3)	1 (5.9)
1	54 (52.4)	46 (53.5)	8 (47.1)
2	42 (40.8)	35 (40.7)	7 (41.2)
3	4 (3.9)	3 (3.5)	1 (5.9)
4	0 (0.0)	0 (0.0)	0 (0.0)
Indication for radiotherapy, n (%)			
Adjuvant therapy	12 (11.6)	8 (9.3)	4 (23.5)
Salvage therapy	91 (88.3)	78 (90.7)	13 (76.5)
WHO grade, n (%)			
1	91 (88.4)	76 (88.4)	15 (88.2)
2	12 (11.7)	10 (11.6)	2 (11.8)
3	0 (0.0)	0 (0.0)	0 (0.0)
Type of radiation, n (%)			
Photon therapy	87 (84.5)	70 (81.4)	17 (100.0)
Proton therapy	16 (15.5)	16 (18.6)	0 (0.0)

Table 1. Summarized characteristics and results of patients with WHO grade 1 and 2 intracranial meningiomas treated with RT.

[1] ECOG = *Eastern Cooperative Oncology Group performance status score*

Groups (WHO grade and tumor volume)	2-year PFS %	5-year PFS %
WHO grade 1	95.6	90.0
WHO grade 2	83.3	83.3
<21 cm^3	96.4	93.8
>21 cm^3	84.2	71.2

Table 2. PFS at 2 and 5 years in different groups based on WHO grade and tumor volume.

Tumor Volume Increment	Hazard Ratio (%)
Increase of 5 cm^3	1.151 (15.1)
Increase of 10 cm^3	1.325 (32.5)
Increase of 15 cm^3	1.525 (52.5)
Increase of 20 cm^3	1.755 (75.5)
Increase of 25 cm^3	2.020 (102.0)
Increase of 30 cm^3	2.325 (132.5)
Increase of 40 cm^3	3.091 (208.1)
Increase of 50 cm^3	4.082 (308.2)
Increase of 60 cm^3	5.408 (440.8)
Increase of 70 cm^3	7.164 (616.4)
Increase of 80 cm^3	9.492 (849.2)
Increase of 90 cm^3	12.575 (1157.5)
Increase of 100 cm^3	16.660 (1566.0)

Table 3. Hazard ratios for different increments in tumor volume.

Side effect	Photon therapy, n (%)	Proton therapy, n (%)
Hypopituitarism	2 (2.3)	0 (0.0)
Inflammation	12 (13.8)	0 (0.0)
Neurology	8 (9.2)	0 (0.0)
Dizziness	6 (6.9)	2 (12.5)
Nausea	5 (5.8)	1 (6.3)
Headache	12 (13.8)	1 (6.3)
Fatigue	18 (20.6)	5 (31.3)
Skin rash	0 (0.0)	2 (12.5)
None	24 (27.5)	10 (62.5)

Table 4. Side effect rates: photon and proton therapy comparison.

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Tables

	Overall, n (%)	**Stable disease (SD), n (%)**	**Progressive disease (PD), n (%)**
Patients included	103 (100)	86 (83.5)	17 (16.5)
Gender, n (%)			
Male	28 (27.2)	23 (26.7)	5 (29.4)
Female	75 (72.8)	63 (73.3)	12 (70.6)
Age at diagnosis in years, mean (range)	58.6 (15.4-86.8)	57.4 (15.4-79.5)	64.41 (31.3-86.9)
Age at radiation start in years, mean (range)	63.9 (20.9-89.6)	62.7 (20.9-89.6)	69.7 (39.9-87.7)
Surgery, n (%)			
Biopsy	2 (1.9)	1 (1.6)	1 (5.9)
Subtotal resection	56 (54.4)	46 (53.5)	10 (58.8)
Total resection	27 (26.2)	23 (36.7)	4 (23.5)
No surgery	18 (17.5)	16 (18.6)	2 (11.8)
No. surgeries, n (%)			
Single	51 (49.5)	42 (48.8)	9 (52.9)
Multiple	34 (33.0)	27 (31.4)	7 (41.2)
None	18 (17.5)	16 (18.6)	2 (11.8)
Surgery after radiation, n (%)	4 (3.9)	0 (0.0)	4 (23.5)
Pre-radiation tumor-size in cm^3, mean (range)	22.7 (0.0-142.4)	21.4 (0.0-142.4)	29.8 (0.0-121.7)
Pre-radiation ECOG[1] score, n (%)			
0	3 (2.9)	2 (2.3)	1 (5.9)
1	54 (52.4)	46 (53.5)	8 (47.1)
2	42 (40.8)	35 (40.7)	7 (41.2)
3	4 (3.9)	3 (3.5)	1 (5.9)
4	0 (0.0)	0 (0.0)	0 (0.0)
Indication for radiotherapy, n (%)			
Adjuvant therapy	12 (11.6)	8 (9.3)	4 (23.5)
Salvage therapy	91 (88.3)	78 (90.7)	13 (76.5)
WHO grade, n (%)			
1	91 (88.4)	76 (88.4)	15 (88.2)
2	12 (11.7)	10 (11.6)	2 (11.8)
3	0 (0.0)	0 (0.0)	0 (0.0)
Type of radiation, n (%)			
Photon therapy	87 (84.5)	70 (81.4)	17 (100.0)
Proton therapy	16 (15.5)	16 (18.6)	0 (0.0)

Table 1. Summarized characteristics and results of patients with WHO grade 1 and 2 intracranial meningiomas treated with RT.

[1] ECOG = *Eastern Cooperative Oncology Group performance status score*

Groups (WHO grade and tumor volume)	2-year PFS %	5-year PFS %
WHO grade 1	95.6	90.0
WHO grade 2	83.3	83.3
<21 cm^3	96.4	93.8
>21 cm^3	84.2	71.2

Table 2. PFS at 2 and 5 years in different groups based on WHO grade and tumor volume.

Tumor Volume Increment	Hazard Ratio (%)
Increase of 5 cm^3	1.151 (15.1)
Increase of 10 cm^3	1.325 (32.5)
Increase of 15 cm^3	1.525 (52.5)
Increase of 20 cm^3	1.755 (75.5)
Increase of 25 cm^3	2.020 (102.0)
Increase of 30 cm^3	2.325 (132.5)
Increase of 40 cm^3	3.091 (208.1)
Increase of 50 cm^3	4.082 (308.2)
Increase of 60 cm^3	5.408 (440.8)
Increase of 70 cm^3	7.164 (616.4)
Increase of 80 cm^3	9.492 (849.2)
Increase of 90 cm^3	12.575 (1157.5)
Increase of 100 cm^3	16.660 (1566.0)

Table 3. Hazard ratios for different increments in tumor volume.

Side effect	Photon therapy, n (%)	Proton therapy, n (%)
Hypopituitarism	2 (2.3)	0 (0.0)
Inflammation	12 (13.8)	0 (0.0)
Neurology	8 (9.2)	0 (0.0)
Dizziness	6 (6.9)	2 (12.5)
Nausea	5 (5.8)	1 (6.3)
Headache	12 (13.8)	1 (6.3)
Fatigue	18 (20.6)	5 (31.3)
Skin rash	0 (0.0)	2 (12.5)
None	24 (27.5)	10 (62.5)

Table 4. Side effect rates: photon and proton therapy comparison.

Figures

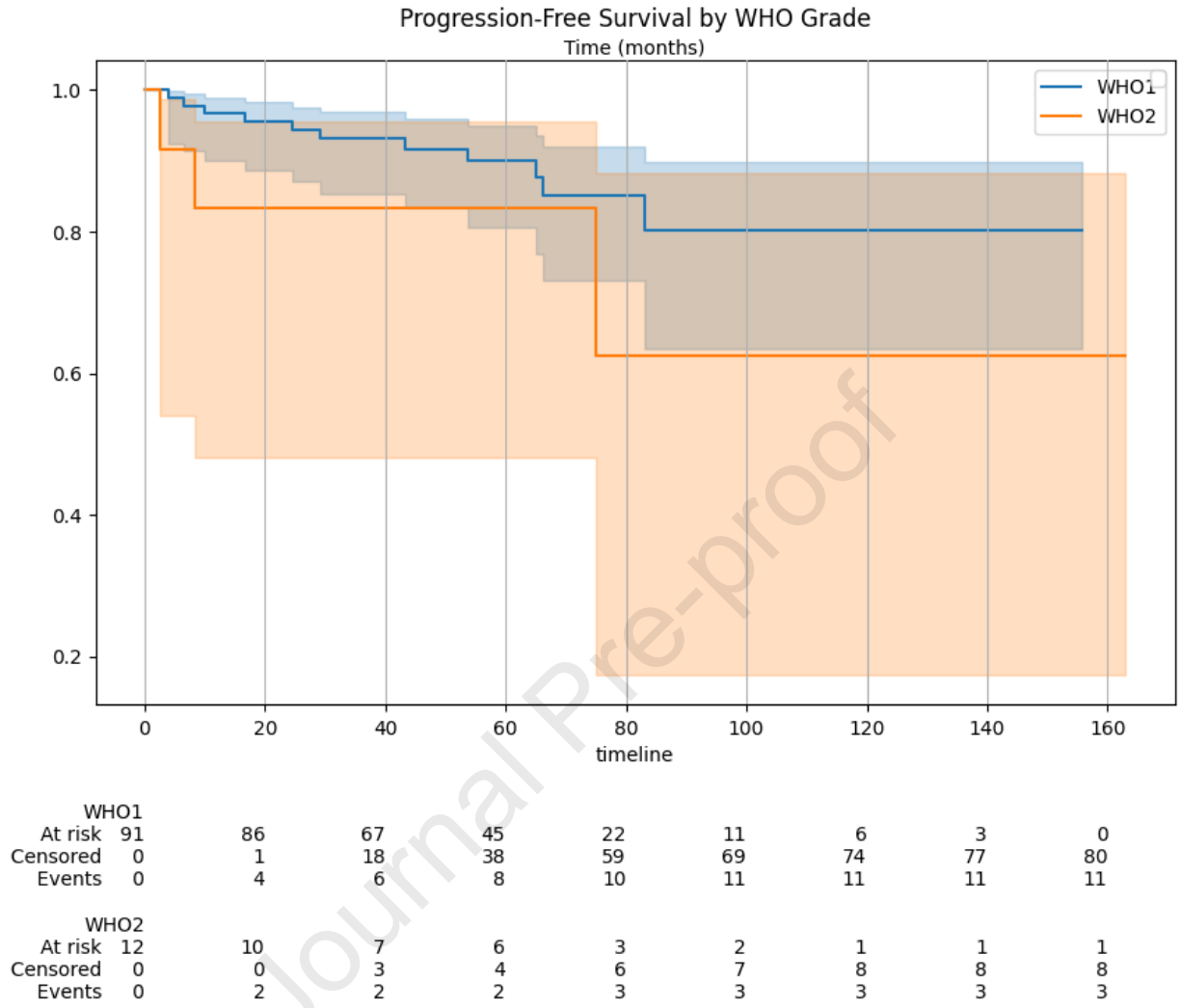

Figure 1. PFS in WHO grade 1 and 2 intracranial meningiomas after RT (p = 0.20).

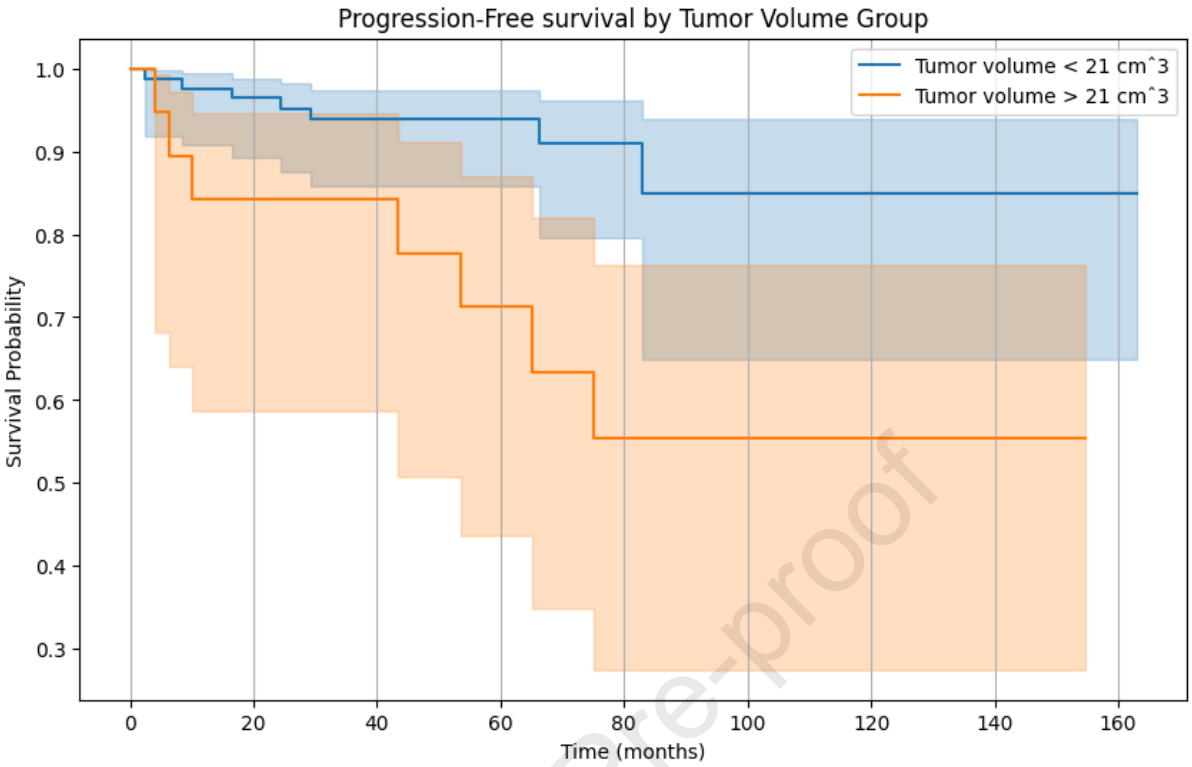

Figure 2. PFS by tumor volume with a cutoff value of 21.013 cm3 comparing the two different group (p< 0.005).

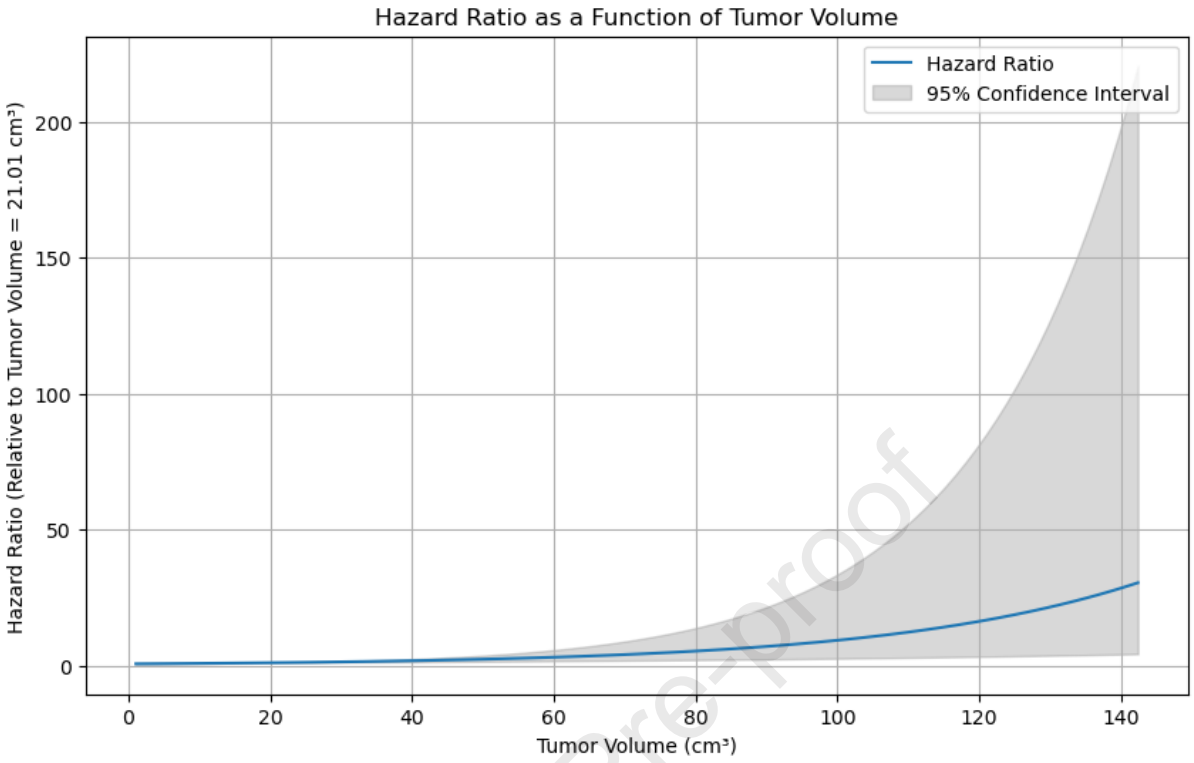

Figure 3. Exponential relationship between tumor volume and HR for tumor progression in meningiomas. HR for every 10 cm³ increase in tumor volume: 1.3249. Percentage increase in hazard for every 10 cm³ increase: 32.49% p = 0.00073.

Abbreviations:

RT: Radiotherapy

WHO: World Health Organization

PFS: Progression Free Survival

HR: Hazard Ratio

CT: Computed Tomography

MR: Magnetic Resonance

ECOG: Eastern Cooperative Oncology Group

PS: Performance Status

GSV: Gross Tumor Volume

CTV: Clinical Target Volume

DCPT: Danish Centre for Particle Therapy

SD: Stable Disease

PD: Progressive Disease

Declaration of interest: the authors of this manuscript has nothing to declare.