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Trends in the use of radiation for meningioma across the United States

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Purpose: Meningiomas are tumors originating from arachnoid cap cells on the surface of the brain or spinal cord. Treatment differs by grade but can consist of observation, surgery, radiation therapy or both. We utilized the National Cancer Database (NCDB) to compare trends in the use stereotactic radiosurgery (SRS) and external beam radiation therapy (EBRT) in the management of meningioma.

Materials and Methods: We queried the NCDB from 2004–2015 for meningioma patients (grade 1–3) treated with radiation therapy, either SRS or EBRT. Multivariable logistic regression was used to identify predictors of each treatment and to generate a propensity score. Propensity adjusted Kaplan-Meier survival curve analysis and multivariable Cox hazards ratios were used to identify predictors of survival.

Results: We identified 5,406 patients with meningioma meeting above criteria with 45%, 44%, and 11% having World Health Organization (WHO) grade 1, 2, and 3 disease, respectively. Median follow up was 43 months. Predictors for SRS were grade 1 disease, distance from treatment facility, and histology. The only predictor of EBRT was grade 3 disease. Treatment year, histology, race and female sex were associated with improved survival. Five- and 10-year survival rates were 89.2% versus 72.6% ($p < 0.0001$) and 80.3% versus 61.4% ($p = 0.29$) for SRS and EBRT respectively. After propensity matching 226 pairs were generated. For SRS, 5-year survival was not significantly improved at 88.2% compared with EBRT ($p = 0.056$).

Conclusion: In the present analysis, predictors of SRS utilization in management of meningioma include WHO grade 1 disease, distance from treatment facility and histology whereas conventional EBRT utilization was associated with grade 2 and 3 disease. Future studies need to be performed in order to optimize management of atypical and malignant meningioma.

Keywords: Meningioma, Radiotherapy, Radiosurgery

Introduction

Meningioma is the most frequent primary central nervous system (CNS) tumor, accounting for 36% of all CNS tumors and 53% of non-malignant CNS tumors [1]. Since the work of Dr. Simpson in the 1950's [2], observation or maximal safe surgical resection has been the historically accepted management approach for meningiomas. More recently, radiation therapy including fractionated external beam radiation therapy (EBRT) and stereotactic radiosurgery (SRS) have been shown to provide durable local control either alone or in the postoperative setting [3]. Utilization of single fraction SRS has been increasing employed in the treatment of small to medium size meningiomas. Although multi-fraction SRS regimens are used, only one prospective trial examining this has been performed, for which long-term results have not yet been published [4]. Other studies using the National Cancer Database (NCDB) and Surveillance, Epidemiology, and End Results (SEER) databases have been performed recently to analyze trends in treatment and outcomes for the disease entity as a whole, however none have done this with a focus on radiotherapy and the use of SRS [5-7]. Keeping in mind that radiation treatment and techniques differ by grade and the known clinicopathologic data, we utilized the NCDB to examine trends in the use of radiation therapy for meningioma and assessed factors that led to the use of radiation as well as predictors of survival in these patients.

Methods and Materials

We queried the most recent NCDB dataset, which was from 2004–2015, for patients with a diagnosis of meningioma who were treated with radiation therapy alone or in conjunction with surgery. The NCDB dataset contains de-identified retrospective data; thus is exempt from the Institutional Review Board oversight. The NCDB is maintained and managed by the American College of Surgeons and the Commission on Cancer. The dataset incudes patients age 18 and above, and records clinicopathologic and treatment data in approximately 70% of newly diagnosed cancer patients each year across 1,500 centers in the United States. It includes the World Health Organization (WHO) grade at initial diagnosis and treatment details including: surgery, radiation, hormonal therapy, and systemic therapy (including immunotherapy or chemotherapy). Note that for systemic therapy, there are no details on type of chemotherapy or number of cycles received.

In terms of recorded radiation data, treatment technique, total dose, number of fractions, and anatomic target are all reported variables. We included patients treated with EBRT or SRS at doses between 12 Gy and 70 Gy to exclude treatment values that are not widely accepted. We then stratified treatment received by WHO grade and examined whether chemotherapy or surgery was used in conjunction with radiation therapy (Fig. 1).

The NCDB also includes various socioeconomic data points including race (Caucasian, African American, other), location (metropolitan, urban, rural), distance to treatment facility, and comorbidities—categorized using Charlson/Deyo index [8]. In addition, median household income and percentage of population with less than a high school education are reported based upon the patient's recorded zip code. Insurance data is also recorded and was categorized as none, private, or governmental (Medicare/Medicaid). Lastly, facility type was also recorded and is categorized as community cancer center, comprehensive community cancer center, or academic/research program as defined by the American College of Surgeons/Commission on Cancer.

Statistical analysis was performed using MedCalc version 18.0 (MedCalc Software, Ostend, Belgium). Median follow-up was recorded from time of diagnosis to last follow-up or death. Multivariable Cox regression was completed to identify predictors of overall survival [9]. Multivariable logistic regression was used to identify predictors of both EBRT and SRS and to calculate a propensity score identifying the likelihood of being treated with a SRS [10]. The propensity score was then used to create a matched set, upon which a Kaplan-Meier analysis was performed [11]. We repeated propensity score generation, matching, and Kaplan-Meier analysis for those patients with WHO grade 2 disease and WHO grade 3 disease who were treated with SRS. As required by the American College of Surgeons, we state that they have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data.

Results

Using the previously described selection criteria, we identified 5,406 meningioma patients, of which, 45% had WHO grade 1 tumors, 44% had grade 2 tumors, and 11% had grade 3 disease. The median age was 57 years (range, 18 to 90 years).

Thirty-eight percent of patients were male and 62% were female. Seventy 9% were Caucasian and the median size of treated tumors was 50 mm (interquartile range [IQR], 35 to 72 mm). Refer to Table 1 for a comprehensive description of patient characteris-

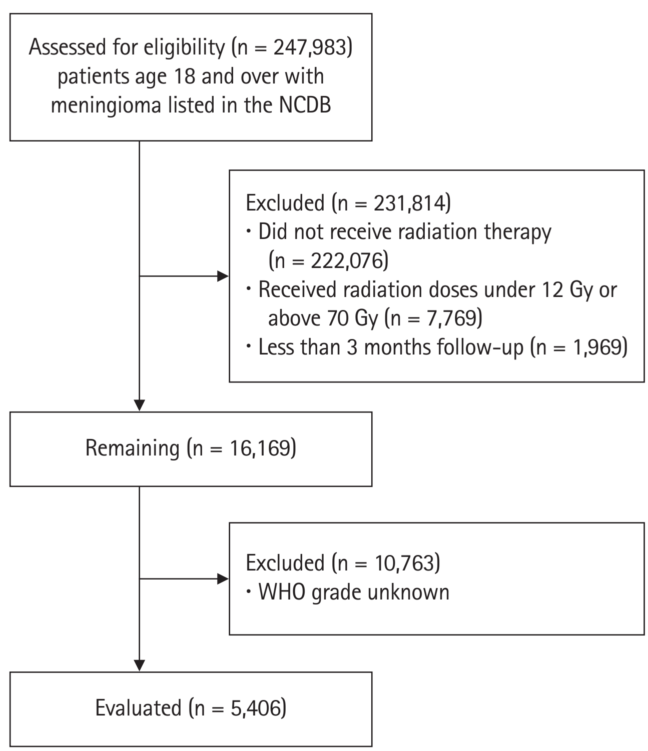

Fig. 1. Consort diagram of patients included in the analysis. NCDB, National Cancer Database; WHO, World Health Organization.

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tics. Regarding treatment details, 21.7% of patients received SRS with a median dose of 19 Gy (IQR, 14 to 25 Gy). Out of these, 674 (54.8%) received 1 fraction, 126 (10.3%) received 3 fractions, and 385 (31.4%) received 5 fractions. Median dose for EBRT patients was 54 Gy (IQR, 45 to 59 Gy) delivered over 30 fractions. Gross total resection occurred in 21.4% of patients, while 46.9% had a partial or gross total resection. A total of 90 patients (1.66%) received chemotherapy, 64% of which had WHO grade 3 tumors. Thirty-five percent of WHO grade 1 patients and 12% of WHO grade 2 patients received SRS. On multivariable logistic regression, the only predictor of EBRT was WHO grade 3 disease, although there is a strong trend toward EBRT with larger tumors (> 4 cm) (Table 2). Predictors of SRS were age under 57, increased distance to treatment facility, and having private insurance.

The median follow-up was 43 months (range, 3 to 165 months); 4,798 patients (88.7%) had follow-up over 12 months, 3,123 patients (57.8%) had follow-up greater than 3 years, and 1,846 (34.1%) patients had follow-up greater than 5 years (Supplementary Fig. S1). We utilized a Kaplan-Meier analysis to assess overall survival in patients receiving SRS or EBRT versus no radiotherapy. In the unmatched cohort of patients, median survival was 156 months ($p = 0.286$) for the EBRT group and median survival was not reached for the SRS group ($p < 0.0001$) (Figs. 2, 3). Five- and 10-year survival rates were 89.2% versus 72.6% and 80.3% versus 61.4% for SRS and EBRT, respectively. A multivariable logistic regression was then used, as explained in the methods section, to generate a propensity score which indicates the likelihood of being treated with SRS. A total of 226 pairs were created and median survival was again not reached, although there was a strong trend toward a survival benefit with SRS ($p = 0.056$). Survival in this

Table 1. Baseline patient characteristics (n = 5,406)

Characteristics	No. (%)
Race	
White	4,279 (79)
African American	782 (14)
Other	345 (6)
Sex	
Male	2,049 (38)
Female	3,357 (62)
Comorbidity score	
0	4,156 (77)
1	867 (16)
2	383 (7)
WHO grade	
1	2,407 (45)
2	2,383 (44)
3	616 (11)
Insurance	
Not insured	267 (5)
Private payer	2,856 (53)
Government	2,210 (41)
Unrecorded	73 (1)
Education (%)	
≥ 29	894 (17)
20–28.9	1,326 (25)
14–19.9	1,772 (33)
< 14	1,398 (26)
Not recorded	16 (0)
Treatment facility type	
Community cancer program	147 (3)
Comprehensive community cancer program	1,159 (21)
Academic/research program	3,428 (63)
Not recorded	672 (12)
Treatment facility location	
Metro	4,439 (82)
Urban	716 (13)
Rural	95 (2)
Not recorded	156 (3)
Income (US dollars)	
< 30,000	902 (17)
30,000–35,000	1,180 (22)
35,000–45,999	1,534 (28)
> 46,000	1,771 (33)
Not recorded	19 (0)
Distance to treatment facility (miles)	
≤ 14.2	2,714 (50)
> 14.2	2,692 (50)
Age distribution (yr)	
≤ 57	2,770 (51)
> 57	2,636 (49)
Type of radiation	
SRS	1,175 (22)
EBRT	5,023 (93)
Tumor size (cm)	
0–1.49	155 (3)
1.5–2.49	410 (8)
2.5–3.99	1,397 (26)
> 4.0	2,443 (45)
Not recorded	1,001 (19)
Systemic therapy (hormonal and/or chemotherapy and/or IO)	
No	5,316 (98)
Yes	90 (2)
Surgical extent	
No surgery	191 (4)
Biopsy	665 (12)
Partial resection	1,375 (25)
Complete resection	1,160 (21)
Not recorded	2,015 (37)

WHO, World Health Organization; SRS, stereotactic radiosurgery; EBRT, external beam radiation therapy; IO, immunotherapy.

Table 2. Multivariable logistic regression

Variable	Predict EBRT		Predict SRS	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (yr)				
≤57	Reference		Reference	
>57	1.14 (0.79–1.66)	0.48	1.44 (1.13–1.82)	0.0027*
Systemic therapy				
No	Reference		Reference	
Yes	3.77×E8 (NR)	0.99	2.92 (0.78–10.9)	0.11
Comorbidity score				
0	Reference		Reference	
1	0.70 (0.46–1.06)	0.09	1.01 (0.76–1.34)	0.97
2	1.26 (0.62–2.56)	0.53	1.08 (0.73–1.60)	0.70
Distance (miles)				
≤14.2	Reference		Reference	
>14.2	0.97 (0.67–1.39)	0.86	1.44 (1.14–1.81)	0.002*
Facility type				
Community cancer center	Reference		Reference	
Comprehensive community cancer center	0.52 (0.12–2.30)	0.39	1.30 (0.62–2.70)	0.48
Academic/research program	0.52 (0.12–2.24)	0.38	1.36 (0.66–2.80)	0.40
WHO grade				
1	Reference		Reference	
2	1.45 (0.85–2.46)	0.17	0.35 (0.24–0.51)	<0.0001*
3	3.60 (1.24–10.46)	0.019*	0.19 (0.08–0.42)	<0.0001*
Education (% w/o high school diploma)				
≥29	Reference		Reference	
20–28.9	1.16 (0.65–2.05)	0.62	0.97 (0.68–1.38)	0.85
14.0–19.9	1.12 (0.61–2.04)	0.72	1.00 (0.69–1.46)	0.98
<14	1.09 (0.55–2.16)	0.80	1.31 (0.85–2.01)	0.22
Income (US dollars)				
<30,000	Reference		Reference	
30,001–35,000	0.96 (0.52–1.76)	0.90	1.29 (0.89–1.87)	0.18
35,001–45,999	0.84 (0.45–1.57)	0.58	0.95 (0.64–1.41)	0.80
>46,000	0.65 (0.32–1.30)	0.22	1.04 (0.67–1.63)	0.85
Insurance				
None	Reference		Reference	
Private	0.58 (0.22–1.56)	0.28	1.95 (1.02–3.74)	0.044*
Government	0.64 (0.23–1.73)	0.37	1.71 (0.88–3.31)	0.11
Sex				
Male	Reference		Reference	
Female	0.93 (0.65–1.34)	0.70	1.22 (0.98–1.54)	0.08
Location				
Metropolitan	Reference		Reference	
Urban	0.82 (0.47–1.43)	0.49	1.06 (0.75–1.49)	0.74
Rural	1.79 (0.40–8.13)	0.45	0.97 (0.46–2.08)	0.94
Tumor size (cm)				
<1.49	Reference		Reference	
1.5–2.49	2.16 (0.97–4.84)	0.06	1.62 (0.92–2.84)	0.09
2.5–3.99	1.42 (0.73–2.74)	0.30	1.37 (0.82–2.29)	0.23
>4.0	2.03 (0.97–4.25)	0.06	1.03 (0.60–1.77)	0.92
Race				
Caucasian	Reference		Reference	
African American	0.82 (0.50–1.35)	0.44	0.68 (0.48–0.98)	0.037*
Other	1.76 (0.78–3.97)	0.17	1.04 (0.69–1.56)	0.86

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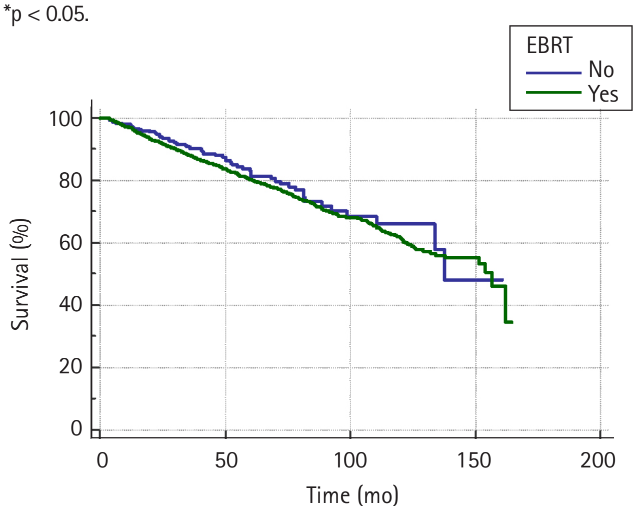
Table 2. Continued

Variable	Predict EBRT		Predict SRS	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Surgical extent				
None	Reference		Reference	
Biopsy	0.84 (0.29–2.42)	0.75	2.19 (0.99–4.86)	0.054
Partial resection	0.87 (0.30–2.56)	0.80	2.05 (0.92–4.58)	0.078
Complete resection	0.69 (0.22–2.19)	0.53	1.81 (0.79–4.19)	0.16

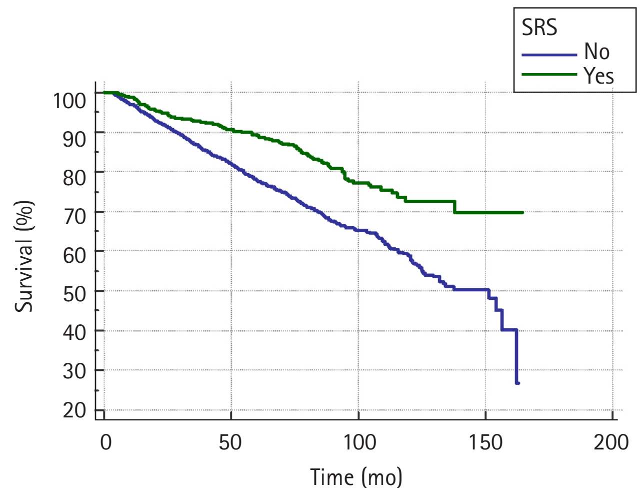
EBRT, external beam radiation therapy; SRS, stereotactic radiosurgery; WHO, World Health Organization; OR, odds ratio; CI, confidence interval; NR, not recorded.
*p < 0.05.



Number at risk

	0	50	100	150	200
Group: No	383	172	39	1	0
Group: Yes	5,023	2,179	490	31	0

Fig. 2. Overall survival for patients with meningioma receiving external beam radiation therapy (EBRT).



Number at risk

	0	50	100	150	200
Group: No	4,231	1,761	378	224	0
Group: Yes	1,175	590	151	8	0

Fig. 3. Overall survival for patients with meningioma receiving stereotactic radiosurgery (SRS).

matched group was also analyzed for patients with WHO grade 2 and 3 meningioma and revealed no significant effect on survival. On multivariable Cox regression, predictors of survival for all patients were treatment in a more recent year, non-Caucasian or African-American race, female sex and higher education rate. Patient age over 57, receipt of chemotherapy and WHO grade 2 or 3 disease predicted for worse survival (Table 3).

Discussion and Conclusion

Radiotherapy utilization in the management of meningioma is dependent on a number of factors including those related to the tumor (grade, size, location, prior surgery), as well as the patient. In our large series of meningioma patients treated with radiotherapy, predictors of SRS appear to be more closely associated with patient specific factors (i.e., distance from treatment facility, age under 57 and private insurance), whereas EBRT was associated with WHO grade 3 disease. Per NCCN guidelines [12], both SRS and EBRT are reasonable treatment approaches for WHO grade 1 tumors. As such, it is conceivable that patient related factors (i.e., convenience, access to care) may play a larger role in treatment related decisions when clinicians and patients have multiple efficacious options to select from. On the other hand, management options for WHO grade 3 meningiomas are often more limited (EBRT alone or surgery followed by EBRT) due to the extensive, infiltrative nature of the disease. Regarding predictors of improved overall survival, treatment in a more recent year, non-Caucasian or African-American race, female sex and higher education rate were all associated with improved outcomes. Receipt of chemotherapy and WHO grade 2 or 3 disease predicted for worse survival. These poor survival outcomes may be a consequence of higher grade tumors having more aggressive biology as shown in prior studies [13]. As stated above, a small number (1.66%) of patients in our study received chemotherapy, of which nearly two-thirds had WHO grade 3 tumors.

Table 3. Multivariable Cox regression for predictors of survival

Variable	HR (95% CI)	p-value
Age (yr)		
≤57	Reference	
>57	1.75 (1.31–2.33)	0.0001
Systemic therapy		
No	Reference	
Yes	1.78 (1.07–2.95)	0.0265
Year of diagnosis		
2004–2006	Reference	
2013–2015	0.31 (0.24–0.39)	<0.0001
WHO grade		
1	Reference	
2	1.49 (1.04–2.14)	0.03
3	3.84 (2.61–5.66)	<0.0001
Education (% w/o high school diploma)		
≥29	Reference	
20–28.9	1.08 (0.77–1.50)	0.663
14.1–19.9	0.73 (0.51–1.04)	0.0825
<14	0.49 (0.32–0.75)	0.001
Income (US dollars)		
<30,000	Reference	
30,001–35,000	1.25 (0.86–1.81)	0.2399
35,001–45,999	1.54 (1.06–2.25)	0.025
>46,000	1.34 (0.87–2.06)	0.189
Race		
Caucasian	Reference	
African American	0.99 (0.73–1.35)	0.956
Other	0.56 (0.32–0.97)	0.037
Sex		
Male	Reference	
Female	0.73 (0.59–0.91)	0.005

WHO, World Health Organization; HR, hazards ratio; CI, confidence interval.

Chemotherapy in this study was associated with worse overall survival, although this is likely a consequence of effect modification, as a majority of patients receiving chemotherapy had grade 3 disease, which portends a worse prognosis.

SRS and EBRT have advantages in distinct clinical scenarios. Factors that may impact the clinical decision to treat with SRS versus EBRT include tumor size, location, and prior radiation/surgery. For example, SRS may not be feasible in cases of larger tumors or in situations where the tumor is located near critical structures. In the aforementioned scenarios, EBRT is advantageous as smaller doses per fraction may help in reducing peritumoral edema and limiting toxicity. In contrast, SRS is typically favored in cases of smaller tumors or those in surgically inaccessible locations. Apart from practical advantages including shorter total treatment length, SRS allows for a smaller tumor treatment volume, a steep radiation fall-off that limits radiation dose to adjacent structures, and provides potential radiobiologic advantages (i.e., vascular damage and indirect cell death) over EBRT [14]. When dose constraints cannot be met with single fraction SRS, hypofractionated SRS can be considered, which has benefits including a shorter treatment course compared to EBRT, while still providing some of the same advantages of SRS. One prior study has shown statistically significant association between development of post-treatment peritumoral edema and single-fraction SRS versus hypofractionated SRS courses [15]. In addition, hypofractionated SRS is preferred over SRS for tumors larger than 10 cm^3 and multiple studies have shown excellent outcomes with low toxicity (less than 5%) [16].

While maximal safe resection remains the objective of treatment, management of meningioma and radiation modalities indicated differ by WHO grade. If total excision is achieved, WHO grade 1 meningioma can be managed by surgery alone, with a cause specific survival (CSS) of 93%, 80%, and 76% and 5, 10, and 15 years [17]. Outcomes with subtotal excision alone are significantly worse. About one-third of meningiomas are not completely resectable due to difficult locations, with significantly lower rates of complete excision, and thus, there is often a need for radiation in an adjuvant or definitive setting [18]. EBRT and SRS are acceptable radiation modalities for WHO grade 1 meningioma patients in these settings. Reported local control rates are comparable to that of surgery (approximately 90%) [19]. One study out of the Mayo Clinic compared patients with benign meningioma under 35 mm in average diameter [20]. At 3 and 7 years, actuarial progression-free survival was found not to be statistically different between SRS and Simpson grade 1 resection, respectively, 100% and 95% versus 100% and 96%. EBRT has been shown to provide similar control with one study out of University of Florida showing a 92% rate of local control at 10 and 15 years, including 66 patients who received radiation alone and 35 patients who received radiation after subtotal resection [21].

WHO grade 2 and 3 tumors tend to be larger and more aggressive, leading to a higher risk of recurrence and therefore more intensive treatment, often a multimodality approach is indicated. Based on the results of RTOG 0539, excellent local control can be achieved for patients with intermediate risk WHO grade 2 meningioma defined as those with recurrent tumors or subtotal resection, who received EBRT to a dose of 54 Gy in 30 fractions with a 3-year local failure rate of 4.1% [22]. WHO grade 3 patients were included in the RTOG 0539 high-risk cohort and after being treated with IMRT to 60 Gy in 30 fractions were found to have a 3-year local failure rate of 31.1%. The primary endpoint of this study, progression-free survival, was 58.8% at 3 years [23]. Multiple studies have

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looked at the use of SRS in WHO grade 2 patients; however there are no prospective trials assessing this treatment modality. One study out of Northwestern University reviewed records of 97 patients with WHO grade 2 meningioma treated postoperatively with Gamma Knife radiosurgery from 1998–2014 [24]. Three- and 5-year actuarial local control rates were 68.9% and 55.7%, respectively. Something notable from this study is that a range of doses was given, and that treating with doses > 14 Gy may increase tumor control. Another retrospective study by Aboukais et al. [25] examined 27 patients with WHO grade 2 meningioma who received SRS as well with a range of doses from 12–21 Gy. At 12, 24, and 36 months, local control was 75%, 52%, and 40%, respectively. Regional control for the same follow-up was 75%, 48%, and 33%. SRS for WHO grade 3 meningioma has been poorly studied and the performed studies have small numbers of patients, making it hard to draw definite conclusions. One study by Pollock et al. [26] analyzed a total of 50 patients with WHO grade 2 or 3 meningioma who underwent SRS from 1990 to 2008. The median number of prior resections was one, and 20 patients had enlarging tumors despite prior EBRT. Disease specific survival at 1 year and 5 years for the WHO grade III group was 69% and 27% compared with 97% and 80% for the WHO grade 2 group.

Some strengths of this study are that in a disease entity such as meningioma, where there are many options for therapy and upfront treatment is often observation or surgery, we have analyzed this dataset with a focus on outcomes, specifically after radiation therapy. SRS is used with good outcomes in early stage disease, and although some studies have looked at the use of SRS in more aggressive disease, we have analyzed outcomes for this population using a population-based set of patients, which can help to drive new hypotheses and trials in the future. Given that details regarding some important variables were not available, propensity matching was performed to limit potential biases, which confirmed a trend toward improvement in survival with SRS [27]. On the other hand, As this study is done retrospectively, there are limitations that we must keep in mind including an inherent selection bias due to the availability of SRS/EBRT treatment to patients depending on where they live and/or their socioeconomic status [28]. In addition, these patients likely have better overall access to care which could impact their survival. Other limitations of the study include lack of availability of speficic data that could affect interpretation of results, such as total treatment volume and exact radiation treatment location/treatment plan. In addition, the study was not designed specifically to assess survival and due to potential confounding of results, survival outcomes should be assessed with scrutiny.

In conclusion, the management of WHO grade 1 meningioma is well-defined and has excellent outcomes with the use of SRS or EBRT. For higher grade tumors, multi-modality treatment is often indicated, taking into account the availability of different treatment modalities and tumor location. Further research needs to be performed to optimize management and improve outcomes, including local control and overall survival.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2021.00563.

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