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TRATTAMENTO CON PROTONTERAPIA DEI TUMORI CEREBRALI PRIMITIVI: ANALISI DEGLI OUTCOMES

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ABSTRACT

Background

Radiation therapy (RT) is an essential and effective part of the management of adult brain tumors. There is a desire within the RT community to further reduce side effects and at the same time maintain or even improve local control of treated tumors. Proton therapy (PT) has emerged as an alternative radiation treatment modality. The main advantage of PT is the deposition of little energy before the end of the proton range where the highest energy deposition is within the target volume (Bragg peak) and minimal residual radiation beyond the target. Thanks to these physical characteristics, PT may offer superior dose distribution. In particular, the dose to the surrounding organs at risk (OARs) can significantly be reduced while maintaining the same equivalent dose to the target. Although the number of patients receiving PT for a brain tumor is increasing, the potential clinical superiority of PT over photon RT in patients with brain tumors remains a matter of debate due to the lacking of comparative trials.

Matherial and methods

Aim of the project was to selected subgroups of patients with primary brain tumors who received focal PT. Corresponding data and clinical outcomes were collected and analyzed. Results are discussed and compared to published photon RT studies.
Data analysis focused on recurrent glioblastomas (rGBM) who received re-irradiation with protons and patients with intracranial WHO grade II (atypical) meningiomas treated with proton therapy.

Results

Concerning rGBM, 54 patients (pts) with rGBM were re-irradiated with PT. Pts were selected for PT because of the large tumor size or proximity to dose-limiting organs at risk that previously had received near-maximum dose tolerance during the first radiation course. All pts received 36 GyRBE in 18 fractions. PT was delivered with or without CHT.
The median OS after PT was 8.5 months. In univariate analysis, surgical resection prior to PT ($p = 0.03$), KPS (< 80 vs > 80, $p = 0.03$), type of GBM (primary vs secondary, $p = 0.05$), and chemotherapy in association with PT ($p = 0.01$) were statistically significant. The Cox's Proportional Hazards Model confirmed chemotherapy in association with PT, type of GBM and surgical resection prior to PT as statistically significant independent covariates.
The median PFS was 4 months for the whole patient population. In univariate analysis, age (< 54 vs > 54 years, $p = 0.03$), type of GBM (primary vs secondary, $p = 0.02$), concomitant administration of TMZ with PT ($p = 0.004$), and KPS (< 80 vs > 80, $p = 0.01$) were statistically significant. The Cox's Proportional Hazards Model confirmed administration of chemotherapy in association with PT, type of GBM and KPS as statistically significant covariates.
There was no grade 3 or higher acute and late toxicities. During follow-up five pts (9%) developed radionecrosis with mild-to-moderate symptoms controlled with steroids.
Regarding AMs, 56 adults and 5 pediatric pts (total of 61) with intracranial AMs were treated with PT at our institution. All adult pts were treated with a PT total dose of 60 GyRBE (2 GyRBE/fraction, 5 fractions/week). In the pediatric population the PT dose ranged from 50.4 to 59.4 GyRBE because it was usually adjusted based on clinical status and proximity to organs at risk (OARs).
After a median follow-up after PT of 43 months, the estimated 3- and 5-year PFS was 77% and 67% for the entire cohort, respectively. The log-rank p-value was 0.2, indicating that

there was no statistically significant difference between pediatric and adult patients. The size of the CTV (median, 75 cc) was associated with a significant decline in PFS, ($p < 0.001$). Moreover, the PFS was found to be significantly influenced by sex ($p = 0.042$). Both CTV and sex remain significant in the multivariate analysis ($p = 0.003$ and $p = 0.025$, respectively).
The 3- and 5-year OS was 89% and 67% respectively for the entire population. Age (median, 56 years), CTV (median, 75 cc) and KPS > 90 played a significant influence on overall survival outcomes. Moreover, higher KPS scores and lower CTV volumes were found to be associated with improved outcomes both at univariate ($p = 0.007$ and $p < 0.001$, respectively) and multivariate analyses ($p = 0.041$ and $p < 0.001$, respectively).
There was no grade 3 or higher acute and late toxicities. Radionecrosis was observed in 6 pts (11%).

Conclusions

Present data are among the largest series to date reporting outcomes of PT for rGBM and AMs pts.
Our analysis indicates that PT is well tolerated and offers efficacy rates similar or even superior to previously reported photon and proton series.
Despite some potential limitations, this study contributes to the growing body of evidence supporting PT as a valuable alternative treatment to conventional radiation techniques, with favorable outcomes and reduced risk of normal tissue damage.
Future studies are warranted to prospectively determine long-term benefits and risks associated with PT compared with photon RT.

1. Introduction

1.1 Epidemiology and current standard of care of primary brain tumors

Primary brain tumors in adults are rare and constitute fewer than 2% of all malignant neoplasms [Price, Kohler]. In children, however, they form the second most common type of tumor, after leukemias. The incidence of a new brain tumor is 6.4 per 100,000 persons per year with an overall five-year survival rate of 33.4%. The peak prevalence is between 55 and 64 years of age, with a slightly higher incidence in men than in women [Price, Kohler].
Of all intracranial tumors, neuroepithelial tumors are the most common neoplasms, representing more than 60% of central nervous system (CNS)–derived lesions. Other lesions are meningothelial tumors (30%), tumors arising from cranial and spinal nerves (7%–8%), CNS lymphomas (4%), and germ cell neoplasms (approximately 1%) [Price, Kohler]. Brain tumors are classified according to international standards, which are established by the World Health Organization (WHO). The WHO classification of CNS tumors is based on consensus criteria developed by an international working group of pathologists and geneticists and forms a comprehensive worldwide standard for tumor definition. Brain tumors are primarily classified according to their histopathologic appearance, which is based on the characterization of constituent cell types and growth patterns. Although the cellular origin of many tumors is still under investigation, the histologic classification relies on morphologic similarities of tumor cells with their presumed
non-neoplastic counterpart, in addition to the presence of certain architectural patterns. The WHO subdivides the large group of neuroepithelial neoplasms into a variety of histologic tumor types, such as glial (astrocytomas, oligodendrogliomas, and ependymomas), neuronal, mixed glial-neuronal, embryonal, pineal, choroid plexus derived and others. Many molecular profiles have been incorporated and contribute to the subclassification of tumor entities. The classification system of the WHO lists more than 120 different tumor types and subtypes for the CNS [Figarella-Branger D]. The WHO classification also has devised a grading scheme, which can be considered a malignancy scale that is used to predict the biologic behavior of neoplasms, therapeutic response, and clinical outcome. The WHO histologic grade, however, is only one of many factors that aid in predicting response to therapy and outcome. Molecular genetic alterations and proliferation indices play another major role. Additional, clinically important attributes are a patient's age and neurologic performance status, tumor location, and extent of surgical resection as well as radiologic aspects. Combinations of these factors are used to provide an estimate of prognosis and outcome for each tumor entity.
Brain cancers do not conform to a standard staging system. Although they may spread to other parts of the brain or spinal cord, they rarely spread beyond that. Treatment decisions are individualized by an experienced multidisciplinary team consisting of medical oncology, radiation oncology, and neurosurgery. Treatment decisions are based on tumor type and location, malignancy potential, and the patient's age and physical condition. Treatment may require only surveillance but commonly includes surgery, radiotherapy, chemotherapy, or a combination.
The preferred treatment for primary brain tumors is the maximal safe surgical removal of the tumor. Although extent of resection is a prognostic variable, the extent of safe tumor resection is dependent on tumor location, patient performance status, and, most importantly, patient age [Hentschel]. Benefits of maximal resection include relief of mass effect, decreased tumor burden, improved diagnosis, and a trend toward prolonged survival [Sanai].
Chemotherapy given in combination with radiation has been shown to improve survival in selected clinical scenarios [Aryal].

Radiotherapy can be used as primary treatment or adjunctively following surgical resection. Standard fractionated external beam radiotherapy is the most common approach, although other options include brachytherapy, fractionated stereotactic radiotherapy, and stereotactic radiosurgery. Depending on the clinical scenario, radiotherapy can improve progression-free survival and overall survival [Grunert].

1.2 Rationale for proton therapy in the treatment of primary brain tumors

Radiation therapy (RT) is an essential and effective part of the management of adult brain tumors. There is a desire within the RT community to further reduce side effects and at the same time maintain or even improve local control of treated tumors.
Radiation dose and fractionation schedules depend on the type, volume, and location of the tumor. Over the past decades, several significant technical developments in photon RT (xRT), such as intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and stereotactic radiotherapy (SRT) have permitted the delivery of more conformal radiation doses to the target while reducing the dose to the surrounding normal tissue compared to conventional three-dimensional (3D) conformal RT (3D-CRT) techniques. In addition, the integration of new technology, eg, 6°C of freedom (6DoF) couch, multileafcollimator (MLC), new immobilization devices, and continuous imaging monitoring in the treatment room during xRT, so-called image-guided RT (image-guided radiation therapy), has led to an increase in the precision and accuracy of radiation delivery [Sahagal, Scaringi].
Proton therapy (PT) has emerged as an alternative radiation treatment modality that directs charged particles instead of photons at the tumor. The main advantage of PT is the deposition of little energy before the end of the proton range where the highest energy deposition is within the target volume (Bragg peak) and minimal residual radiation beyond the target [Eekers DBP 2019, Lesueur P]. Thanks to these physical characteristics, PT may offer superior dose distribution. In particular, the dose to the surrounding organs at risk (OARs) can significantly be reduced while maintaining the same equivalent dose to the target [Harrabi SB, Eekers DB 2018].
Advances in proton technology and decreasing equipment costs have led to the expansion of proton beam facilities and increased use of this modality. Although the number of patients receiving PT for a brain tumor is increasing, the major obstacles regarding its use in clinical practice are: less availability, lack of randomized studies comparing PT with xRT, and the current greater cost of PT treatment. As a consequence, there is the need of data analysis regarding patients with primary brain tumors treated with proton therapy.

1.3 Aim of the project

In the absence of randomized trials, the potential clinical superiority of PT over xRT in patients with brain tumors remains a matter of debate. The main question is if substantial improvements in the dose distribution observed with protons may provide a clinical benefit for patients with either malignant or benign brain tumors.
Aim of the project was to select subgroups of patients with primary brain tumors who received focal PT at the Trento Proton Therapy Center. Corresponding data and clinical outcomes were collected and analyzed. Results are discussed and compared to published xRT studies. Data analysis focused on recurrent glioblastomas who received re-irradiation with protons and patients with intracranial WHO grade II (atypical) meningiomas treated with proton therapy.

2. Proton therapy re-irradiation in patients with recurrent glioblastoma

2.1 Introduction

Currently treatment of glioblastoma (GBM) is based on a multi-disciplinary approach including surgery and adjuvant radio-chemotherapy, followed by maintenance chemotherapy [Stupp]. Although the use of temozolomide (TMZ) has improved outcomes considerably, long-term control of such malignancy is rarely achieved and almost all patients develop tumor recurrence at the primary tumor site [Minniti 2010].
For patients (pts) with recurrent GBM (rGBM), no standard of care exists. Once progression of a tumor occurs, treatment options include repeated surgical resection, re-irradiation, chemotherapy with standard agents, novel therapies, or a combination of the above [Niyazi]. Re-irradiation is an effective strategy [Minniti 2021], but is usually employed for small lesions and has the potential risk of both early and late side effects that could adversely affect the quality of life (QoL) of the patient. Proton therapy (PT), thanks to the typical dose fall off of the Bragg peak, could minimize the risk of side effects compared to conventional photon therapy, allowing the treatment of large recurrent tumors and ultimately reducing the possible detrimental effect of re-irradiation on QoL.
In the present study, we have evaluated the efficacy and toxicity profile of active scanning PT re-irradiation with or without CHT for rGBM. Data have been prospectively collected and analyzed retrospectively. The protocol was reviewed and approved by the local ethics committee (Ethics committee for clinical trials, Azienda Provinciale per i Servizi Sanitari, Trento, Italy. Reference Code – A574).

2.2 Materials and Methods

Patient selection

All patients treated with PT re-irradiation for rGBM at our institution between January 2015 and January 2022 were identified using the department database. Only patients with histologically proven rGBM, and/or 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine positron emission tomography (18F-DOPA PET)/magnetic resonance imaging (MRI) proven rGBM and macroscopic tumor were re-irradiated.

Proton therapy and chemotherapy administration

Pts were immobilized with customized individual head-neck support and thermoplastic mask (CIVCO, Iowa – USA).
Treatment planning and target definition were based on CT, MR, and 18F-DOPA PET imaging. Gross Tumor Volume (GTV) included any area of contrast enhancement after contrast medium administration plus any pathological PET uptake regions [Pafundi]. For pts who were re-irradiated after partial resection of the recurring tumor, surgical cavity was included into the GTV. Clinical Target Volume (CTV) was generated by adding to GTV a 3-mm uniform margin manually corrected in proximity of anatomical barriers. CTV was expanded by 3-4 mm to create Planning Target Volume.
All pts were treated with active pencil beam scanning PT using 2-3 fields. A relative biologic effectiveness (RBE) factor for protons of 1.1 (relative to 60Co) was employed and proton doses were expressed in terms of Gray Equivalent (GyRBE = proton Gy X 1.1) [Paganetti]. Treatment planning was performed using on either XiO, Elekta CMS (St. Louis, MO), version 4.2.2 or the RayStation software (RaySearch Laboratories, Stockholm, Sweden).
All pts received 36 GyRBE in 18 fractions. PT was delivered with or without CHT as follows: 24 (44%) pts (Group 1) received PT only; 7 (13%) pts (Group 2) also received concomitant TMZ (75 mg/m2/die, 7 days/week); 19 (35%) pts (Group 3) received PT followed by CHT

(different regimens/drugs - Table 1); 4 (8%) pts (Group 4) also received concomitant (as above) and adjuvant TMZ (150-200 mg/m2/die, 5 days/month).

Response and Toxicity evaluation

Registered side effects were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment response was assessed according to Response Assessment in Neuro-Oncology (RANO) criteria [Wen].

QoL evaluation

The health-related quality of life (HRQoL) was assessed by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30, version 3) [Aaronson] and EORTC Quality of Life Questionnaire Brain Cancer Module (QLQ-BN20) [Taphoorn]. The patients completed the EORTC questionnaires before starting PT, the last day of PT, and every follow-up visit (1-month, 3-months, and every 3 months thereafter) until progression of disease. The methods of such analysis have been previously reported [Scartoni].

Follow-up

Patients were seen for follow-up visits 4 weeks after completion of PT, then in 3 months' intervals or as needed clinically. All follow-up visits included a thorough neurologic assessment as well as contrast-enhanced MRI scans. Additional diagnostic procedures, including PET and MRI spectroscopy, were scheduled as required.

Statistics

Overall survival (OS) and progression-free survival (PFS) after re-irradiation were calculated from initiation of PT until tumor progression or death (by any cause) using Kaplan-Meier estimates. Differences between groups were assessed using the logerank test. The logerank test was used to compare different survival functions according to various clinical (age, sex, etc.) and therapeutic factors (association with CHT, CTV volume, etc.). Statistical tests were based on a two-sided significance level, and a p-value of 0.05 or less was considered to be statistically significant. A Cox's proportional hazards model (with Efron approximation) was chosen to explain the effect of covariates on time until event (death and tumor progression); results are presented as hazard ratios (HRs) and 95% confidence intervals (CI). All analyses were performed using the SAS-system® software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

2.3 Results

Patient characteristics

Between January 2015 and January 2022 fifty-four pts with rGBM were re-irradiated with PT. Pts were selected for PT because of the large tumor size or proximity to dose-limiting organs at risk that previously had received near-maximum dose tolerance during the first radiation course. The use of PT as well as the administration of CHT was discussed and approved for each case by the internal multi-disciplinary tumor board. All pts had been previously treated with Stupp regimen (60 Gy photon radiotherapy with concomitant and adjuvant temozolomide). World Health Organization (WHO) Grade II-III glioma was initially diagnosed in seven (13%) pts progressing to a secondary GBM. Median time interval

between initial radiotherapy and PT was 16 months (range, 5-69). All tumors recurred at the original site within the previous high-dose region. Twenty-eight (52%) pts were re-irradiated at first relapse/progression, twenty-six at second/third one. Fifteen pts (28%) were re-irradiated after partial resection of the recurring tumor. The median age at the time of PT was 54 years (range, 30–70), and median Karnofsky performance status (KPS) was 80 (range, 50–100). Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

Characteristic	Patients (N = 54)
Sex (M/F)	35/19
Median age at PT (years) (range)	54 (30-70)
Median KPS (range)	80 (50-100)
Type of GBM (Primary/Secondary*)	47/7
MGMT status (Methylated/Unmethylated)	25/29
Dose of primary RT (Gy)	60
Median N. of cycles of TMZ (range)	6.5 (1-24)
Median time to previous RT (months) (range)	16 (5-69)
Dose of re-irradiation (Gy)	36
Surgery prior to re-irradiation (yes/no)	15/39
Timing of PT	
At 1st relapse/progression	28
At 2nd-3rd relapse/progressione	26
Median re-irradiation CTV size (cm^3)	54 (8-185)
Chemotherapy with PT	
PT only (Group 1)	24
PT and concomitant TMZ (Group 2)	7
PT followed by CHT (Group 3)	19
TMZ	6
Fotemustine	7
Bevacizumab + Lomustine	6
PT with concomitant and adjuvant TMZ (Group 4)	4

Abbreviations: M: male; F: female; PT: proton therapy; KPS = Karnovsky performance status; GBM: glioblastoma; *: initial diagnosis of World Health Organization Grade II-III glioma who progressed to secondary GBM; MGMT = O-6-methylguanine-DNA methyltransferase; RT = radiotherapy; N.: number; TMZ = temozolomide; CTV: Clinical Target Volume; CHT: chemotherapy

OS and PFS

The median OS after PT was 8.5 months (Figure 1). Six- and 12-month survival rates were 76.6% and 30.7%, respectively. There was no statistical difference in survival with regard to gender, age, CTV volume (< 54 vs > 54 cm3), number of relapse/progressions prior to PT, and MGMT status. In univariate analysis, surgical resection prior to PT (p = 0.03), KPS (< 80 vs > 80, p = 0.03), type of GBM (primary vs secondary, p = 0.05), and chemotherapy in association with PT (p = 0.01) were statistically significant. The Cox's Proportional Hazards Model confirmed chemotherapy in association with PT, type of GBM and surgical resection prior to PT as statistically significant independent covariates: in detail group 1 (only PT) showed a risk of death almost 3 times higher than group 2 (PT + CHT) [HR=2.70, 95% IC

1.07 – 7.50]; primary GBM showed a risk of death 3 times higher than secondary GBM [HR=2.99, 95% IC 1.02 – 8.95]; finally, those who had an operation before radiation treatment showed a 2.3 times higher risk of death than those who did not have it [HR=2.31, 95% IC 1.09 – 4.89].

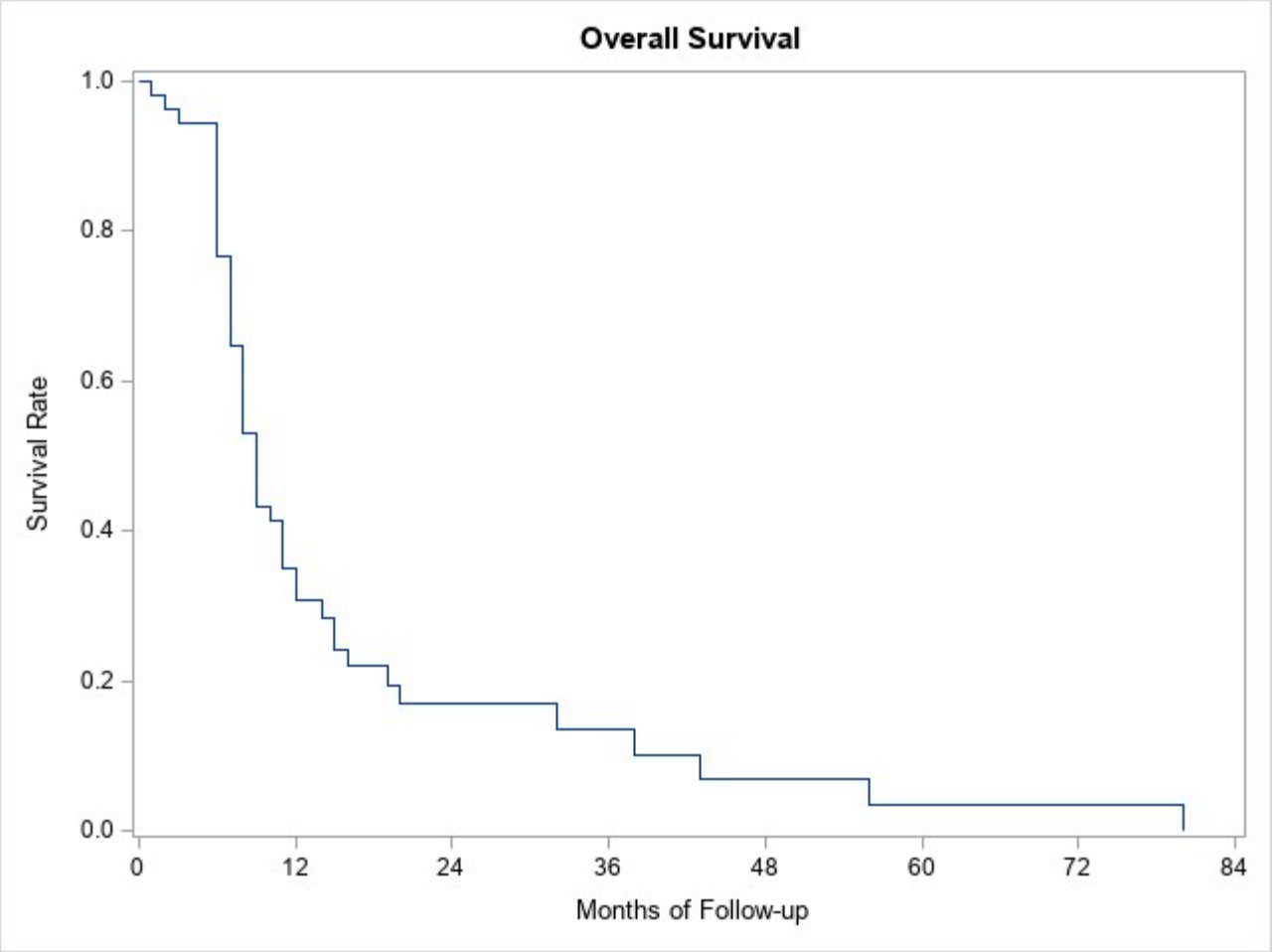
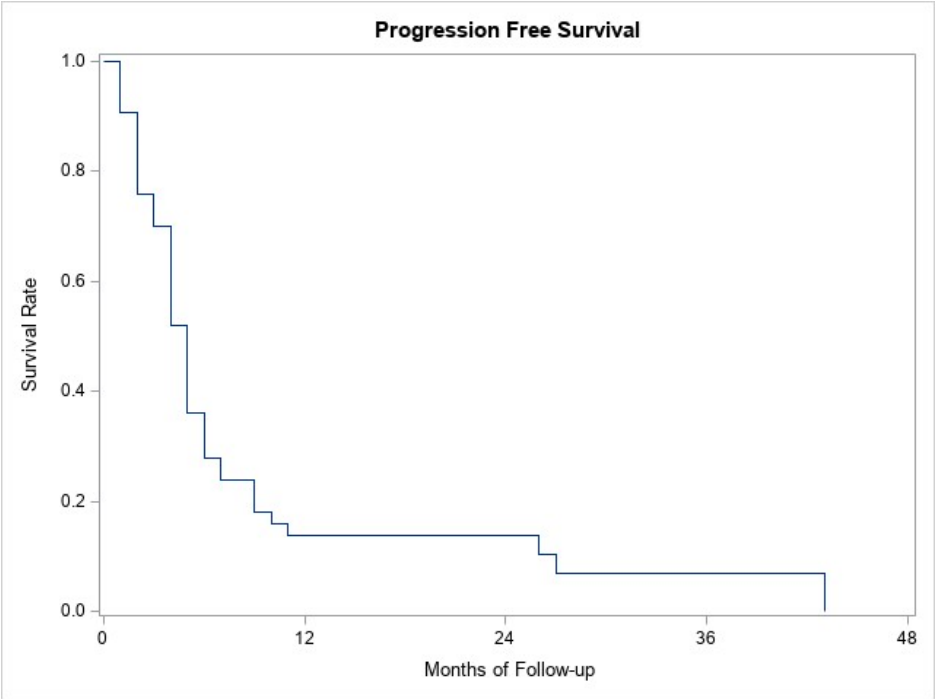


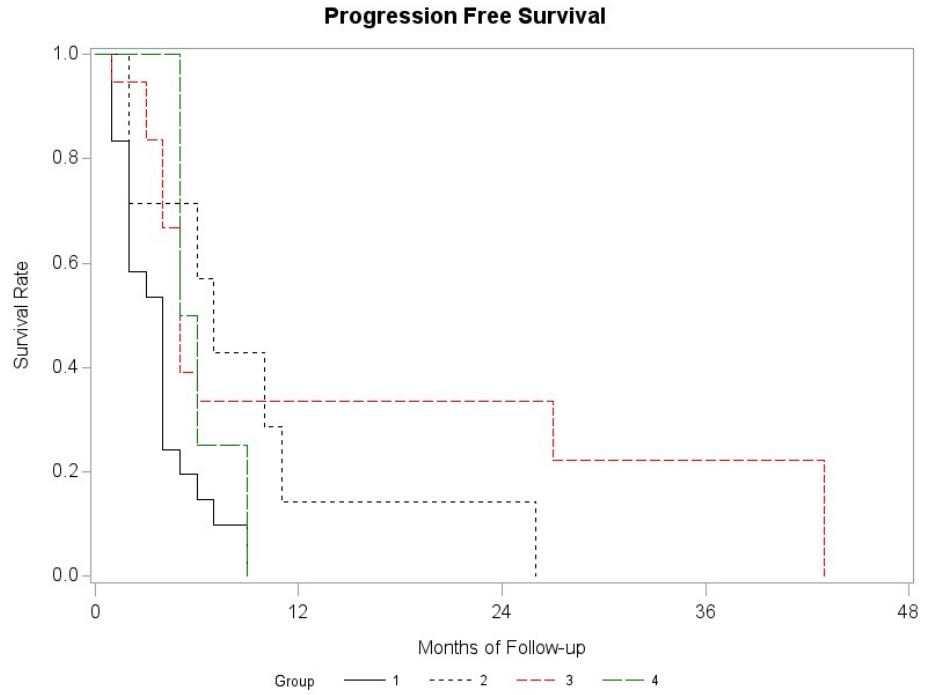
Figure 1. Kaplan–Meier analysis of overall survival.

The median PFS was 4 months for the whole patient population, while 6-month PFS rate was 28%. The median PFS was 2.5, 7, 5, and 5.5 months for Group 1-2-3-4, respectively (Figure 2). Number of relapse/progressions prior to PT, MGMT status, surgical resection prior to PT, and CTV volume (< 54 vs > 54 cm3) were not significant prognostic factors. In univariate analysis, age (< 54 vs > 54 years, p = 0.03), type of GBM (primary vs secondary, p = 0.02), concomitant administration of TMZ with PT (p = 0.004), and KPS (< 80 vs > 80, p = 0.01) were statistically significant.

Regarding PFS, the Cox's Proportional Hazards Model confirmed administration of chemotherapy in association with PT, type of GBM and KPS as statistically significant covariates. Group 1 (only PT) showed a risk of disease progression almost 3 times higher than group 2 (PT + CHT) [HR=2.60, 95% IC 1.02 – 7.37]; primary GBM showed a risk of disease progression 3 times higher than secondary GBM [HR=2.99, 95% IC 1.01 – 9.25]; finally, pts with KPS < 80 showed a 2 times higher risk of disease progression than those with KPS ≥ 80 [HR=1.97, 95% IC 1.04 – 4.13].



(a)



(b)

Figure 2. Kaplan–Meier analysis of progression-free survival for the whole patient population (a) and according to treatment modality (b). Group 1: patients received PT only; group 2: patients received irradiation and concomitant temozolomide; group 3: patients received irradiation followed by chemotherapy (different regimens/drugs); group 4: patients received irradiation with concomitant and adjuvant temozolomide.

Toxicity

In general, PT was well tolerated, and the treatment was completed without interruption in all pts. There was no grade 3 or higher acute toxicities. The most common acute adverse events were mild (grade 1) fatigue, which occurred in 24 pts (44%), grade 2 alopecia (16 pts, 30%), and grade 1 headache (11 pts, 20%). There was no grade 3 or higher late toxicities. The most common late adverse event was alopecia (grade 2), which occurred in 12 pts (22%). During follow-up five pts (9%) developed radionecrosis (diagnosed at imaging) with mild-to-moderate symptoms controlled with steroids.

QoL

Preliminary results have been already published [Scartoni]. For the aim of present the study, data have been updated and a new analysis was accomplished. Published results were confirmed: the treatment was associated with a substantial stability in all the preselected HRQoL domains without a detrimental effect on QoL. Despite none of the subscales showed a minimum clinically meaningful change (>10 points), a near-meaningful positive change (> 5–10 points) was seen in global health status (7 points) and cognitive functioning (6 points). Physical functioning did not show a clear trend and was associated with a not significant negative change (3 points). Main results are depicted in Figure 3.

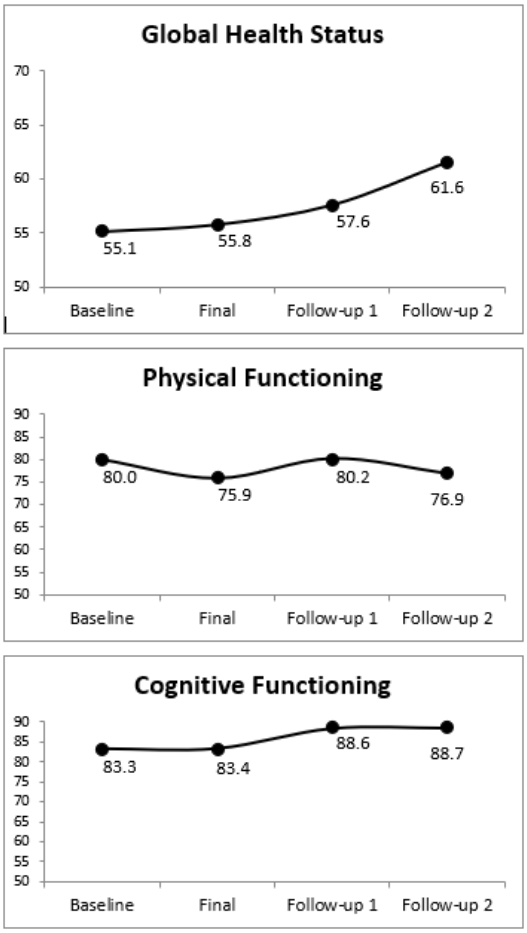


Figure 3. Main changes over time in mean health-related quality of life.

Questionnaires were completed before starting of radiation therapy (Baseline), the last day of radiotherapy (Final), and every follow-up visit (1-month/Follow-up 1, 3-months/Follow-up 2, and every 3 months thereafter) until progression of disease. Data analysis was limited to 2nd follow-up (3 months after radiotherapy) because at this time point, most of the patients were still free of progression. Thereafter, most of the patients already experienced tumor progression.

2.4 Discussion

Re-irradiation has been reported as an effective treatment option in terms of local control and overall survival in pts with rGBM, at least comparable to the second-line chemotherapy regimens [Niyazi, Amelio, Scoccianti, Minniti].
To date, the improvement of imaging modalities and the development of high-precision RT techniques allow better target definition and more accurate radiation delivery. This ultimately does enable the safe administration of a second course of irradiation.
Depending on the RT modality and administration of CHT, re-irradiation can achieve a median PFS of 4-7 months with a radionecrosis rate of 2-30% [Niyazi, Amelio, Scoccianti, Minniti]. However, a careful selection of eligible pts has to be done due to the risk of acute and late side effects that may affect QoL. As a consequence, pts suitable for re-irradiation usually have small lesions and good performance status, while large recurrent tumors are excluded.
Thanks to its better dose distribution and its inherent property of lacking an exit dose compared to conventional photon therapy, PT could help spare adjacent healthy tissue located beyond the target minimizing the risk of side effects. This is useful in the reirradiation setting, especially for GBM reirradiation, given the typical initial radiation dose of 60 Gy and the likelihood of either previously having reached or at least contributed significantly toward maximum OAR tolerances. Thus, given the opportunity to spare the cumulative radiation dose to critical OARs, PT may permit the safe delivery of RT in patients for whom reirradiation may not otherwise be safely feasible using photons. In details it could allow the treatment of large recurrent tumors without increasing the possible detrimental effect of re-irradiation on QoL.
Outcomes after photon-based reirradiation have been well described [Niyazi, Amelio, Scoccianti, Minniti], but the specific use of PT reirradiation is limited [Eekers 2024].
In the present analysis, we report on the outcomes of patients with rGBM treated with PT reirradiation. To the best of our knowledge, this represents one of the largest GBM PT reirradiation analyses to date.
Compared with previous studies evaluating the role of reirradiation in patients with rGBM, our current analysis results compare favorably. Literature reviews on photon-RT [Niyazi, Amelio, Scoccianti, Minniti] found a median PFS range of 4.2 to 12 months (4-6 months in most of the studies). Median OS was 4.9 to 15.9 months (8-10 months in most of the studies) for available series. Outcomes demonstrated a trend for improvement when chemotherapy was administered in association with reirradiation. With regard to the specific use of PT for reirradiation of recurrent GBM, a recent review [Eekers 2024] found a median PFS range of 5.9 to 9.3 months. Median OS was 8.7 to 18.3 months. In our current analysis median OS and PFS were 8.5 and 4 months, respectively while six-month PFS rate was 28%. It is worth noting that lesions were difficult-to-treat due to the large volume (median CTV 54 cc). When reirradiation was administered without chemotherapy PFS was 2.5 months. It was significantly better when reirradiation was administered in association with chemotherapy. It is worth noting that most of patients that received reirradiation only were failing after 2nd and 3rd line chemotherapy (2nd and 3rd relapse/progression). This feature can explain the worst outcomes scored by reirradiation only. With regard to toxicities, we found that PT reirradiation was generally well tolerated with a low overall incidence of toxicities. We found a total of 5 pts (9%) who developed radionecrosis. Our data compare favorably with those reported in photon-reirradiation series [Niyazi, Amelio, Scoccianti, Minniti] where the registered radionecrosis rate is 0% to 24% (8-10% in most of the studies). Concerning such an issue, it is worth noting that lesions treated with PT were difficult-to-treat due to the large volume (median CTV 54 cc). As a consequence, it seems that PT allow the irradiation of large recurrent tumors without the increase of radionecrosis risk.

Although we used prospectively collected data from our own database and had a relatively large sample size, some limitations should be noted: given the single-cohort, nonrandomized nature of our study, confounding factors are possible and a direct comparison of our outcomes against that of previous studies is difficult.

2.5 Conclusions

This is one of the largest series to date reporting outcomes for PT-reirradiation of rGBM pts. Our analysis indicates that in difficult-to-treat lesions PT is well tolerated and offers efficacy rates similar to previously reported photon reirradiation series even with concomitant and adjuvant chemotherapy administration. PT does not negatively effect on HRQoL, but rather it seems to preserve HRQOL until the time of disease progression. PT in association with chemotherapy seems to achieve better results in comparison with re-irradiation only and could deserve further evaluation in a large pts sample. Future studies are warranted to prospectively determine the benefits and risks associated with PT compared with photon RT.

3. Proton therapy in patients with intracranial atypical meningiomas

3.1 Introduction

Meningiomas are extra-axial central nervous system (CNS) tumors that arise from the arachnoid cells of the meninges. They represent the most common primary intracranial tumors in adults [Combs].
Atypical meningiomas (AMs), classified as World Health Organization (WHO) grade II tumors, are known for their aggressive behavior, with a higher rate of recurrence compared to benign (grade I) meningiomas.
While surgery remains the primary treatment modality, adjuvant radiotherapy is often recommended to reduce the risk of tumor recurrence and improve long-term outcomes. Adjuvant radiotherapy plays a crucial role in the management of AMs, particularly in cases where surgical resection is incomplete or when there is a high risk of recurrence. Conventional external beam radiotherapy (EBRT) has been the standard approach for adjuvant treatment of AMs. However, due to the proximity of these tumors to critical brain structures, the risk of radiation-induced damage to healthy tissues is a significant concern. This has led to the exploration of more advanced techniques, such as proton therapy (PT), which provides superior dose distribution while minimizing exposure to surrounding healthy tissue.
Although PT treatment offers advantages, most existing literature emphasizes photon and stereotactic RT, and there is a lack of studies on the clinical outcomes for AMs patients (pts) who have undergone PT.
In the present study, we have evaluated the efficacy and toxicity profile of active scanning PT of a large group of Ams pts who received PT at our Institution. We investigated the correlation between outcomes and clinical as well as treatment-related factors. Data have been prospectively collected and analyzed retrospectively. The protocol was reviewed and approved by the local ethics committee (Ethics committee for clinical trials, Azienda Provinciale per i Servizi Sanitari, Trento, Italy. Reference Code – A574).

3.2 Materials and Methods

Patient selection

All consecutive AMs pts who underwent PT with curative intent between 2018 and 2024 were included. Histologically confirmed AMs, with a minimum follow-up duration of six months following the completion of PT, were identified using the department database. Pts received PT for residual or progressive lesions after surgery; also, pts without residual tumor progressing after second or third surgery were included. Moreover, pts without residual tumors after first surgery were evaluated for irradiation. Considering there is no current consensus for AMs who undergo complete resection, the decision for adjuvant treatment was discussed and approved for each case by the internal multi-disciplinary tumor board. Considered risk factors were Simpson grade ≥ 2, brain tissue invasion, high Ki67 index, skull base location. For pts with 2 or more risk factors, adjuvant irradiation was proposed even in case of gross total resection. Pts who received PT as re-irradiation were excluded. The study population included both pediatric and adult population.

Proton therapy and chemotherapy administration

Pts were immobilized with customized individual head-neck support and thermoplastic mask (CIVCO, Iowa – USA).
Treatment planning and target definition were based on CT, MR, and 68Ga-DOTATOC PET imaging. Gross tumor volume (GTV) was defined as the macroscopic visible tumor, and included any area of contrast enhancement on MRI plus any pathological PET uptake areas [Milker-Zabel]. Clinical target volume (CTV) was generated by adding to the GTV a 5-mm uniform margin manually edited out of anatomical barriers to microscopic tumor spread. Moreover, CTV was expanded to include the surgical cavity and any area at risk of relapse based on pre-operative imaging. Finally, the CTV was expanded by 3 mm to create the planning target volume (PTV). Following the implementation of the robust optimization at our institution, pts treated after September 2023 were planned by performing a robust optimization to prescribe the dose at the clinical target volume (CTV) without the creation of PTV. The robust optimization settings were the 2 mm isotropic set-up uncertainties and 3.5% range uncertainty.
All pts were treated with active pencil beam scanning PT using 3-4 fields. A relative biologic effectiveness (RBE) factor for protons of 1.1 (relative to 60Co) was employed and proton doses were expressed in terms of Gray Equivalent (GyRBE = proton Gy X 1.1) [Paganetti].
All adult pts were treated with a PT total dose of 60 GyRBE (2 GyRBE/fraction, 5 fractions/week). In the pediatric population the PT dose ranged from 50.4 to 59.4 GyRBE because it was usually adjusted based on clinical status and proximity to organs at risk (OARs).

Response and Toxicity evaluation

Local failure was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 observed on MRI [Schwartz]. Registered side effects were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The terms "acute toxicity" and "late toxicity" were used to describe radiation-related side effects within or after three months from the beginning PT, respectively.

Follow-up

Pts were followed up according to an institutional follow-up protocol. Pts were seen for follow-up visits 4 weeks after the completion of PT, then in 3 months' intervals or as needed clinically. Pts were evaluated every six months until two years after the completion of PT, and annually thereafter. All follow-up visits included a through neurologic assessment as well as contrast-enhanced MRI scans. Additional diagnostic procedures or examinations

(e.g. assessment of visual acuity, optic campimetry, hearing tests, pituitary function evaluation) were scheduled as required or depending on the location.

Statistics

Baseline characteristics were reported as absolute numbers and percentages for categorical data and as medians with interquartile ranges (I–III quartile) for continuous data. Comparisons were performed using the chi-squared test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Overall survival (OS) was defined as the time from the date of proton therapy to the date of death from any cause or the last follow-up. Progression-free survival (PFS) was defined as the time from the conclusion of proton therapy to the date of recurrence detection, the last follow-up, or death. The distributions of OS and PFS were evaluated using the Kaplan–Meier method. Differences in survival curves between groups were assessed with the log-rank test. Univariable Cox proportional hazards models were constructed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for potential predictors.
Age, gender, KPS, CTV volume, lesion site (skull base vs. non-skull base), timing of PT (primary treatment vs. recurrence), presence of residual disease and number of surgeries or local recurrences before proton therapy were evaluated as potential prognostic clinical variables for PFS and OS endpoints. Quantitative variables were stratified relying on their median value. Multivariable Cox proportional hazards models were then developed using backward stepwise elimination with a threshold of P=0.10. For all analyses, a P<0.05 was considered statistically significant. Statistical analyses were performed using R version 4.3.3, with the gtsummary, survival, and survminer packages [Kassambara, Therneau, R Core Team, Sjoberg].

3.3 Results

Patient characteristics

Between April 2015 and July 2024, 56 adults and 5 pediatric pts (total of 61) with intracranial Ams were treated with PT at our institution. Pts and treatment characteristics are detailed in Table 1. Notably, 9 patients had previously undergone photon radiation therapy for other diseases (the majority of which were hematological diseases) before the treatment of AMs. The median age at PT was 56 years (range 1–82 years).
56% (n = 34) of AMs were skull base tumors (located along the sphenoid wing, clivus, cavernous sinus, or foramen magnum). All the pts underwent surgery: 59% of subjects received a single surgical approach prior to radiation treatment. More than half of the cohort (59%, n= 36) had symptoms due to the disease before radiotherapy. Adjuvant PT after the first complete and/or incomplete tumor resection was performed in 69% of patients (n = 42), while the remaining 31% (n = 19) underwent PT in the setting of tumor progression or recurrence after previous surgery.

OS and PFS

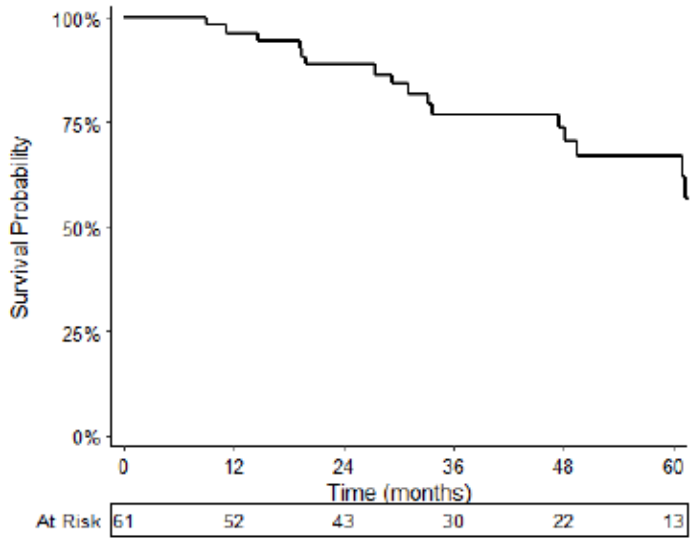
After a median follow-up after PT of 43 months (range 6 – 81), 11 pts (7%) developed progression. Of these, 9 were in the PT field, 1 marginal and 1 out of the radiotherapy field. The remaining 2 pts developed both in-field and out-of-field progression. For progressing tumors, the median time of relapse after PT was 29,2 months (range 9 – 61 months). Following progression disease, 6 patients were followed up radiologically due to the general condition of the patient or the slow kinetic of the disease. One of these patients underwent salvage surgery followed by re-irradiation at our center. Three patients were treated with

systemic salvage therapy with hydroxyurea or bevacizumab and the last one underwent metabolic therapy with 177Lu-DOTATATE. In the remaining 50 pts, a reduction in tumor size and stable disease were noted in 20 and 23 pts with visible lesions at PT, respectively. At the time of the analysis, absence of macroscopical relapse was maintained by 7 pts after GTR followed by PT.

	Value	Range or %
Age (years)	56 years	range 2 - 70
Adults	n= 56	92%
Paediatric	n = 5	8%
KPS > 90	n= 40	66%
Gender		
Male	27	44%
Female	34	56%
Primary site		
Skullbase	34	56%
Non-Skullbase	27	44%
Residual disease after surgery		
Yes	52	85%
No	9	15%
Number of surgeries		
Single surgery	36	59%
More than 1	25	41%
Timing of PT		
Adjuvant	42	69%
Relapse	19	31%
Prescription dose in Gy (RBE)	60 GyRBE	range 54 - 60 GyRBE
Number of fractions	30	range 28-30 fractions
CTV (cc)	75 cc	range 54-115 cc

Table 1: Patients' and treatment characteristics of the entire cohort

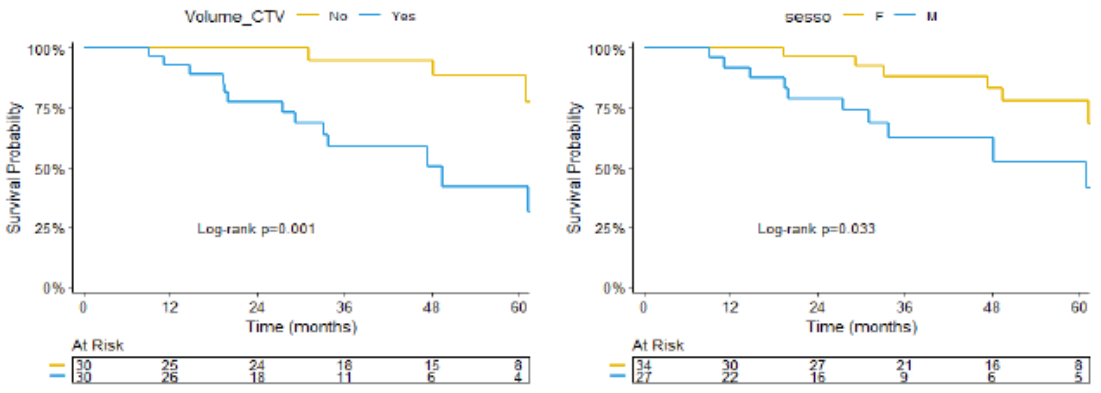
The estimated 3- and 5-year PFS was 77% and 67% for the entire cohort, respectively (Figure 2). The log-rank p-value was 0.2, indicating that there was no statistically significant difference between pediatric and adult patients. Furthermore, the presence of residual disease or the timing of PT (at relapse vs adjuvant setting) did not appear to have a significant impact on PFS (95% CI: 0.24 – 2.34, p = 0.6). The 3-year and 5-year progression-free survival rates were found to be 73% and 63% for patients treated after surgery (adjuvant setting), and 88% and 77% for patients treated for recurrence, respectively.
However, the size of the CTV (median, 75 cc) was associated with a significant decline in PFS, ([95%CI: 1.00 - 1.02], p <0.001): in patients with CTV < 75 cc, the estimated PFS at 3 and 5-years were 95% and 89%, as opposed to 59% and 42% for CTV larger than 75 cc.



Characteristic	12 Months	24 Months	36 Months	48 Months	60 Months
Overall	96% (91%, 100%)	89% (81%, 98%)	77% (66%, 90%)	74% (62%, 88%)	67% (54%, 84%)

Figure 2: Kaplan Meier curves for progression-free survival (PFS) in the entire cohort

Moreover, the PFS was found to be significantly influenced by sex ([95%CI: 1.04 – 8.01], p = 0.042). The rate of 3-year and 5-year PFS was 62% and 52% in male pts, which was significantly different from the 88% and 78% observed in female pts (Figure 3). Both CTV and sex remain significant in the multivariate analysis ([95%CI: 1.00 – 1.01], p = 0.003 and 95%CI: [1.18 – 11.8], p = 0.025]).

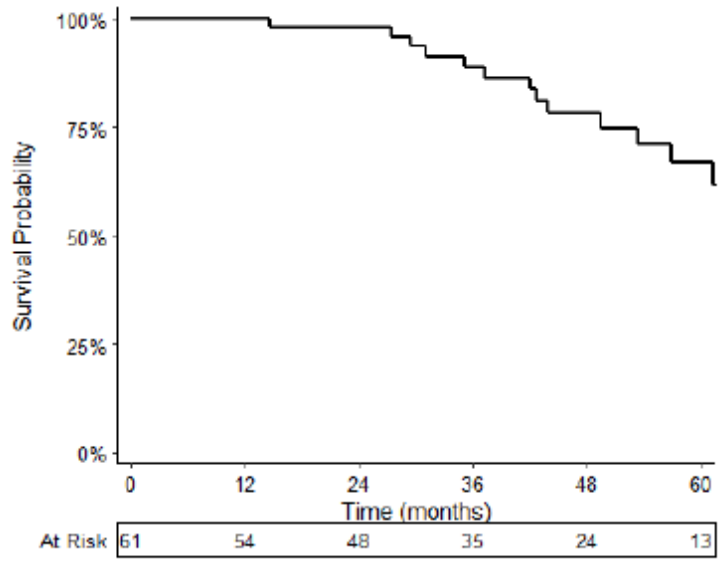


Characteristic	12 Months	24 Months	36 Months	48 Months	60 Months
CTV > a 75 cc					
No	100% (100% 100%)	100% (100%, 100%)	95% (86%, 100%)	95% (86%, 100%)	89% (75%, 100%)
Yes	93% (84%, 100%)	78% (63%, 95%)	59% (42%, 83%)	50% (32%, 80%)	42% (24%, 75%)

Characteristic	12 Months	24 Months	36 Months	48 Months	60 Months
Sex					
F	100% (100% 100%)	97% (90%, 100%)	88% (77%, 100%)	83% (69%, 100%)	78% (62%, 97%)
M	92% (82%, 100%)	79% (64%, 97%)	62% (44%, 88%)	62% (44%, 88%)	52% (32%, 85%)

Figure 3 Kaplan Meier curves for progression-free survival in the overall population based on CTV volume (on the left) and on gender (on the right)

During the follow-up period 13 pts died, 8 of whom because of disease progression. The 3- and 5-year OS was 89% and 67% respectively for the entire population (Figure 4). Age (median, 56 years), CTV (median, 75 cc) and KPS > 90 played a significant influence on overall survival outcomes. In details, pts younger than 56 years achieved a significantly better OS compared to older pts (at 5 years 78% vs. 50% [95%CI 1.00 – 1.09], p = 0.033). Moreover, higher KPS scores and lower CTV volumes were found to be associated with improved outcomes both at univariate ([95%CI 0.88 – 0.98], p = 0.007, [95%CI 1.01 – 1.02], p < 0.001 respectively) and multivariate analyses ([95%CI0.86 – 1.00], p = 0.041, [95%CI 1.00 – 1.02], p < 0.001 respectively). In contrast, the timing of radiation treatment (adjuvant setting vs at relapse), did not appear to have a significant impact on survival.



Characteristic	12 Months	24 Months	36 Months	48 Months	60 Months
Overall	100% (100%, 100%)	98% (95%, 100%)	89% (80%, 99%)	78% (66%, 92%)	67% (52%, 85%)

Figure 4: Kaplan Meier curves for progression-free survival (OS) in the entire cohort

Toxicity

PT was well tolerated in all pts; there were no unplanned interruptions due to treatment-related toxicity. Of note, no severe acute or late side effect (grade 3 or above) was seen in any patient. While more than half of the pts had disease-related symptoms before proton therapy, 11 reported an improvement in their condition after treatment. Most common acute toxicities were focal radiation dermatitis (80%, n = 49), moderated fatigue (57%, n = 35) and focal alopecia (74%, n= 45). In the present case series, late alopecia was reported in 61% of patients, constituting the most prevalent late toxicity. In most cases, its complete resolution was reported to occur approximately 10 to 15 months after the conclusion of treatment. Even though more than half of the pts had been treated for AMs of the skull base, only 4 pts developed slow subclinical hypopituitarism over time: of these, 2 have since started medical treatment and are being followed up regularly by endocrinologists. Most common toxicities and relative grades are reported in Table 2.
Radionecrosis was observed in 6 pts (11% of the cohort). Of these, only one patient exhibited grade 1 radionecrosis and did not require medical therapy. The remaining patients with grade 2 (n = 2) and grade 3 (n = 3) radionecrosis underwent medical steroid therapy and eventually bevacizumab administration. At the time of the analysis, two of these patients

completed medical treatment with radiological evidence of remission of the radionecrosis. In our cohort, the overall incidence of RICE (radiation-induced contrast enhancement) lesions after PT was very low (15%, n=5) and limited to MRI findings without any clinical symptoms. Three of these pts were treated with low-dose steroids, with a radiological complete remission at follow-up MRIs.

Acute toxicities	None	G1	G2	G3	%None	%G1	%G2	%G3
Alopecia	16	8	37	-	26%	13%	61%	-
Dermatitis radiation	12	25	24	-	20%	41%	39%	-
Nausea	56	2	3	-	92%	3%	5%	-
Fatugue	26	34	1	-	43%	56%	2%	-
Headache	50	10	1	-	82%	16%	2%	-
Ataxia	55	6	0	-	90%	10%	0%	-
Late toxicities	**None**	**G1**	**G2**	**G3**	**%None**	**%G1**	**%G2**	**%G3**
Alopecia	24	16	21	-	39%	26%	34%	-
Skin hyper/hypopigmentation	60	1	0	-	98%	2%	0%	-
Hair colour/texture (G1 if present)	59	2	-	-	97%	3%	-	-
Fatigue	45	13	3	-	74%	21%	5%	-
	None	**G1**	**G2**	**G3**	**%None**	**%G1**	**%G2**	**%G3**
Radionecrosis	54	1	2	4	89%	2%	3%	7%

Table 2: Frequency rates of major acute and late toxicities observed during proton therapy and reported at follow-up with their relative grades according to CTCAE. 5.0

3.4 Discussion

Radiotherapy is a key component in the current therapeutic options for the management of meningiomas. Adjuvant radiotherapy and gross total resection, particularly in combination, have been reported as independent favorable outcome predictors for AMs. This aggressive management has gained general support, even though there is still controversy about timing, type and dose of radiation.
In our center, PT has been favored for recurrent AMs diseases after initial choice of surgery and in the adjuvant setting for residual disease or in the presence of risk factors after gross total resection. The main rationale for the utility of PT lies in the unique physical and biological properties of protons, characterized by maximum energy deposition within the sharply defined Bragg peak, resulting in low entrance and exit doses. Dosimetric studies have shown improved dose distributions in terms of target dose conformity and homogeneity and healthy tissue sparing for intracranial tumors compared to photon-based radiation [Kosaki]. Minimizing treatment-related side effects and ensuring the delivery of an effective dose to control the disease is very important given the long-life expectancy of these pts. PT is well suited to these challenging cases, as demonstrated for skull base lesions and large lesions [Weber].
This study reports on the efficacy and toxicity profile of PT as a treatment for AMs and represents one of the most extensive collection of cases of AMs treated with PT to date.

At a quite long follow-up time (median, 43 months), favorable outcomes were achieved in terms of both progression-free survival (77% at 3 years and 67% at 5 years) and overall survival (89% at 3 years and 67% at 5 years). Proton therapy treatment has been shown to be both safe and well tolerated by pts of all ages, including children. Although PT is well tolerated, patient performance status and age are reported to be critical factors influencing overall survival (OS). As a consequence, a tailored approach to patient selection can help optimize treatment plans, improve survival rates, and reduce unnecessary risks. Conversely, the presence of residual disease did not appear to have a significant impact on either overall survival or progression-free survival, suggesting that other factors may also play a role in tumor progression and affect the individual biological behavior of the tumor. In the present series, the location of the lesion (whether in the skull base or in the convexity) does not appear to influence the clinical outcome. This suggests that proton therapy provides adequate target coverage even in areas where healthy tissue is in proximity, and where a rapid dose reduction is necessary to avoid short- and especially long-term toxicity.
To date, relatively little data is available on the use of proton therapy and no studies have prospectively compared xRT and PT in patients with AMs. Moreover, given the low incidence of the disease, the sample size of published clinical trials is frequently limited. Consequently, pts treated for AMs have often been analyzed in combination with those treated for WHO III tumors (anaplastic meningiomas). Table 3 shows selected retrospective studies published between 2000 and 2024 reporting the outcome of PT in pts with AMs.

Reference	Institution	Period	Tumor type	Median dose	Median FUP (months)	LC	OS	Severe tox ≥ G3
Murray et al. 2012	PSI	1997-2015	G1 n=61 G2 n=35	54 GyRBE 62 GyRBE	56.9	95.7 % at 5y 68.6 % at 5y	92.1% at 5y 80.7% at 5y	10.9%
Champeaux-Depond et al. 2021	SNDS	2008-2017	G1 n=171 G2 n=13 G3 n=9	54 GyRBE 54 GyRBE	52	G1: 71.5 % at 5y G2: 55.6 % at 5y G3: 35.6 % at 5y	G1: 93% at 5y G2: 77.4% at 5y G3: 44.4% at 5y	N.R
Hug et al. 2021	PSI Florida	1973-1995	G2 and 3, n=56	62.5 GyRBE	59	G2: 38 % at 5y G3: 52 % at 5y	G2: 89 % at 5y G3:51 % at 5y	9%
Boskos et al. 2021	CPO	1999-2006	G2 and 3, n= 68	68 GyRBE	45.5	46.7% at 5y	53.2% at 5y	N.R
McDonald et al. 2021	Indianapolis	2005-2013	G2, n=35	63 GyRBE	39	71.1% at 5y	100% at 5y	4.5%
Qiu et al. 2023	Shangai	2015-2022	G2 n=28 G3 n=8	60 GyRBE	23.3	G2: 94.1% at 3y G3: 25% at 3y	85.5 % at 5y overall	N.R
Iannalfi et al. 2024	CNAO	2014-2021	G1/ radiological n= 141 G2 n=26 G3 n=3	55.8 GyRBE 66 GyRBE	41		G1: 95% at 5y G2 + G3: 79% at 5y	1.2% acute G3 toxicity

Table 3: Largest and most recent series including intracranial meningioma patients submitted to PT

For AMs, the 5-year local control and overall survival rates range from 38% to 71% and 53% to 100%, respectively. However, it is worth nothing that the definition of WHO grade II and III meningiomas has varied greatly between different editions of the WHO classification systems. As a consequence, results based on older data or data collected over decades should be interpreted with caution. However, our results compare favorably or are even superior

with already published data. Pts have been treated with a median dose of 60 GyRBE, which falls within the range of doses reported in previous case series. Furthermore, the follow-up period in this study aligns or exceeds the duration of follow-up observed in prior studies, ensuring the relevance and reliability of the findings.
Although we used prospectively collected data from our own database and had a relatively large sample size, some limitations should be noted. First, given the single-cohort, nonrandomized nature of our study, confounding factors, such as pts selection bias, are possible and a direct comparison of our outcomes against previous studies has limitations.
Second, the median follow-up of 43 months needs to be extended to report and evaluate long-term side effects and efficacy. Third, the small number of children (n=5) in comparison to the larger group of adults (n=56) makes it difficult to draw any reliable conclusions about pediatric pts: despite our results seem superior to previously published data, the small number of pediatric pts and a short follow-up time should be considered for data interpretation. Finally, tumors were graded according to the WHO classification in use at time of diagnosis: as a consequence, different WHO classifications have been employed.

3.5 Conclusions

This is one of the largest series to date reporting outcomes for PT of AMs pts. Our analysis indicates that PT is well tolerated and offers efficacy rates similar or even superior to previously reported photon and proton series. Despite some potential limitations, this study contributes to the growing body of evidence supporting PT as a valuable alternative treatment to conventional radiation techniques, with favorable outcomes and reduced risk of normal tissue damage.
Future studies are warranted to prospectively determine long-term benefits and risks associated with PT compared with photon RT.

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