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ORIGINAL ARTICLE

The survival benefits of adjuvant radiotherapy for malignant meningioma: a retrospective cohort study

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ABSTRACT

BACKGROUND

Malignant meningiomas (MM) are rare aggressive tumors associated with poor survival outcomes. Due to their rarity, there is limited data on the outcomes and prognostic factors of MM patients, particularly on adjuvant radiotherapy roles in this tumor population. This study aims to investigate the clinical characteristics, prognostic factors, and survival outcomes of MM with focus on survival benefits of adjuvant radiotherapy.

METHODS

This retrospective cohort study analyzed 19 MM patients, who were initially subjected to postoperative radiotherapy, at Dr. Kariadi General Hospital, Semarang, from 2013 to 2023. Kaplan-Meier analysis was used to estimate survival rates at 1, 2, and 5 years. Univariate and multivariate Cox regression analyses were performed to identify factors associated with overall survival (OS). Variables with a p-value ≤0.25 in univariate analysis were included in the multivariate models.

RESULTS

The median OS was 16 months (95% CI 0.0–40.2), with estimated 1-year, 2-year, and 5-year survival rates of 52.6%, 42.1%, and 15.8%, respectively. Adjuvant radiotherapy (RDT) was associated with a significantly improved OS ($p<0.001$). However, sex, age, tumor location, and extent of resection did not show a significant association with OS. Cox regression showed that RDT had no statistically significant effect on OS in the multivariate model (HR=0, 95% CI 0–1.8, p=0.923).

CONCLUSION

Adjuvant radiotherapy is critical for improving OS in MM patients, and gross-total resection (GTR) alone does not guarantee better long-term outcomes. Further studies with larger cohorts and molecular analysis are necessary to refine treatment strategies for MM.

Keyword: Adjuvant radiotherapy, malignant meningioma, prognostic factor, survival outcome

INTRODUCTION

Meningiomas commonly arise from mesodermal arachnoid cells of the dura.[1] Meningiomas are more frequently found in the central nervous system (CNS) compared to other malignancies, and constitute 36% of all CNS malignancies.[1] In contrast, malignant meningiomas (MM) are considered uncommon and aggressive tumors. Malignant meningiomas represent only 1–3% of all meningiomas and are correlated with poor survival outcomes.[3,4] It is mentioned that 80% of MM recur 5 years after complete resection.[4] Men are more commonly afflicted by MM rather than woman. In addition, the 5–year survival rates of MM are reported to be around 28–61%. In contrast, low-grade meningiomas are more frequently found in women and have more favorable survival outcomes.[5]

The study by Seo et al.[1] showed that in the US the five-year survival rate of anaplastic meningioma patients was 41.4%. In Asia, Seo et al.[1] reported a similar five-year survival rate of 47.9%. Advanced age, high comorbidity scores, subtotal resection (STR), and lack of adjuvant therapy are factors linked to increased morbidity in patients.[6]

There have been a number of inconsistent results regarding prognostic variables for patients with MM. Grade I and II meningiomas have shown promising outcomes with surgical resection. However, MM have shown suboptimal results with surgical intervention alone.[7] Previous studies found a significant correlation between complete resection after surgery and improved patient survival outcomes.[7-9] However, Sughrue et al.[10] mentioned that there are no improved survival outcomes for anaplastic meningioma patients who underwent gross total resection (GTR). Previous literature has agreed that radiotherapy is a substantial positive predictive factor of overall survival (OS) in patients with MM, independent of previous resection treatment results.[1] Due to the rarity of MM, there is a paucity of research in its prognostic factors. Most of the available data on MM place the emphasis more on the treatment implication of surgery in patients with MM.[3,6,11]

A retrospective study involving 102 patients with atypical or malignant meningiomas who underwent microsurgical resection found that total resection of atypical and malignant meningiomas provided better outcomes and local control. Adjuvant radiation therapy is indicated for patients with MM with incompletely excised tumors; or with tumors in the parasagittal or posterior fossa area.[12] Another study involving 275 adult patients with histologically confirmed MM showed that surgical resection is recommended for elderly patients with MM in the absence of surgical contraindications, but gross total resection (GTR) does not present survival benefit in the elderly patients compared with subtotal resection (STR).[13]

Currently, there is a lack of data on the outcomes of various treatment strategies for MM patients. Further information regarding patient characteristics and outcomes is necessary to better guide management decisions for these patients. In this study, we aimed to investigate the prognostics factors related to the survival of MM patients, with particular focus on the use of adjuvant radiotherapy in treatment, accompanied by long-term follow-up.

METHODS

Research design

This was a retrospective cohort study of MM patients located in Dr. Kariadi General Hospital, Semarang from 2013 to 2023.

Research subjects

A total of 23 patients were diagnosed with MM based on histopathological findings after surgical resection. The data were retrieved from a prospectively maintained local brain tumor database. Included patients were selected based on several criteria: (i) patients diagnosed with WHO grade III MM based on histopathological evaluation; (ii) surgery performed in Kariadi Hospital; (iii) complete pre- and postoperative radiological data. Patients who died before the 30-day follow-up period and patients with intracranial metastases that originated from spinal meningioma were excluded from the study.

Data collection

Baseline characteristics of patients were recorded such as age at diagnosis, sex, weight, height, clinical manifestations, previous history of chemotherapy, previous history of neurosurgical radio-intervention, chemotherapy, post-operative adjuvant radiotherapy, post-operative histopathology diagnosis and post-surgery treatment or follow-up.

Radiologic data of those diagnosed with primary MM were evaluated based on the following criteria: tumor location (deep vs superficial), peritumoral edema (mild vs severe), and shape (rounded vs "mushroom"-shaped). Tumors located in convexity or parasagittal locations were considered "superficial". Opposite to that, falcine, intraventricular, and skull base–located tumors were considered "deep". Tumor size was defined as the greatest tumor diameter measured by radiological examination. Edema index (EI) was defined as greatest area of tumor edema in comparison to tumor size. Patients were grouped into two subgroups based on an EI cutoff of 0.5. EI < 0.5 was considered "no edema to mild edema" and EI ≥ 0.5 was considered "moderate to severe edema."[14] Tumor shape was assessed by CT scan or MRI, and "mushroom"-shaped tumors were defined if there was prominent pannus from globoid portions of the tumor spreading over the cerebral surface.[1] Postoperative computed tomography (CT) or magnetic resonance imaging (MRI), along with the surgical record, were used to determine the extent of resection, which was defined by the Simpson grading system.[14] Grades 1 and 2 were considered as gross-total resection (GTR) and grades 3–5 as subtotal resection (STR).

In our study, only one patient received preoperative chemotherapy with doxorubicin regimen. The chemotherapy was done in the previous hospital, before the patient was referred to our institution (Dr. Kariadi General Hospital) for further treatment.

In Dr. Kariadi General Hospital, all patients were subjected to postoperative adjuvant radiotherapy to ensure that the tumors diminished completely. All patients were subjected equally, unless the patients refused the treatment or had major adverse events that prevented treatment continuation.

Ethical clearance

The Dr. Kariadi General Hospital Institutional Review Board (IRB) has approved this study under number 167/EC/KEPK-RSDK/2024.

Statistical analysis

The primary outcome of this study was overall survival (OS), which we defined as the interval from the surgical procedure to the time of death. We categorized continuous variables, such as age and tumor size, into two groups using the median as a cutoff point. Differences in baseline data were evaluated using either independent t-tests or Mann-Whitney U tests for continuous variables, and chi-square tests or Fisher's exact tests for categorical variables. Both univariate and multivariate Cox regression analyses were performed. Variables that showed a statistically significant relationship with OS (p=0.251) in the univariate analysis were included in the multivariate Cox regression model. Kaplan-Meier analysis was used to generate survival curves, and the log-rank test was applied to compare these curves between different groups. For patients who were still living at the last follow-up, their data were censored. Statistical Package for the Social Sciences (SPSS) version 26 (IBM, USA) and R software (including the survival, survminer, readxl, and ggsurvplot packages) [R Foundation for Statistical Computing, Vienna, Austria] were used to perform all data analysis throughout the study. Statistical significance was determined at a p-value of <0.05.

RESULTS

Participant baseline data

The baseline characteristics of the study subjects indicate several trends between the surgery and surgery + radiotherapy groups. Both groups had similar ages (39.6 years for the surgery group and 39.5 years for the surgery + radiotherapy group; p=1.000). The surgery + radiotherapy group had a higher but statistically non-significant proportion of males (75% vs. 25%) (p=0.123) and a greater incidence of superficial tumors (66.7% vs. 33.3%; p=0.723). Notably, this group also exhibited more moderate to severe edema (70% vs. 30%; p=0.434). In terms of tumor shape, the surgery group had more round tumors (75% vs. 25%; p = 0.341). Diagnosis types were similar, with the surgery + radiotherapy group having a slightly higher percentage of primary diagnoses (55.6% vs. 44.4%; p=1.000). Simpson grades and subtype pathology showed no significant differences, with the surgery group having a higher proportion of WHO grade III, anaplastic meningiomas (35.3% vs. 64.7%; p=0.221). From 23 successfully extracted patients' medical records, 19 patients were included in this study. One patient was excluded for not meeting the 2016 WHO criteria for MM, one for missing clinical and radiological data, and two patients for having a follow-up period of less than 1 month (Table 1).

Table 1. Baseline characteristics of study subjects (n=19)

Variables	Surgery (n = 8)	Surgery + Radiotherapy (n = 11)	p-value
Age (years)	39.63 ± 19.96	39.45 ± 13.04	0.981¶
Sex			
Male	3 (25.0)	9 (75.0)	0.071§
Female	5 (71.4)	2 (28.6)	
Tumor location			
Superficial	3 (33.3)	6 (66.7)	0.653§
Deep	5 (50.0)	5 (50.0)	
Tumor size (mm)	46.88 ± 16.02	58.18 ± 16.22	0.154¶
< 55 mm	4 (50.0)	4 (50.0)	0.659§
≥ 55 mm	4 (36.4)	7 (63.6)	
Edema index			
No edema–mild	3 (30.0)	7 (70.0)	0.366§
Moderate–severe	5 (55.6)	4 (44.4)	
Tumor shape			
Round	3 (75.0)	1 (25.0)	0.261§
Mushroom	5 (33.3)	10 (66.7)	
Diagnosis type			
Primary	8 (44.4)	10 (55.6)	1.000§
Secondary	0 (0.0)	1 (100.0)	
Preoperative chemotherapy			
Yes	0	1 (100)	1.000§
No	8 (45.5)	10 (55.5)	
Simpson grade			
1–2	7 (43.8)	9 (56.3)	1.000§
3–5	1 (33.3)	2 (66.7)	
Subtype of pathology			
Grade III papillary	1 (100.0)	0 (0.0)	0.223§
Grade III rhabdoid	1 (100.0)	0 (0.0)	
Grade III anaplastic	6 (35.3)	11 (64.7)	

Note : Data presented as n (%), except age and tumor size as mean ± SD; ¶Independent T-test; §Fisher-Exact test

Patients' treatment outcomes

Postoperatively, GTR was achieved in 16 patients (84.2%). Simpson grade 1–2 was achieved in 16 patients (84.2%), while 3 patients (15.8%) achieved Simpson grade 3–4. There were no patients with Simpson grade 5 in this cohort. After tumor removal of confirmed WHO grade 3 meningioma, 12 patients (63.2%) underwent adjuvant external beam radiotherapy, and only one patient received adjuvant chemotherapy using doxorubicin regimen (Supplementary Material, Table S1). In general, adjuvant radiotherapy is recommended; however, there were eight patients who did not receive or finish radiotherapy due to COVID-19 mobility restrictions and the considerable distance they needed to travel to reach the hospital.

All patients were irradiated in our institution (Dr. Kariadi General Hospital). Adjuvant radiotherapy was started 1 month after surgery. All patients were treated with intensity-modulated radiotherapy (Varian, California, USA). Patients received single doses of 1.8–2 Gy up to a total dose of 54–60 Gy. Three patients stopped radiotherapy because of nonrelated illnesses. The patients' treatment index could not be retrieved from the medical records because these patients were treated before the electronic medical records era in our institution. Complete information regarding individual patients' treatment may be found in supplementary Table S1.

Analysis of survival

During the follow-up, sixteen patients (representing 84.2%) did not complete the observation period. The median overall survival (OS) was 16 months (95% confidence interval [CI] 0.0–40.2). The estimated OS probabilities at 1, 2, and 5 years were 52.6% (95% CI 40.1–65.3), 42.1% (95% CI 30.5–55.0), and 15.8% (95% CI 8.2–30.1), respectively (Fig. 1A). Patients treated with adjuvant radiotherapy (RDT) demonstrated a

significant increase in survival relative to non-RDT patients (p<0.001) (Fig. 1B). However, this study did not find a significantly longer OS based on sex (hazard ratio [HR] 2.01, 95% CI 0.74–5.47; p=0.163), a greater extent of resection (HR 0.93, 95% CI 0.26–3.29; p=0.913), or age (HR 1.12, 95% CI 0.41–3.06; p=0.823). (Figs. 1C–E)

Following univariate Cox regression analyses, we included all variables with a p-value less than 0.2 in the multivariate models (presented in Table 2). However, the results of the multivariate Cox regression analysis indicated that none of the examined factors, including sex (HR 0.85, 95% CI 0.2–3.0, p=0.831), tumor location (HR 2.7, 95% CI 0.9–8.6, p=0.963), and adjuvant radiotherapy (HR 0, 95% CI 0–1.8, p=0.923), had a statistically significant impact on OS (Table 2).

Supplementary Table S1. Detailed information on anaplastic meningioma patients' surgical and adjuvant radiotherapy intervention

Sex	Age (year)	Diagnosis Type	Location	Extent of resection	Adjuvant	Chemotherapy	Status	OS (month)
F	43	Primary	Olfactory Groove	GTR	RDT	-	Death	33
M	30	Primary	Convexity	GTR	-	-	Death	4
F	51	Primary	Tuberculum Sellae	GTR	RDT	-	Death	44
F	43	Primary	Tentorial	STR	RDT	-	Death	12
F	44	Primary	Convexity	GTR	RDT	-	Alive	84
F	50	Primary	Parasagittal	GTR	RDT	-	Death	27
M	64	Primary	Convexity	GTR	-	-	Death	6
M	31	Primary	Convexity	STR	RDT	-	Death	48
M	55	Primary	Convexity	GTR	RDT	-	Death	36
M	71	Primary	Convexity	GTR	-	-	Death	6
M	22	Primary	Petro-clival	STR	Not complete RDT	-	Death	10
F	52	Primary	Spheno-orbital	GTR	Not complete RDT	-	Death	4
F	29	Primary	Sphenoid wing	GTR	-	-	Death	2
F	45	Primary	Planum Sphenoid	GTR	RDT	-	Death	16
F	19	Primary	Parasagittal	GTR	RDT	-	Alive	91
M	18	Primary	Sphenoid wing	GTR	Not complete RDT	-	Death	2
F	14	Primary	Convexity	GTR	RDT	Doxorubicin	Death	31
F	39	Primary	Parasagittal	GTR	RDT	-	Alive	71
F	31	Primary	Parasagittal	GTR	-	-	Death	9

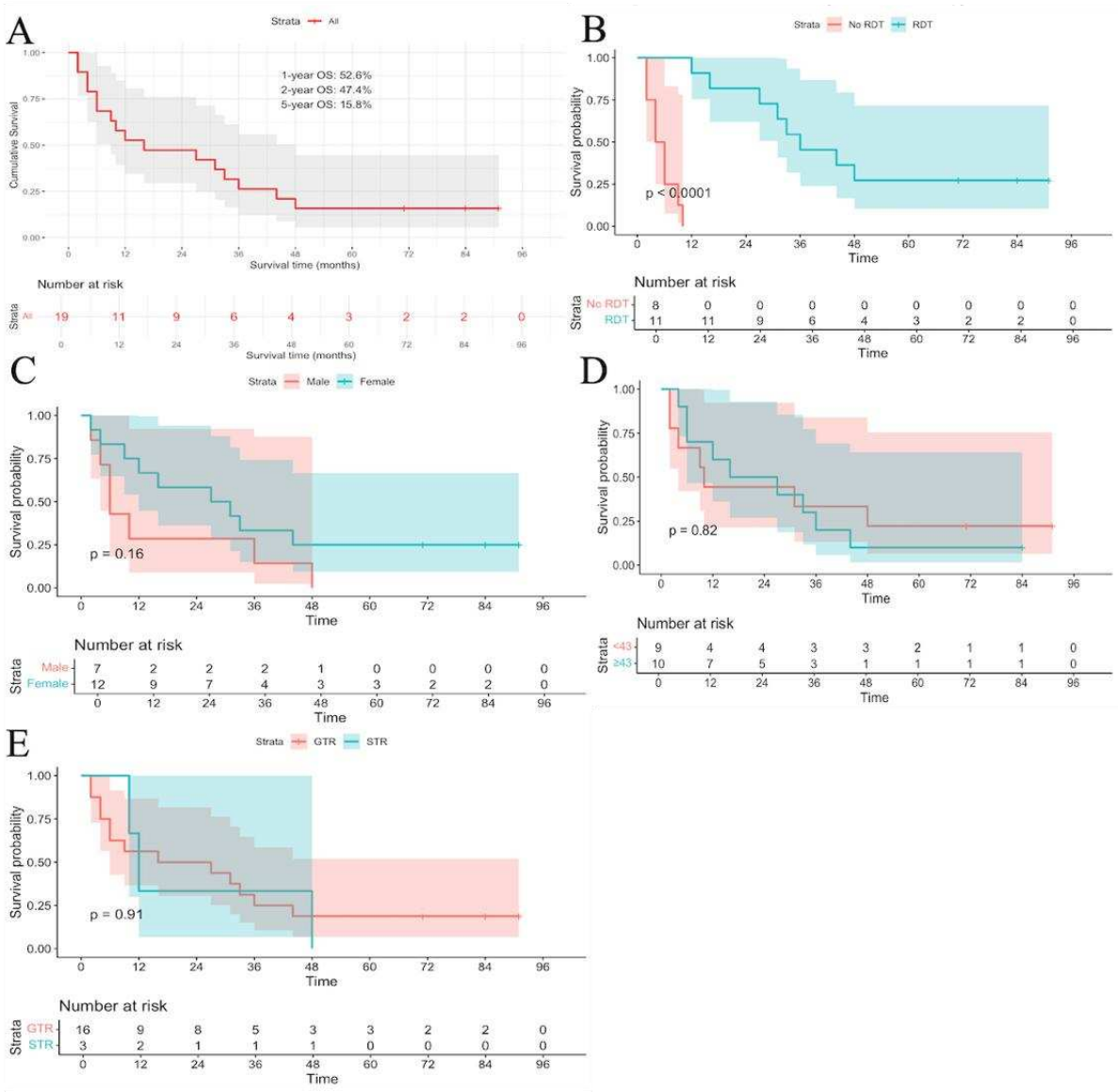

Figure 1. A: OS curve for patients diagnosed with malignant meningioma. **B:** Differences in OS for patients who received adjuvant radiotherapy versus those who did not. **C:** Differences in OS for males versus females. **D:** Differences in OS for patients aged < 43 versus ≥ 43 years. **E:** Differences in OS between patients receiving STR versus GTR. *Shaded areas* in the survival curves represent 95% confidence intervals. RDT = adjuvant radiotherapy; GTR = gross total resection; STR = subtotal resection.

DISCUSSION

Based on the results of this study, it can be inferred that the median OS of this cohort was 16 months, with estimated OS probabilities at 1, 2, and 5 years ranging from 15% to 52. In addition, we did subgroup analyses of the patients based on adjuvant radiotherapy. Our results showed significantly longer OS in the RDT group of patients compared to non-RDT patients, which implies the importance of postoperative RDT in the management of MM.

Malignant meningiomas are very rare and strongly linked to unsatisfactory patients' survival outcomes. A nationwide study in the USA found a 5-year OS rate of 41.4% among 755 patients with MM.[1] Similarly, the study by Seo et al. [1] at a single institution reported a 5-year OS rate of 47.9%, aligning with the results from the United States of America (USA) national cancer database. In contrast, our single-institution study conducted in Indonesia found a much lower 5-year OS rate of 15.8% for patients with MM, which is not comparable to the findings from either the

USA national cancer database[2] or the study of Seo et al.[1] Our study included only 19 patients, while similar studies accounted for 48 cases in Korea[1] and 29 cases in Germany.[6] In our cohort, there was a high incidence (36.8%) of discontinuation and/or refusal of adjuvant treatment. Individual interviews discovered that the main reason for this finding was a demographic problem. The majority of the patients were from the island of Kalimantan, which is a long distance from our institution on the island of Java, making travel hard and costly. Furthermore, some patients were also faced with travel restrictions due to the COVID-19 pandemic. Hence, this factor significantly affects the OS in our cohort.

Gross-total resection is a gold-standard treatment for all subtypes of meningiomas. However, compared to other subtypes of meningiomas, there have been few results on the correlation between surgery and survival outcomes in MM, because the number of cases is very limited. In our cohort, GTR had no statistically significantly better OS in MM patients. Sughrue et al.[10] reported that aggressive attempts to achieve GTR in MM patients has resulted in significantly poor neurologic outcomes. Furthermore, Tian et al.[14] showed that surgery did not significantly improve survival in high-grade meningiomas. Other authors mentioned similar survival outcomes measured using progression-free survival (PFS) and OS; both parameters did not improve significantly in correlation with the extent of resection.[12, 15] These results indicate that surgery alone cannot achieve better survival outcomes for MM patients, emphasizing the importance of adjuvant therapy in MM compared to other WHO grade meningiomas.

Previous literature has emphasized the importance of postoperative adjuvant radiotherapy for MM patients irrespective of the extent of previous surgery.[11] However, our findings did not show similar results to previous literature. The analyses performed in this study, both univariate and multivariate, revealed no statistically significant association between adjuvant radiotherapy and OS. The surveillance, epidemiology, evidence, and end results (SEER) database study revealed that postoperative radiotherapy in anaplastic/malignant meningioma populations has imparted significant survival benefits following both subtotal and gross-total resection compared to gross-total resection alone.[16] Others revealed that radiotherapy results in a better local tumor control.[7,11] Moreover, Zeng et al.[17] found that high-grade meningioma patients responded better to radiation doses of >60 Gy, which further improved patient's PFS.

Systemic chemotherapy has demonstrated limited efficacy and yielded negligible results in treating high-grade meningioma. Within our patient group, only one individual received doxorubicin-based chemotherapy. Regarding systemic treatments for MM, the evidence supporting the effectiveness of antiangiogenic agents such as bevacizumab, vatalanib, and sunitinib is scarce.[18] However, somatostatin receptor–targeted peptide receptor radionuclide therapy has indicated potential in decelerating the progression of recurrent meningioma that is refractory to treatment.[18] Ongoing research is investigating immunotherapies and targeted treatments guided by tumor molecular profiling or mutation burden.[18] Due to the infrequent occurrence of MM, a comprehensive multi-center study is vital for identifying effective therapeutic targets and establishing treatment efficacy.[18]

It has been suggested that men are relatively more associated with high-grade disease. Cao et al.[19] showed that men are more at risk of developing MM than women. However, in our study, the proportions of men and women are not statistically different due to their limited numbers. Further univariate analysis did not find a statistically significant association of sex with OS in MM patients. Other investigators have reported similar results.[20,21] Conversely, Cain et al.[9] found that the 3-year OS was elevated for females relative to males. Similarly, our univariate analysis indicated greater OS in women than men, despite the statistically nonsignificant results (Table 2).

Although prior research suggests that certain radiological features, including tumor size, location, peritumoral edema, a "mushroom" shape, as well as the presence of necrosis, cystic degeneration, and hemorrhage, can be indicative of specific histologic grades in meningiomas[22, 23], our univariate analysis found no statistically significant relationship between these radiologic features and survival outcomes in patients with MM.

Table 2. Significant prognostic factors for overall survival using Cox regression analysis

Variables	Overall Survival					
	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)						
<43	1.12	0.41–3.06	0.821			
≥43						
Sex						
Male	2.01	0.74–5.47	0.173	0.85	0.24–2.98	0.791
Female						
Location						
Superficial	3.26	1.07–9.89	0.042	2.73	0.87–8.56	0.083
Deep						
Tumor size						
<55 mm	0.37	0.13–1.07	0.648			
≥55 mm						
Edema index						
None–mild	1.54	0.57–4.15	0.391			
Moderate–severe						
Tumor shape						
Round	0.67	0.21–2.10	0.491			
Mushroom						
Extent of resection						
GTR	0.93	0.26–3.29	0.913			
STR						
Adjuvant radiotherapy						
No	0.00	0.00–3.24	0.100	0.00	0.00–1.79	0.923
Yes						

HR, hazard ratio; 95% CI, 95% confidence interval; GTR, gross-total resection; STR, subtotal resection

Taken together, this study highlights the significance of adjuvant radiotherapy as prognostic factors related to OS in MM patients. The findings suggest that postoperative radiotherapy should be routinely implemented following surgery to enhance the local control and tumor management. By recognizing these significant findings and integrating them with other factors such as achieving GTR, surgeons can tailor treatments more effectively and reduce the risk of long-term disability.

In the future, we suggest implementing multicenter studies with larger and more diverse patient populations, as well as genomic mutation analysis to validate these findings and improve the management strategies for MM patients.

CONCLUSION

To conclude, this study underscores the critical role of adjuvant radiotherapy following any extent of prior surgery in prolonging OS for patients with MM. Gross-total resection alone does not significantly lead to better long-term outcomes or control for these patients. Nonetheless, survival outcomes of MM remain unsatisfactory. Further research is necessary to enhance adjuvant therapy options and to incorporate mutation point analysis, which may contribute to improved outcomes for patients with this condition.

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Conflict of Interests

None to be disclosed.

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Author Contributions

All authors have reviewed the final version of the manuscript and agreed to be held accountable

for all aspects of work. YB, FES, KTP, DP, FRAS, MTA, ZM: concept and design: YB, FES, KTP, RI, FRAS: acquisition, analysis, or interpretation of data: YB, FES, RI: drafting of the manuscript: YB, DP, MTA, ZM: critical review of the manuscript for important intellectual content.

Data Availability Statement

The datasets generated or used in this study are available from the corresponding author on request.

Declaration the Use of AI in Scientific Writing

The authors declare that this manuscript involved the use of generative AI (ChatGPT, developed by OpenAI) during the writing process. The AI was utilized to assist with editing, paragraph restructuring, and refinement of academic phrasing. All AI-generated content has been critically reviewed by the author(s) to ensure intellectual integrity and adherence to academic standards.

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