Journal of Multidisciplinary Healthcare

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Overall Survival of Primary Single Intracranial Atypical Meningioma with Different Surgical and Postoperative Treatment Options: Evidence from the SEER Database

Jia-Jun Qin*, Chao Li*, Jin Fu, Xian-Zhen Chen

Department of Neurosurgery, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai, 200092, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xian-Zhen Chen; Jin Fu, Department of Neurosurgery, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, No. 301, Yanchang Middle Road, Jing'an District, Shanghai, 200072, People's Republic of China, Tel +8613901793331; +86 13262727292, Email fujinfu0226@126.com; chenxianzhencxzk@126.com

Objective: The aim of this study is to evaluate the impact of different surgical and postoperative treatment options on the long-term overall survival (OS) in patients with primary single intracranial atypical meningioma.

Methods: In this retrospective study, participants were drawn from the Surveillance, Epidemiology, and End Results (SEER) database. Inclusion criteria comprised patients who underwent either gross total resection (GTR) or subtotal resection (STR). The inverse probability weighting (IPW) method using generalized boosted models was used to achieve balance in variables across various treatment groups. Subsequent to IPW, multivariate Cox analysis and Kaplan–Meier analysis were conducted, with OS as the endpoint.

Results: GTR was conducted on 1650 patients, while STR was conducted on 1109 patients. Among these, 432 patients who underwent GTR and 401 patients who underwent STR received postoperative radiotherapy (PORT). In the case of patients who were under 60 years old, PORT emerged as a significant protective factor for OS in those who underwent STR (HR 0.44; 95% CI 0.23–0.84; p = 0.013). Survival curves demonstrated that patients who underwent STR with PORT exhibited comparable OS to those who underwent GTR without PORT (p = 0.546). Conversely, for patients aged 60 years or older, PORT emerged as an independent risk factor for both GTR (HR 1.42; 95% CI 1.00–2.00; p = 0.048) and STR (HR 1.81; 95% CI 1.26–2.60; p = 0.001).

Conclusion: PORT may contribute to improving OS in primary single atypical meningioma patients under 60 years old who receive STR. However, in older patients who underwent either GTR or STR, the administration of PORT may be associated with a potential risk of OS. Therefore, age should be taken into account in applying PORT therapy, and the optimal treatment strategy for PORT in patients with atypical meningiomas needs to be further explored and validated.

Keywords: age, atypical meningioma, gross total resection, postoperative radiotherapy, subtotal resection

Introduction

Meningiomas are the most prevalent primary intracranial tumors,[1] with the predominant subtype among WHO Grade II meningiomas being atypical meningioma (AM).[2] Surgical intervention is the preferred treatment approach for symptomatic or progressively enlarging meningiomas,[3,4] with a primary focus on achieving Simpson Grade I resection.[5] However, attaining Simpson Grade I resection is not universally feasible for all patients, due to variables such as the anatomical position, size, and other factors of the tumor.[6] In contemporary neurosurgical practices, resections categorized as Simpson Grade I–III are classified as Gross Total Resection (GTR), while Grades IV–V fall under Subtotal Resection (STR).[7,8]

Despite the endorsement of postoperative radiotherapy (PORT) in patients with AM post-surgery by the 2016 and 2021 European Association of Neuro-Oncology (EANO) guidelines, particularly for those undergoing STR, the effectiveness of

Received: 25 January 2024
Accepted: 10 May 2024
Published: 27 May 2024

PORT in enhancing patient outcomes remains uncertain.[3,4] The impact of PORT on survival, as evidenced by existing retrospective studies, remains a topic of contention. While some studies propose that PORT enhances both overall survival (OS) and progression-free survival (PFS) in post-surgical patients, irrespective of whether they underwent GTR or STR,[9–12] conflicting conclusions are presented by other investigations.[13–16] Additionally, conflicting findings exist regarding the extent of resection (EOR) when examining the impact of PORT in patients with AM who underwent either GTR or STR.[9,11,12,14,16–20]

Hence, in this population-based study, we seek to assess the role of PORT in a substantial group of patients diagnosed with AM, using data from the Surveillance, Epidemiology and End Results (SEER) database.

Methods

Ethics Statement

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Shanghai Tenth People's Hospital (Approval number:SHSY-LYZX-202). In conducting this study, the SEER database, a publicly accessible resource, was utilized. All participants selected for our research were exclusively derived from this database. Consequently, the design of this study, which exclusively relies on publicly available data, obviates the requirement for obtaining patient consent for participation and publication.

Participant Selection

Patients who had undergone surgery and were diagnosed with a primary, solitary intracranial AM were selected for inclusion in the study. The data was extracted from a subset of the SEER database, which comprises 17 registries [Nov 2021 Sub (2000–2019)]. Inclusion criteria encompassed: 1) The diagnosis of AM was based on the WHO classification;[21] 2) Primary tumor site in the intracranial region; 3) Microscopic confirmation of diagnosis for each case. Exclusion criteria for this study were: 1) Previous history of tumors; 2) Clinical information that was incomplete or ambiguous; 3) Cases where surgery was not performed; 4) Patients who received chemotherapy; 5) Patients aged younger than 18 years old; 6) Follow-up duration of three months or less.

Variables

The study encompassed the collection and analysis of demographic, oncological, treatment, and survival data. Demographic details, including age, race, gender, and marital status, were included. Oncological information, such as the year of diagnosis, size, site, and laterality, were meticulously recorded. Surgical procedure categorization involved patients with a "Surg Prim Site (1998+)" entry recorded as '55' or '30,' indicating GTR, while codes '20', '21', and '40' were indicative of STR. Additionally, the documentation included the administration of PORT.

Outcome

The primary endpoint of this study is OS, with the maximum survival duration set at 120 months. Due to the SEER database not recording cause-specific deaths for patients with AM, we established our own definition for AM-specific death (AMSD). The specifics of the AMSD definitions are outlined in Supplement Note 1.

Statistical Analysis

To mitigate bias and address imbalances across the four treatment groups—GTR without PORT, GTR with PORT, STR without PORT, and STR with PORT—an inverse probability weighting (IPW) method, using generalized boosted models, was used.[22] The balance between two groups was assessed by absolute standardized mean difference (ASMD), where an ASMD less than 0.1 indicated no major imbalance. For the analysis of OS, both univariate and multivariate Cox regression models were used. The factors with significant differences in the Cox univariate regression were included in the Cox multivariate regression. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. Kaplan–Meier analysis with Log rank test was used to estimate survival curves.

Competing risk analysis was performed using both Fine and Gray's proportional subhazards model and Cause-specific proportional hazards model.[23,24] A p-value < 0.05 was considered indicative of statistical significance. All statistical analyses were carried out using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 25 (Statistical Package for the Social Sciences, Chicago, IL, USA).

Results

Patient Demographics

A total of 2759 patients were included in this study, and their demographic information are presented in Table 1. In terms of treatment, GTR was performed on 1650 patients (59.8%), while STR was undertaken in 1109 patients (40.2%). Among those in the GTR group, the predominant proportion (1218 patients, 73.8%) underwent post-surgical observation, with a minority (432 patients, 26.2%) receiving PORT. In the STR group, 708 patients (63.8%) were placed under observation after surgery, whereas 401 patients (36.2%) received PORT.

Among these four treatment groups, certain variables revealed statistically significant differences, including age (p = 0.009), year of diagnosis (p < 0.001), and tumor size (p < 0.001). To address potential imbalances between the four treatment groups, the IPW method was employed. Following the application of the IPW method, the ASMD values (maximum pairwise) for all variables decreased and were all less than 0.1 (Table 1 and Supplement Figure 1), indicating successful balance in variables across the four treatment groups.

Table 1 Characteristics of Patients Diagnosed with Atypical Meningioma

	All	GTR no-PORT	GTR with PORT	STR no-PORT	STR with PORT	*P*	ASMD[a]	
							Before	After
Subjects, n (%)	2759	1218	432	708	401			
Age, years	60 (48, 69)	60 (49, 70)	60 (49, 68)	60 (48, 71)	58 (47, 66)	0.009	0.173	0.042
Gender						0.963	0.030	0.022
Male, n (%)	1164 (42.2)	512 (42.0)	181 (41.9)	297 (41.9)	174 (43.4)			
Female, n (%)	1595 (57.8)	706 (58.0)	251 (58.1)	411 (58.1)	227 (56.6)			
Race						0.286	0.108	0.050
White	2028 (73.5)	913 (75.0)	321 (74.3)	497 (70.2)	297 (74.1)			
Black	388 (14.1)	165 (13.5)	58 (13.4)	116 (16.4)	49 (12.2)			
Others	343 (12.4)	140 (11.5)	53 (12.3)	95 (13.4)	55 (13.7)			
Year of diagnosis						< 0.001	0.197	0.062
2004–2007	378 (13.7)	195 (16.0)	50 (11.6)	96 (13.6)	37 (9.2)			
2008–2011	596 (21.6)	207 (17.0)	66 (15.3)	244 (34.5)	79 (19.7)			
2012–2015	761 (27.6)	348 (28.6)	127 (29.4)	160 (22.6)	126 (31.4)			
2016–2019	1024 (37.1)	468 (38.4)	189 (43.8)	208 (29.4)	159 (39.7)			
Tumor size, mm	49 (38, 60)	47 (37, 60)	50 (39, 60)	48 (37, 60)	50 (40, 60)	0.007	0.182	0.027
Primary site						0.467	0.089	0.034
Cerebral meninges	2740 (99.3)	1206 (99)	430 (99.5)	704 (99.4)	400 (99.8)			
Brian	19 (0.7)	12 (1.0)	2 (0.5)	4 (0.6)	1 (0.2)			

(*Continued*)

Table 1 (Continued).

	All	GTR no-PORT	GTR with PORT	STR no-PORT	STR with PORT	*P*	ASMD[a]	
							Before	After
Laterality						0.225	0.044	0.034
Left	1346 (48.8)	585 (48.0)	217 (50.2)	347 (49.0)	197 (49.1)			
Right	1276 (46.2)	569 (46.7)	201 (46.5)	316 (44.6)	190 (47.4)			
Paired site	137 (5.0)	64 (5.3)	14 (3.2)	45 (6.4)	14 (3.5)			
Marital Status						0.057	0.187	0.084
Married	1615 (58.5)	723 (59.4)	263 (60.9)	378 (53.4)	251 (62.6)			
Divorced	235 (8.5)	108 (8.9)	32 (7.4)	65 (9.2)	30 (7.5)			
Widowed	217 (7.9)	97 (8.0)	29 (6.7)	70 (9.9)	21 (5.2)			
Single	548 (19.9)	232 (19.0)	89 (20.6)	147 (20.8)	80 (20.0)			
Other	144 (5.2)	58 (4.8)	19 (4.4)	48 (6.8)	19 (4.7)			

Notes: ASMD, absolute standardized mean difference; GTR, gross total resection; STR, subtotal resection; PORT, postoperative radiotherapy. a[a]Only the largest ASMD between groups before and after inverse probability weighting are displayed.

Cox Analysis Following IPW in the Overall Population

Following the application of the IPW method, univariate and multivariate Cox analyses for OS were conducted (Table 2). In the multivariate Cox analysis conducted subsequent to employing the IPW method, age (HR 1.06; 95% CI 1.05–1.07; $p < 0.001$), male gender (HR 1.34; 95% CI 1.08–1.66; $p = 0.007$), black race (HR 1.47; 95% CI 1.13–1.92; $p = 0.004$),

Table 2 Univariate and Multivariate Cox Analysis of Patients with Meningioma After Inverse Probability Weighting (IPW)

	Univariable Analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, years	1.06 (1.05, 1.07)	< 0.001*	1.06 (1.05, 1.07)	< 0.001*
Gender				
Female	Ref		Ref	
Male	1.20 (0.99, 1.47)	0.068*	1.34 (1.08, 1.66)	0.007*
Race				
White	Ref		Ref	
Black	1.41 (1.09, 1.82)	0.009*	1.47 (1.13, 1.92)	0.004*
Others	0.91 (0.66, 1.26)	0.567	0.98 (0.72, 1.33)	0.883
Tumor size, mm	1.01 (1.01, 1.02)	< 0.001*	1.01 (1.01, 1.02)	< 0.001*
Operation Type				
GTR	Ref		Ref	
STR	1.23 (1.01, 1.50)	0.040*	1.34 (1.10, 1.63)	0.004*

(*Continued*)

Table 2 (Continued).

	Univariable Analysis		Multivariable analysis	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
PORT				
No	Ref		Ref	
Yes	1.11 (0.90, 1.36)	0.324	1.30 (1.05, 1.61)	0.017*
Primary site				
Cerebral meninges	Ref			
Brian	0.97 (0.26, 3.58)	0.961		
Laterality				
Left	Ref			
Right	1.16 (0.95, 1.42)	0.155		
Paired site	1.01 (0.61, 1.67)	0.970		
Marital Status				
Married	Ref		Ref	
Divorced	1.23 (0.88, 1.72)	0.222	1.26 (0.89, 1.79)	0.190
Widowed	3.30 (2.50, 4.34)	< 0.001*	1.90 (1.41, 2.57)	< 0.001*
Single	1.09 (0.84, 1.42)	0.529	1.58 (1.21, 2.08)	< 0.001*
Other	1.62 (1.01, 2.61)	0.046*	1.94 (1.22, 3.09)	0.005*

Notes: Gender, PORT, and variables with p < 0.1 in univariate COX analysis were included in the multivariate COX analysis; GTR, gross total resection; STR, subtotal resection; PORT, postoperative radiotherapy. *p<0.05.

tumor size (HR 1.01; 95% CI 1.01–1.02; p < 0.001), and STR (HR 1.34; 95% CI 1.10–1.63; p = 0.004) were all identified as independent risk factors for OS. Marital status also emerged as a factor influencing the outcome of patients. Furthermore, the multivariate Cox analysis post-IPW indicated that PORT was an independent risk factor for OS with statistical significance (HR 1.30; 95% CI 1.05–1.61; p = 0.017).

Cox Analysis Following IPW for Different Treatment Groups

Univariate and multivariate Cox analyses for OS were applied to different treatment groups, including GTR no-PORT, GTR with PORT, STR no-PORT, and STR with PORT. As presented in Table 3, the multivariate Cox analysis post IPW indicated that compared to patients who underwent GTR alone, those who underwent STR with or without PORT experienced significantly worse outcomes (STR no-PORT vs GTR no-PORT: HR 1.36; 95% CI 1.10–1.69; p = 0.004; STR with PORT vs GTR no-PORT: HR 1.72; 95% CI 1.29–2.30; p < 0.001). Moreover, the analysis revealed that PORT did not significantly enhance or worsen the OS of patients who had undergone GTR (HR 1.33; 95% CI 0.99–1.77; p = 0.055) or STR (HR 1.26; 95% CI 0.94–1.70; p = 0.125).

These findings underscore the continued importance of EOR as a crucial prognostic factor for OS in patients with AM. Patients who underwent GTR demonstrated significantly better OS compared to those who underwent STR. However, the role of PORT remains unclear.

Explorations into the role of PORT were conducted in different age subgroups, specifically the younger age group (< 60 years old) and the older age group (≥ 60 years old). For each subgroup, the IPW method was used to balance variables

Table 3 Univariate and Multivariate Cox Analysis for Different Treatment Groups After Inverse Probability Weighting (IPW)

Pairwise comparison[a]	Univariable		Multivariable[b]	
	HR (95% CI)	*p*	HR (95% CI)	*p*
GTR with PORT vs GTR no-PORT	1.20 (0.91, 1.58)	0.206	1.33 (0.99, 1.77)	0.055
STR no-PORT vs GTR no-PORT	1.31 (1.06, 1.62)	0.011*	1.36 (1.10, 1.69)	0.004*
STR with PORT vs GTR no-PORT	1.38 (1.04, 1.84)	0.025*	1.72 (1.29, 2.30)	< 0.001*
STR no-PORT vs GTR with PORT	1.10 (0.82, 1.46)	0.525	1.03 (0.76, 1.39)	0.853
STR with PORT vs GTR with PORT	1.16 (0.82, 1.63)	0.407	1.30 (0.92, 1.84)	0.137
STR with PORT vs STR no-PORT	1.05 (0.79, 1.41)	0.726	1.26 (0.94, 1.70)	0.125

Notes: GTR, gross total resection; STR, subtotal resection; PORT, postoperative radiotherapy. [a]The reference group is to the right of "vs"; [b]In multivariate Cox analysis, the confounders included age, gender, race, tumor size, year of diagnosis, and marital status. *p < 0.05.

among different treatment groups. The ASMD values (maximum pairwise) before and after IPW for the two subgroups are depicted in Supplement Figure 2, indicating that variables were generally well-balanced after IPW.

The results of univariate and multivariate Cox analyses for OS post-IPW are presented in Table 4. In patients < 60 years old, PORT emerged as a statistically significant protective factor for OS in those who had undergone STR (HR 0.44; 95% CI 0.23–0.84; p = 0.013). However, PORT neither worsened nor improved OS in patients who had undergone

Table 4 Univariate and Multivariate Cox Analysis for Different Treatment Groups After Inverse Probability Weighting (IPW) in Subgroups

Pairwise comparison[a]	Univariable		Multivariable[b]	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age < 60 years old				
GTR with PORT vs GTR no-PORT	1.39 (0.79, 2.43)	0.252	1.28 (0.72, 2.28)	0.406
STR no-PORT vs GTR no-PORT	1.71 (1.12, 2.60)	0.013	1.75 (1.13, 2.71)	0.012
STR with PORT vs GTR no-PORT	0.80 (0.40, 1.61)	0.536	0.77 (0.40, 1.49)	0.433
STR no-PORT vs GTR with PORT	1.23 (0.70, 2.15)	0.467	1.37 (0.77, 2.44)	0.284
STR with PORT vs GTR with PORT	0.58 (0.27, 1.26)	0.169	0.60 (0.28, 1.29)	0.192
STR with PORT vs STR no-PORT	0.47 (0.24, 0.94)	0.032	0.44 (0.23, 0.84)	0.013
Age ≥ 60 years old				
GTR with PORT vs GTR no-PORT	1.21 (0.88, 1.66)	0.244	1.42 (1.01, 2.01)	0.043
STR no-PORT vs GTR no-PORT	1.23 (0.96, 1.57)	0.102	1.25 (0.97, 1.61)	0.079
STR with PORT vs GTR no-PORT	1.72 (1.23, 2.41)	0.002	2.26 (1.59, 3.21)	<0.001
STR no-PORT vs GTR with PORT	1.02 (0.73, 1.42)	0.927	0.88 (0.62, 1.26)	0.495
STR with PORT vs GTR with PORT	1.42 (0.95, 2.14)	0.088	1.60 (1.06, 2.40)	0.024
STR with PORT vs STR no-PORT	1.40 (0.99, 1.99)	0.059	1.81 (1.26, 2.60)	0.001

Notes: GTR, gross total resection; STR, subtotal resection; PORT, postoperative radiotherapy.[a] The reference group is to the right of "vs"; [b] In multivariate Cox analysis, the confounders included gender, race, marital status, age, year of diagnosis, and tumor size.

GTR (HR 1.28; 95% CI 0.72–2.28; p = 0.406). Additionally, STR alone proved to be a significant risk factor for all-cause mortality compared to GTR alone (HR 1.75; 95% CI 1.13–2.71; p = 0.012).

PORT was strongly indicated as a risk factor of OS for patients ≥ 60 years old who had undergone either GTR (HR 1.42; 95% CI 1.00–2.00; p = 0.048) or STR (HR 1.81; 95% CI 1.26–2.60; p = 0.001). STR alone also resulted in poorer OS when compared to GTR alone. The p-value, however, did not reach statistical significance after applying IPW (HR 1.25; 95% CI 0.97–1.61; p = 0.079), although it did meet significance prior to IPW (HR 1.27; 95% CI 1.01–1.60; p = 0.045).

The survival curves depicting OS after IPW are illustrated in Figure 1. In the subgroup of patients aged < 60 years (Figure 1A), those who underwent GTR alone exhibited superior OS compared to those who underwent STR alone

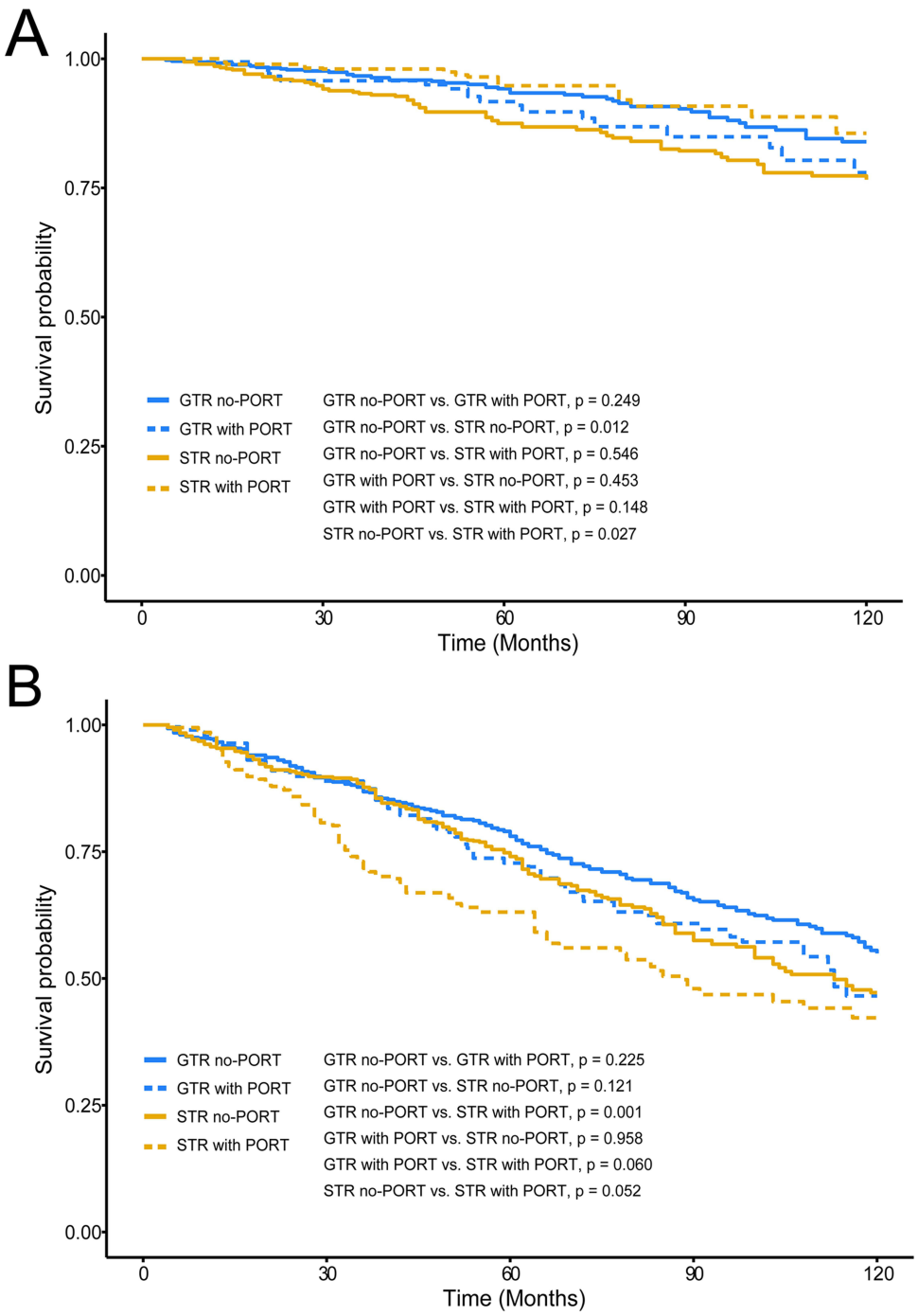

Figure 1 Kaplan–Meier survival curves of patients with four treatments in different subgroups, including patients with age < 60 years old (**A**) or ≥ 60 years old (**B**).
Abbreviations: PORT, postoperative radiotherapy; GTR, gross total resection; STR, subtotal resection.

(p = 0.012). Furthermore, patients who underwent STR with PORT demonstrated superior OS than those who underwent STR only (p = 0.027). The patients who underwent STR with PORT had a similar OS to patients who underwent GTR no-PORT (p = 0.546), indicating that STR with PORT could be an alternative treatment for GTR no-PORT in patients with AM < 60 years old. In the case of patients aged ≥ 60 years (Figure 1B), the OS of those who underwent STR alone was found to be superior to that of patients who underwent STR with PORT (p = 0.052).

These results highlight the divergent impact of PORT between younger and older patients. In the case of younger patients, PORT demonstrated a beneficial effect on the OS of those who had undergone STR. Conversely, for older patients, PORT adversely affected the OS of patients who underwent either GTR or STR. These results underscore the age-dependent nature of the relationship between PORT and OS in AM. Once again, these findings emphasize the significance of EOR in relation to OS in the context of AM. EOR continues to play a crucial role in determining the survival outcomes for patients with this condition.

Competing Risk Analysis

To assess the impact of PORT on AM-specific survival, a competing risk analysis was conducted. Given that the SEER database lacks the "SEER cause-specific death classification" for patients diagnosed with AM, we defined AMSD ourselves by examining the variable "COD to site recode". Three groups of AMSD definitions were established (see Supplement Note 1), and the results are presented in Table 5. For patients aged < 60 years old who underwent STR, PORT significantly decreased the HR of deaths from other causes. Conversely, for patients aged ≥ 60 years old who underwent STR, PORT significantly increased the HR of deaths from other causes.

Table 5 Multivariate Competing Risk Analysis for Patients in Age Subgroups

	Fine-Gray method		**Cause-specific method**	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
Definition A				
Age < 60 years old				
GTR: PORT vs no-PORT				
AMSD	1.50 (0.43, 5.20)	0.520	1.51 (0.44, 5.12)	0.509
Other cause death	1.04 (0.55, 1.98)	0.900	1.04 (0.56, 1.94)	0.910
STR: PORT vs no-PORT				
AMSD	0.32 (0.07, 1.43)	0.140	3.09 (0.07, 1.41)	0.129
Other cause death	0.50 (0.25, 1.00)	0.048*	0.49 (0.24, 0.98)	0.044*
Age ≥ 60 years old				
GTR: PORT vs no-PORT				
AMSD	1.23 (0.61, 2.46)	0.560	1.38 (0.68, 2.78)	0.370
Other cause death	1.32 (0.92, 1.91)	0.140	1.34 (0.93, 1.93)	0.113
STR: PORT vs no-PORT				
AMSD	1.34 (0.74, 2.42)	0.330	1.59 (0.88, 2.88)	0.127
Other cause death	1.68 (1.15, 2.46)	0.008*	1.88 (1.28, 2.77)	0.001*

(*Continued*)

Table 5 (Continued).

	Fine-Gray method		Cause-specific method	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
Definition B				
Age < 60 years old				
GTR: PORT vs no-PORT				
AMSD	0.99 (0.26, 3.75)	0.990	0.99 (0.27, 3.68)	0.985
Other cause death	1.14 (0.60, 2.15)	0.690	1.14 (0.62, 2.10)	0.679
STR: PORT vs no-PORT				
AMSD	1.49 (0.41, 5.45)	0.550	1.32 (0.37, 4.75)	0.668
Other cause death	0.33 (0.16, 0.69)	0.003*	0.33 (0.16, 0.71)	0.004*
Age ≥ 60 years old				
GTR: PORT vs no-PORT				
AMSD	1.24 (0.53, 2.88)	0.620	1.33 (0.57, 3.09)	0.507
Other cause death	1.32 (0.94, 1.88)	0.110	1.36 (0.96, 1.93)	0.083
STR: PORT vs no-PORT				
AMSD	1.86 (0.81, 4.28)	0.140	2.24 (0.96, 5.25)	0.062
Other cause death	1.59 (1.11, 2.29)	0.012	1.73 (1.22, 2.45)	0.002
Definition C				
Age < 60 years old				
GTR: PORT vs no-PORT				
AMSD	1.18 (0.47, 2.94)	0.720	1.18 (0.48, 2.86)	0.719
Other cause death	1.07 (0.51, 2.24)	0.870	1.07 (0.52, 2.17)	0.861
STR: PORT vs no-PORT				
AMSD	0.70 (0.28, 1.77)	0.450	0.65 (0.25, 1.65)	0.361
Other cause death	0.35 (0.15, 0.83)	0.017*	0.34 (0.14, 0.82)	0.016*
Age ≥ 60 years old				
GTR: PORT vs no-PORT				
AMSD	1.25 (0.73, 2.15)	0.410	1.36 (0.79, 2.33)	0.264
Other cause death	1.29 (0.86, 1.93)	0.220	1.34 (0.90, 2.01)	0.155
STR: PORT vs no-PORT				
AMSD	1.52 (0.94, 2.45)	0.089	1.76 (1.08, 2.86)	0.022*
Other cause death	1.50 (0.97, 2.32)	0.070	1.81 (1.17, 2.79)	0.008*

Notes: GTR, gross total resection; STR, subtotal resection; PORT, postoperative radiotherapy; AMSD, atypical meningioma specific death. In multivariate Cox analysis, the confounders included gender, race, marital status, age, and tumor size. *p < 0.05.

Discussion

Given the small number of cases with AM in a single center, several researchers have turned to public databases to investigate the role of PORT in patients diagnosed with WHO Grade II meningioma, yielding diverse results. For instance, Aizer et al used the SEER database, and included 575 patients diagnosed with AM.[25] Their findings reinforced that EOR was a robust predictor of OS, with those undergoing GTR exhibiting better OS than those undergoing STR. Regarding PORT, they reported that it did not impact OS in the overall population. However, they did not separately analyze the effect of PORT in patients who underwent GTR or STR. Rydzewski et al included 3529 patients diagnosed with AM from the National Cancer Data Base.[26] Their analysis revealed that both GTR and PORT were significant factors in improving OS on multivariate analysis, independently and in combination. Notably, in the combined analysis, the reference group consisted of patients who underwent non-GTR and received no RT, leaving the role of PORT in different EOR groups unclear. Li et al utilized the SEER database, incorporating 426 patients diagnosed with AM, and employed a propensity score matching method to achieve a balance between the GTR and STR patient groups.[27] They separately analyzed the effect of PORT in patients who underwent GTR or STR but only employed the Kaplan–Meier method, which is a univariate approach. Their findings indicated that PORT did not improve OS regardless of EOR.

Our research boasts several strengths in comparison to traditional studies. Firstly, it encompasses a substantial group of patients diagnosed with AM, specifically focusing on those with intracranial afflictions. Secondly, our investigation surpasses the confines of solely assessing the independent role of PORT; instead, we integrated the effects of EOR and conducted a comprehensive multivariate analysis across four distinct treatment groups. To ensure methodological rigor, we employed IPW to balance variables and mitigate potential biases. Finally, our findings emphasize the significant impact of age on the efficacy of PORT, as evidenced by our subgroup analyses. Additionally, we delved deeper into the implications of PORT by employing competing risk analysis. The RTOG 0539 study classified meningioma into 3 risk groups according to WHO grade, surgical extent, and whether the tumor was newly diagnosed or recurrent.[28,29] In this trial, adjuvant radiotherapy (RT) was recommended for newly diagnosed atypical meningioma, whereas it was omitted for patients with newly diagnosed benign meningioma irrespective of other prognostic factors. The recursive partitioning analysis (RPA) classification revealed a subgroup of patients who could be potentially indicated for adjuvant RT even after gross total resection or for whom adjuvant RT could be deferred.[28–30] Therefore, risk analysis was conducted to assess the impact of PORT on AM-specific survival. The observation that age can impact the effect of PORT is not surprising. Radiotherapy can induce long-term toxicity, including hypopituitarism, neurocognitive impairment, and radiation-reduced tumors.[3] Previous research has indicated that elderly patients are more vulnerable to radiation-induced brain atrophy and dementia compared to their younger counterparts.[31,32] Consequently, it appears that younger patients with AM may derive benefits from PORT, showing a favorable tolerance to radiation toxicity. In contrast, older patients may not tolerate radiation toxicity as well, potentially experiencing poorer outcomes following PORT.

Limitations

This study is subject to several limitations. Firstly, specific details regarding PORT, such as dosage, timing, and fractionation, are not accessible from the SEER database. Previous studies have demonstrated that the dose of RT in atypical meningioma has a dose-response relationship with local control and survival outcomes.[33,34] Secondly, comprehensive pathological data about the tumors, such as the Ki-67 index, is also unavailable. Thirdly, information on PFS and AMSD is absent in the SEER data. Due to this limitation, further analyses on PFS are not feasible, and the impact of PORT on AM recurrence requires investigation through prospective studies, such as the ROAM/EORTC-1308 trial.[7] For AMSD, we established our own definition, and competing risk analysis revealed that PORT exerted an influence on the HR associated with causes of death other than those attributed to AMSD. However, the lack of a standardized cause-specific death classification for patients diagnosed with AM in the SEER database necessitates a cautious interpretation of our findings from the competing risk analysis. However, the outcomes of our study, centered on OS, warrant consideration, given that OS stands as the primary gold standard endpoint in tumor-related investigations within clinical research.[35,36] Finally, the absence of Simpson grade information prevents the analyses of the effect of PORT in different Simpson grades.

Conclusions

In conclusion, we investigated the role of PORT in patients with a single primary intracranial AM who had undergone GTR or STR. We discovered that PORT enhanced the OS in younger patients diagnosed with AM (< 60 years old) following STR. Younger patients who underwent STR with PORT exhibited a similar outcome to patients who underwent GTR without PORT. However, for older patients (≥ 60 years old), PORT emerged as a risk factor for OS, irrespective of whether they underwent GTR or STR. Additionally, our results highlighted the significance of EOR as a crucial predictor of OS. We recommend exercising caution when considering PORT for older patients with AM following surgery.

Abbreviations

AM, atypical meningioma; GTR, gross total resection; STR, subtotal resection; PORT, postoperative radiotherapy; OS, overall survival; EOR, extent of resection; SEER, Surveillance, Epidemiology and End Results; IPW, inverse probability weighting; ASMD, absolute standardized mean difference; HR, hazard ratio; CI, confidence interval; LOWESS, locally weighted scatterplot smoothing.

Data Sharing Statement

According to the "SEER Research Date Use Agreement", data are not available from the authors.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Shanghai Tenth People's Hospital (Approval number:SHSY-LYZX-202). Additionally, the SEER database, a public resource, has been accessed for this study. All participants included in our research were selected from this database. Consequently, the nature of this study, which solely utilizes publicly available data, negates the requirement for patient consent for participation and publication.

Acknowledgments

We are particularly grateful to all the people who have given us help on our article.

Funding

There is no funding to report.

Disclosure

These authors report no conflicts of interest in this work.

References

1. Ostrom QT, Price M, Neff C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2015-2019. *Neuro Oncol*. 2022;24(Suppl 5):v1–v95.
2. Ren L, Hua L, Deng J, et al. favorable long-term outcomes of chordoid meningioma compared with the other WHO Grade 2 Meningioma Subtypes. *Neurosurgery*. 2022.
3. Goldbrunner R, Stavrinou P, Jenkinson MD, et al. EANO guideline on the diagnosis and management of meningiomas. *Neuro-Oncology*. 2021.
4. Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol*. 2016;17(9).
5. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. *J Neurol Neurosurg Psych*. 1957;20(1):22–39.
6. Lemée JM, Corniola MV, Da Broi M, et al. Extent of Resection in Meningioma: predictive Factors and Clinical Implications. *Sci Rep*. 2019;9(1):5944.
7. Jenkinson MD, Javadpour M, Haylock BJ, et al. The ROAM/EORTC-1308 trial: radiation versus Observation following surgical resection of Atypical Meningioma: study protocol for a randomised controlled trial. *Trials*. 2015;16:519.
8. Jungwirth G, Warta R, Beynon C, et al. Intraventricular meningiomas frequently harbor NF2 mutations but lack common genetic alterations in TRAF7, AKT1, SMO, KLF4, PIK3CA, and TERT. *Acta Neuropathol Commun*. 2019;7(1):140.
9. Li H, Zhang YS, Zhang GB, et al. Treatment protocol, long-term follow-up, and predictors of mortality in 302 Cases of Atypical Meningioma. *World Neurosurg*. 2019;122:e1275–e1284.
10. Ozsoy KM, Oktay K, Cetinalp NE, et al. Impact of Adjuvant Radiotherapy on Recurrence of Surgically Treated Atypical Meningiomas and Retrospective Analysis of Prognostic Factors. *Turk Neurosurg*. 2022.

11. Dohm A, McTyre ER, Chan MD, et al. Early or late radiotherapy following gross or subtotal resection for atypical meningiomas: clinical outcomes and local control. *J Clin Neurosci*. 2017;46:90–98.
12. Park HJ, Kang HC, Kim IH, et al. The role of adjuvant radiotherapy in atypical meningioma. *J Neurooncol*. 2013;115(2):241–247.
13. Yoon H, Mehta MP, Perumal K, et al. Atypical meningioma: randomized trials are required to resolve contradictory retrospective results regarding the role of adjuvant radiotherapy. *J Cancer Res Ther*. 2015;11(1):59–66.
14. Champeaux C, Dunn L. World Health Organization Grade II Meningioma: A 10-year retrospective study for recurrence and prognostic factor assessment. *World Neurosurg*. 2016;89:180–186.
15. Champeaux C, Wilson E, Shieff C, Khan AA, Thorne L. WHO grade II meningioma: a retrospective study for outcome and prognostic factor assessment. *J Neurooncol*. 2016;129(2):337–345.
16. Garcia-Segura ME, Erickson AW, Jairath R, Munoz DG, Das S. Necrosis and brain invasion predict radio-resistance and tumor recurrence in atypical meningioma: a retrospective cohort study. *Neurosurgery*. 2020;88(1):E42–e48.
17. Komotar RJ, Iorgulescu JB, Raper DM, et al. The role of radiotherapy following gross-total resection of atypical meningiomas. *J Neurosurg*. 2012;117(4):679–686.
18. Hammouche S, Clark S, Wong AH, Eldridge P, Farah JO. Long-term survival analysis of atypical meningiomas: survival rates, prognostic factors, operative and radiotherapy treatment. *Acta Neurochir*. 2014;156(8):1475–1481.
19. Bagshaw HP, Burt LM, Jensen RL, et al. Adjuvant radiotherapy for atypical meningiomas. *J Neurosurg*. 2017;126(6):1822–1828.
20. Chen WC, Magill ST, Wu A, et al. Histopathological features predictive of local control of atypical meningioma after surgery and adjuvant radiotherapy. *J Neurosurg*. 2018;130(2):443–450.
21. Modha A, Gutin PH. Diagnosis and treatment of atypical and anaplastic meningiomas: a review. *Neurosurgery*. 2005;57(3):538–550.
22. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med*. 2013;32(19):3388–3414.
23. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496–509.
24. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics*. 1978;34(4):541–554.
25. Aizer AA, Bi WL, Kandola MS, et al. Extent of resection and overall survival for patients with atypical and malignant meningioma. *Cancer*. 2015;121(24):4376–4381.
26. Rydzewski NR, Lesniak MS, Chandler JP, et al. Gross total resection and adjuvant radiotherapy most significant predictors of improved survival in patients with atypical meningioma. *Cancer*. 2018;124(4):734–742.
27. Li D, Jiang P, Xu S, et al. Survival impacts of extent of resection and adjuvant radiotherapy for the modern management of high-grade meningiomas. *J Neurooncol*. 2019;145(1):125–134.
28. Rogers L, Zhang P, Vogelbaum MA, et al. Intermediate-risk meningioma: initial outcomes from NRG oncology RTOG 0539. *J Neurosurg*. 2018;129(1):35–47.
29. Rogers CL, Won M, Vogelbaum MA, et al. High-risk meningioma: initial out- comes from NRG oncology/RTOG 0539. *Int J Radiat Oncol Biol Phys*. 2020;106(4):790–799.
30. Chang WI, Kim IH, Choi SH, et al. Risk Stratification to Define the Role of Radiotherapy for Benign and Atypical Meningioma: A Recursive Partitioning Analysis. *Neurosurgery*. 2022;90(5):619–626.
31. Asai A, Matsutani M, Matsuda T, Tanaka Y, Funada N. Radiation-induced brain atrophy. *Gan No Rinsho*. 1989;35(11):1325–1329.
32. Stylopoulos LA, George AE, de Leon MJ, et al. Longitudinal CT study of parenchymal brain changes in glioma survivors. *AJNR Am J Neuroradiol*. 1988;9(3):517–522.
33. Kim D, Chang WI, Byun HK, et al. Dose-response relationship in patients with newly diagnosed atypical meningioma treated with adjuvant radiotherapy. *J Neurooncol*. 2023;161(2):329–337.
34. Sethi RA, Rush SC, Liu S, et al. Dose-response relationships for meningioma radiosurgery. *Am J Clin Oncol*. 2015;38(6):600–604.
35. Driscoll JJ, Rixe O. Overall survival: still the gold standard: why overall survival remains the definitive end point in cancer clinical trials. *Cancer J*. 2009;15(5):401–405.
36. Mailankody S, Prasad V. Overall survival vs disease-specific survival-reply. *JAMA Oncol*. 2018;4(4):586–587.