Toxicity of Radiosurgery for Brainstem Metastases

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BACKGROUND: **Although stereotactic radiosurgery (SRS) is an effective modality in the treatment of brainstem metastases (BSM), radiation-induced toxicity remains a critical concern. To better understand how severe or life-threatening toxicity is affected by the location of lesions treated in the brainstem, a review of all available studies reporting SRS treatment for BSM was performed.**

METHODS: **Twenty-nine retrospective studies investigating SRS for BSM were reviewed.**

RESULTS: **The rates of grade 3 or greater toxicity, based on the Common Terminology Criteria for Adverse Events, varied from 0 to 9.5% (mean 3.4 ± 2.9%). Overall, the median time to toxicity after SRS was 3 months, with 90% of toxicities occurring before 9 months. A total of 1243 cases had toxicity and location data available. Toxicity rates for lesions located in the medulla were 0.8% (1/131), compared with midbrain and pons, respectively, 2.8% (8/288) and 3.0% (24/811).**

CONCLUSIONS: **Current data suggest that brainstem substructure location does not predict for toxicity and lesion volume within this cohort with median tumor volumes 0.04–2.8 cc does not predict for toxicity.**

INTRODUCTION

Stereotactic radiosurgery (SRS) for brainstem metastases (BSM) has been shown to be a safe and effective modality.[1-31] Reported rates of local tumor control in patients who received SRS for BSM vary from 74% to 100%, and the median survival ranges from 4 to 12 months.[1-28,30,31] Despite the promising results of SRS with respect to local control and survival, toxicity due to radiation is always a concern, with severe to life-threatening toxicities being reported in 0%–9.5% of patients with BSM treated with SRS.[2-10,12-14,16-18,20-28,30,31] The majority of papers have not analyzed the impact of location on toxicity or volume of lesions on toxicity.[2-10,12-14,16-18,20-28,30,31] As the result of a relatively small sample size, the preferred dose to treat BSM remains controversial, with the literature varying on the dosing strategies.[2-10,12-14,16-18,20-28,30,31] This review paper aims to synthesize the collective literature available on SRS to BSM.

METHODS

To identify brainstem location specific toxicity after SRS, "brainstem metastases radiosurgery" was searched as a key word in PubMed and Ovid (Medline). Primary literature specific to treatment of BSM with SRS was reviewed. Only retrospective studies of patients treated with SRS for BSM were available; (shown in Figure 1). This literature review does not include BSM that are described in larger non-brainstem studies. Some authors were contacted for the details regarding the reported toxicities.[2,15,30] Of the 2 papers by Trifiletti et al. including the institutional and international papers, only the data from the institutional paper, which provided the pertinent information, were used for the location based toxicity analysis to avoid duplicate inclusion of cases.[22,23] The remainder of papers were included with no obvious concern for duplication in reported cases. For 1 report that did not specify the number of lesions per patient, the number of lesions were assumed to be equal to the number of patients for the purposes of this review ($n = 41$).[18]

Key words
- Brainstem
- Metastasis
- Stereotactic radiosurgery
- Toxicity

Abbreviations and Acronyms
BSM: Brainstem metastases
SRS: Stereotactic radiosurgery
WBRT: Whole-brain radiation therapy

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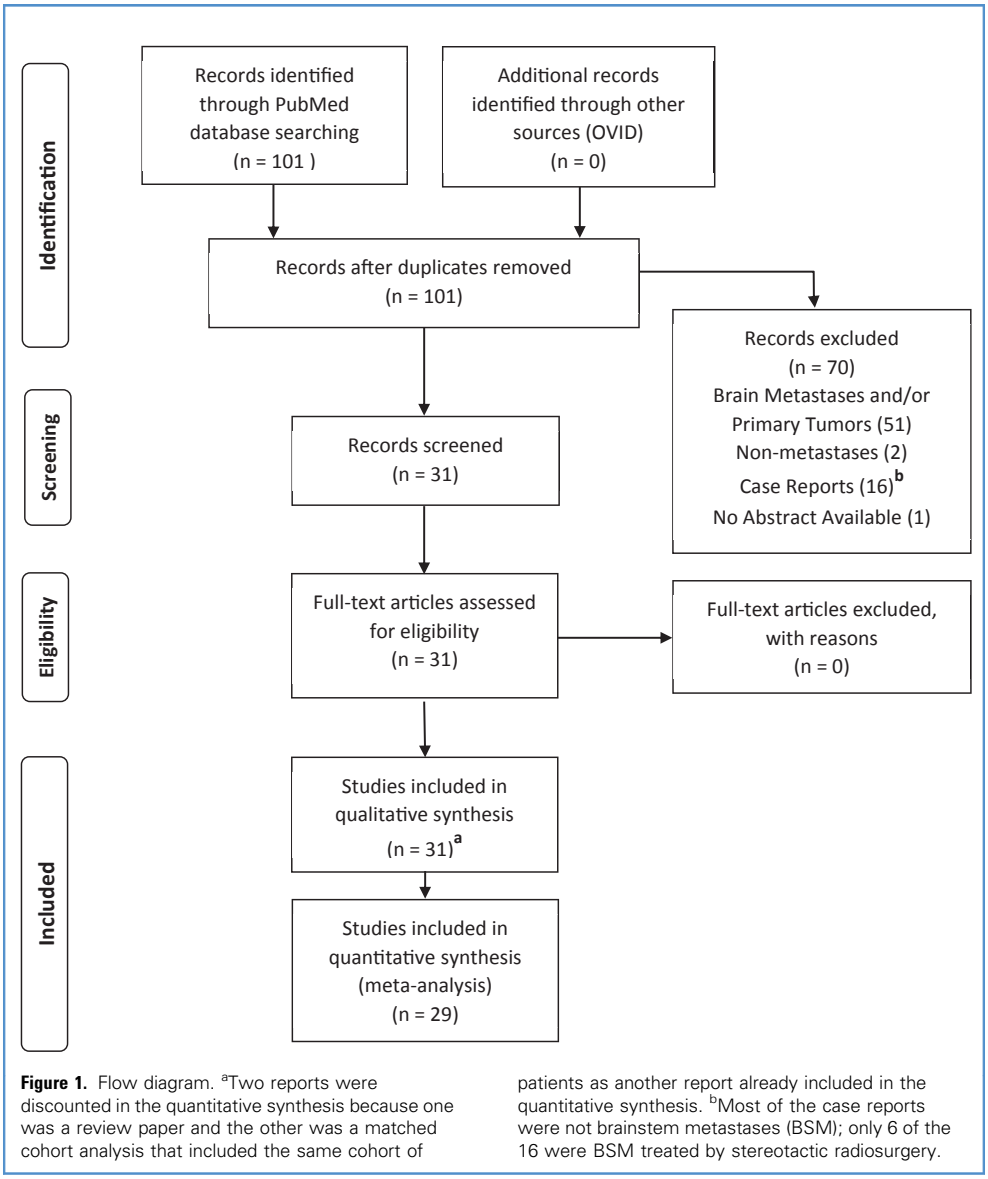

Figure 1. Flow diagram. [a]Two reports were discounted in the quantitative synthesis because one was a review paper and the other was a matched cohort analysis that included the same cohort of patients as another report already included in the quantitative synthesis. [b]Most of the case reports were not brainstem metastases (BSM); only 6 of the 16 were BSM treated by stereotactic radiosurgery.

The following data were collected from each manuscript: method of SRS, total number of patients, total number of lesions, locations of lesions, median or mean age, median or mean Karnofsky Performance Status, median or mean prescription dose (most reports included only margin dose information and prescription isodose information was often not available), number of patients who received whole-brain radiation therapy (WBRT), mean or median survival after SRS, local tumor control rate, radiation-induced toxicity, and mean or median tumor volume. The mean rate of local control, toxicity, and WBRT were calculated based on values in all reports.

For this analysis, only toxicities of grade 3 or greater were included in this review.[32] Not all reports explicitly stated whether the toxicity was grade 3 or greater based on the Common Terminology Criteria for Adverse Events, but it was inferred based on the description of toxicity and treatment if it could be classified as grade 3 or greater. For example, if a manuscript described a case of toxicity in which radionecrosis was refractory to steroids, then this was counted as a toxicity grade 3 or greater. The details of the grading of toxicity are presented in Table 1. Grade 2 toxicity could not be reviewed because there was no specification on exactly how many patients developed grade 2 toxicities in the manuscripts. There were 2 papers by Trifiletti et al. that could have obscured the data, so care was taken to avoid this. In one instance, the institutional data were removed to tabulate the occurrence of metastases in the substructures and in the other instance the international paper by Trifiletti et al. was removed because it did not report both location and toxicity. This was clarified by the authors of the paper as well.

Table 1. Relevant Nervous System Specific Toxicity Grading for Adverse Events from NIH NCI CTCAE

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
General	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.	Life-threatening consequences; urgent intervention indicated.	Death related to AE.
Edema	—	—	—	Life-threatening consequences; urgent intervention indicated.	
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated.	Moderate symptoms; medical intervention indicated.	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated.	Life-threatening consequences; urgent intervention indicated.	Death
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated.	Moderate symptoms; corticosteroids indicated.	Severe symptoms; medical intervention indicated.	Life-threatening consequences; urgent intervention indicated.	Death

NIH NCI CTCAE, National Institutes of Health National Cancer Institute Common Terminology Criteria for Adverse Events; ADL, activities of daily living; AE, adverse events; ICP, intracranial pressure.

The following variables were included when tabulating the toxicities, to the extent available: sex, age, primary cancer histology, location of treated lesion, volume of tumor, dosage of SRS, whether WBRT was given, the type of toxicity, time to toxicity from SRS treatment, and status of local control. An unpaired *t* test was used to compare the means of the volumes of the lesions with toxicity and those without toxicity.

RESULTS

The searches identified 29 retrospective studies of BSM treated with SRS published from 1999 to 2017. The details of these reports are summarized in **Table 2**,[1-10,12-28,30,31] listed chronologically and by first author. SRS modalities reported include Gamma Knife, linear accelerator, and Cyber Knife. A total of 2037 SRS-treated metastases were reported in 1878 patients. The median age ranged from 50 to 69 years old, and the mean age ranged from 52.9 to 64 years old. The median Karnofsky Performance Status ranged from 70 to 90.

Summary of Literature

Of 29 reports, 26 specified the locations of the lesions. One report did not account for the location of 8 of 52 lesions, and 2 other reports did not comment on the location of BSM.[9,10,18] This resulted in a total of 1945 lesions with the location of the BSM specified; the most common location was the pons, representing 62.8% (1222/1945) of the cases; the midbrain was the next most common, representing 22.4% (436/1945) of cases; and 9.6% (186/1945) of cases were found in the medulla. Other structures represented 5.2% of cases; the pontomesencephalic junction accounted for 2.7% (52/1945) of cases, the pontomedullary junction accounted for 1.4% (27/1945) of cases, and the cerebellopontine angle that extended into brainstem proper accounted for 1.2% (24/1945) of cases. Removing the institutional report by Trifiletti et al. to avoid accounting for some patients twice resulted in 22.8% (400/1756) of cases in the midbrain, 62.2% (1093/1756) in the pons, 9.8% (172/1756) in the medulla, and the other 5.2% in junctions among the substructures of the brainstem.[23]

The radiosurgery characteristics were as follows. The median prescription dose ranged between 13 and 18 Gy. WBRT before or after SRS ranged from 6.5% to 96.4%, with the mean being 48.4 ± 19.8%. The local control rate at 12 months varied from 74% to 100%. The median overall survival ranged from 3.9 to 17.2 months. The local control rate at 12 months based on the mean of all the reported values in literature turned out to be 86.7 ± 5.9%, all but one manuscript reported local control rates at 12 months.[12] Removing the institutional study by Trifiletti et al. resulted in less than 1% variation in the mean of the local control rate.[23] The median tumor volume ranged from 0.04 to 2.8 cc, and the mean tumor volume ranged from 0.7 to 2.8 cc.

Toxicity

A total of 2037 cases were reviewed; 58 were excluded for lack of comments on toxicity.[1,19] A total of 79 patients were reported in the literature to have suffered from toxicity of 1979 potential cases. Rate of toxicity reported in patients treated with SRS for BSM varied from 0% to 9.5%. The average rate of toxicity based on reported percentages per report was 3.4 ± 2.9%.

To analyze location-based toxicity, 1979 cases reviewed, 84 were excluded because there was no comment on location,[10,18] and 644 were excluded for lack of location associated with toxicity.[17,22] This resulted in 1251 cases that commented on both location and toxicity. It is imperative to note that this exclusion accounted for any potential overlap between the studies of Trifiletti et al. and only the institutional one was used for the location-based toxicity analysis.[22,23] In the studies that contained locations of toxicities, 23.0% (288/1251) of all treated BSM were in the midbrain, 64.8% (811/1251) in the pons, and 10.5% (131/1251) in the medulla. An

Table 2. Summary of BSM Treated by SRS Studies

Author	Method	Patients/Lesions	Location Mb/(MP) /Po/(PM)/ Mu/(CP)	Median Age, Years	Median KPS	Median Margin Dose, Gy	No. Patients with WBRT	Median Survival, Months	Local Tumor Control Rate, %	Toxicity, %	Median Tumor Volume, cc
Huang et al., 1999[3]	GK	26/27	6/21/0	56*	80*	16	24/92%†	9	95	0	1.1
Shuto et al., 2003[21]	GK	25/31	10/19/2	57.1*	NR	13*	7/28%†	49	77.4	8	2.1*
Fuentes et al., 2006[1]	GK	28/28	9/17/2	57.7*	80*	19.6*	6/21%†	12	92	NR	2.1*
Yen et al., 2006[26]	GK	53/53	8/42/3	57.3*	80	18	21/40%	11	86.5	0	2.8*
Hussain et al., 2007[28]	GK	22/25	9/12/4	60	90	16	3/14% (after)	8.5	100	4.5	0.9
Kased et al., 2008[6]	GK	42/44	7/31/6	55	90	16	24/57%†	9	77	9.5	0.3
Lorenzoni et al., 2009[16]	GK	25/27	9/14/4	54*	90	20*	17/68%†	11.1	95	0	0.6*
Samblas et al., 2009[19]	LINAC	28/30	8/20/2	52.9*	NR	11.1*	27/96.4%†	16.8*	96.4	NR	1.9*
Koyfman et al., 2010[10]	GK	43/43	NR	59	80	15	34/79%†	5.8	85	0	0.4
Valery et al., 2011[24]	LINAC	30/30	9/16/5	57	80*	13.4	8/27%	10	79	0	2.8
Kelly et al., 2011[8]	LINAC	24/24	10/13/1	57	80	13	23/96%	5.3	78.6	8.3	0.2
Yoo et al., 2011[27]	GK	32/32	6/23/3	56.1*	NR	15.9	NR	7.7*	87.5	3.1	1.5*
Hatiboglu et al., 2011[2]	LINAC	60/60	15/39/6	61	90	15	15/25%†	4	76	3.3	1
Lin et al., 2012[14]	LINAC	45/48	7/35/6	59.9*	80	14	21/44%	11.6	88	4.7	0.4
Leeman et al., 2012[12]	LINAC	36/38	11/25/2	62	80	17	18/47%	3	93‡	0	0.9
Li et al., 2012[13]	GK	28/32	8/21/3	61	80	16	0/0%	9	90.6	3.6	0.8
Kawabe et al., 2012[7]	GK	200/222	65/121/36	64*	90	18	13/6.5%	6	81.8	0.5	0.2
Sengoz et al., 2013[20]	GK	44/46	14/30/2	57	80	16	29/66%†	8	96	0	0.6
Jung et al., 2013[5]	GK	32/32	9/18/5	50	NR	13	19/59%†	5.2	87.5	0	0.7
Peterson et al, 2014[18]	GK	41/?	NR	59	NR	17*	19/46%	4.4	91	2.4	0.7*
Kilburn et al., 2014[9]	GK	44/52	9/(3)/28/4§	57	80	18	25/57%	6	74	9.1	0.1
Voong et al., 2015[25]	GK	74/77	11/60/6	59	90	16	43/58%†	3.9	94	8	0.1
Liu et al., 2016[15]	CK	54/66	12/49/5	59	70	17.9f	34/51.5%‖	5	80	1.5	0.1
Trifiletti et al., 2015[23]	GK	161/189	36/129/14/(10)	60.5	80	18	83/51.6%	5.5	87.3	1.8	0.4
Joshi et al., 2016[4]	GK	48/51	10/34/7	62	90	15	19/40%	7.6	89	4	0.1
Trifiletti et al., 2016[22]	GK	547/596	126/(44)/345/ (22)/45/(14)	61	90	16	266/49%	5.5	81.8	7.4	0.8
Murray et al., 2017[17]	GK	44/48	5/(3)/29/(5)/6	58	NR	15	33/75%†	5.4	76.9	8.3	1.3

Nakamura et al., 2017[30]	CK	20/26	4/18/4	69	90	16.4¶	5/19%#	11.5	90	5	0.33
Patel et al., 2018[31]	GK	14/19	3/13/3	56	85	17.5	6/42.8% †	17.2	87.5	0	0.04
Total		1878/2037	436/(50)/1222/(27)/186/(24)				48.4 ± 19.8%		86.7 ± 5.9	3.4 ± 2.9	

BSM, brainstem metastases; SRS, stereotactic radiosurgery; Mb, midbrain; MP, pontomesencephalic junction, Po, pons; PM, pontomedullary junction; Mu, medulla; CP, cerebellopontine angle; KPS, Karnofsky Performance Status; WBRT, whole-brain radiation therapy; GK, Gamma Knife; NR, not reported; LINAC, linear accelerator; CK, Cyber Knife.
*The mean value is reported instead of the median.
†Patients received WBRT either before or after with no specification in manuscript or it was unclear whether patients received WBRT before or after.
‡This is the local tumor control rate at 6 months; the others are reported at 12 months.
§Location of other 8 lesions not specified in report.
||The number of lesions that received WBRT were reported, not number of patients.
¶Single-session equivalent dose.
#Lesions receiving WBRT, not patients.

additional 8 lesions did not account for the location in 1 report and the other 1% of lesions were either in the cerebellopontine angle or midbrain pons junction.[9] The rates of grade 3 or greater toxicity associated with treatments to metastases in the midbrain, pons, and medulla were 2.8% (8/288), 3.0% (24/811), and 0.8% (1/131), respectively.

To compare treatment and tumor characteristics among the substructures, 7 reports were examined that commented on both toxicity and location, with patient level data available for 260 cases (of 1251 possible).[6,15-17,21,28,31] One report was missing tumor volume data for 3 lesions.[6] A total of 30 patients had metastases that were treated in the medulla. The median volume was 0.5 cc (mean 1.1 cc, range 0.01–12.2 cc). The median prescription dose was 16 Gy (mean 16.8 Gy, range 10–24 Gy). In the midbrain, 56 cases were reported with 16 Gy as the median prescription dose (mean 16.7 Gy, range 8–24 Gy) and 0.3 cc as the median volume (mean 0.8 cc, range 0.01–6.1 cc). In the pons, 174 cases were available with a median prescription dose of 16 Gy (mean 16.3 Gy, range 8–24 Gy) and a median volume of 0.3 cc (mean 1.2 cc, range 0.004–12 cc), suggesting that treatments and lesions were similar among the brainstem substructures in the subset of patients with available data.

To compare the volumes of the lesions with and without toxicity, the same 7 reports from the previous paragraph were used. This resulted in 260 possible patients that could be analyzed based on patient level data available and development of toxicity.[6,15-17,21,28,31] For the lesions that developed toxicity ($n = 10$), this resulted in a mean volume of 1.6 ± 1.0 cc. For the rest of the patients in the reports ($n = 247$), the mean volume was 1.1 ± 1.2 cc. The 2-tailed P value equals 0.2 for the comparison of these 2 means.

The reported 79 cases with toxicity were reviewed to summarize patient and treatment factors potentially associated with toxicity. Only 35 of the 79 toxicity cases reported in the literature were described in more detail.[2,4,6-9,13,14,17,18,21,23,25,27,28,30] The details of the 35 cases are summarized in **Table 3**. In this toxicity cohort, 22.8% of cases were in the midbrain, 68.6% in the pons, 2.9% in the medulla, and 5.7% did not have a location reported. All reported toxicities occurred before 18 months and with a median time to toxicity of 3.0 months. The median prescription dose was 15 Gy for midbrain cases and 16.3 Gy for pons cases. Midbrain BSM had a median volume of 0.9 cc (range: 0.1–3.3 cc) and pons cases a median volume of 1.3 cc (range: 0.1–5.8 cc).

DISCUSSION

Radiosurgery has consistently been proven to be a safe and effective treatment for BSM, yet toxicity remains a concern for both the patient and physician.[1-28,30,31] The last review article that addressed clinical outcomes after SRS for BSM was published in 2013 and synthesized 12 reports.[11] Based on limited number of cases in previously published reports about BSM, it has been difficult to synthesize data and comment on the treatment preferences for BSM and other characteristics that influence toxicity rates. Thus, a review of the available literature was performed to comment on the varying doses used in the literature and analyze the rate of radiation induced toxicities with respect to different locations in the brainstem and volume.

Table 3. Characteristics of the 35 Detailed Reports of Toxicity in the Literature

Total 35 Cases	Median/Percentage
Age (17), years	
30—73	59
30—50	17.6%
50—60	41.2%
>60	41.2%
Sex (22), M/F	
13/9	59%/41%
Histology (29)	
NSCLC	24.1%
SCLC	3.4%
Breast	13.8%
Melanoma	24.1%
RCC	10.3%
Thyroid	3.4%
Sarcoma	3.4%
Colon	3.4%
Ovarian	3.4%
Unknown	10.3%
Location (34)	
Midbrain	23.5%
Pons	73.5%
Medulla	2.9%
Tumor volume (29), cc	
0.1—5.8	1.4cc
0—1	41.4%
1—2	34.5%
>2	24.1%
Margin dose (31), Gy	
12—20	16
12—15.9	35.5%
16—17.9	22.6%
≥18	41.9%
WBRT (15)	
Yes	33.3%
No	66.7%
Toxicity (27)	
Hemorrhage	29.6%
RN	29.6%
Edema	25.9%
Edema and RN	7.4%
RN and HMG	3.7%
Unknown*	3.7%
Time to toxicity from SRS (30), months	
0—18	3 months
≤3	60.0%
≤6	83.3%
≤9	93.3%
≤18	100%
Local failure (16)	
Yes	18.8%
No	81.2%
Dose by location (31)	
Midbrain (6)	15 Gy
12—15.9 Gy	50.0%
16—17.9 Gy	16.7%
≥18 Gy	33.3%
Pons (24)	16.3 Gy
12—15.9 Gy	25.0%
16—17.9 Gy	29.2%
Medulla (1)	
≥18 Gy	45.8%
15 Gy	100%
Tumor volume by location (29)	
Midbrain (6)	0.9 cc
0—1 cc	50%
1—2 cc	33.3%
>2 cc	16.7%
Pons (22)	1.3 cc
0—1 cc	40.9%
1—2 cc	31.8%
Medulla (1)	
>2 cc	27.3%
1.3 cc	100%

The number in parentheses after the characteristic is the number of 35 that reported that specific detail.
M, male; F, female; NSCLC, non—small cell lung cancer; SCLC, small cell lung cancer; RCC, renal cell carcinoma; WBRT, whole-brain radiation therapy; RN, radionecrosis; HMG, Hemorrhage; SRS, stereotactic radiosurgery.
*Unknown due to no imaging.

Table 2 shows that the most common site of BSM is unequivocally the pons. The median prescription dose varied from 13 to 18 Gy. The mean local control rate was 86.7 ± 5.9%, with the rate of toxicity being 3.4 ± 2.9%.

Interestingly, the median time to development of toxicity from SRS to BSM was 3 months, with greater than 90% occurrence before 9 months. In contrast, lesions in the cerebral parenchyma exhibited median time to toxicity at 4.5 months (range: 0.5–36.0 months) in randomized controlled trials.[33] In another randomized controlled trial evaluating the combination of SRS and WBRT for brain metastases in which 9% of the patients developed toxicity; one third of the 9% developed toxicity before 3 months and the other two thirds after 3 months.[34] Reasons for the accelerated onset of toxicity associated with brainstem lesions remain to be determined but may be due to lack of compressibility in the surrounding space for edema compared with the cerebral hemispheres.

Consistent with previous reports suggesting that both melanoma and renal cell carcinoma are known to spontaneously result in intracranial hemorrhages,[35,36] 4 of the 6 melanoma BSM toxicities and 1 of the 3 renal cell carcinoma toxicities were hemorrhages. Based on the aforementioned results of the 35 toxicities summarized in Table 3, development of toxicity occurs at a variety of prescription doses of SRS. The median prescription dose of cases with reported toxicity was 16 Gy, and two thirds of the cases were accounted for by a prescription dose up to 18 Gy. It has previously been reported that greater doses lead to more toxicity, but based on the data in Table 3, it seems toxicity can occur at a wide range of doses.[22] Patient-level data on tumor volume or radiation dose were not available in all toxicity cases for this analysis. Thus, the impact of tumor volume and radiation dose on toxicity could not be analyzed on a larger scale in a location-specific manner.

Interestingly, only one toxicity in the medulla was reported. A large study reporting 44 grade 3 and greater toxicities concluded that location did not predict toxicity.[22] Location-specific toxicity data were not available in this report and thus was not incorporated into the location analysis. Location-specific treatment volumes and radiation dose are reported only on a small subset of patients, and thus there is a possibility that treatment preferences and lesion characteristics based on location differ.[6,16,21,28] Six case reports were excluded from the review that involved BSM treated via SRS, but none of the lesions in those reports were in the medulla.[37-42] The greater prevalence of toxicity in pontine lesions is likely associated with the frequency of occurrence of BSM in the pons.

There are several limitations to this report. Given the design of this study, it is inherently limited by the quality of the reports included. For instance, the prescription dose was commonly reported as the "marginal dose," with no reference of the isodose line to which the prescription dose was defined in the majority of the studies. Sadly, in retrospective studies planning details such as rapid dosage drop to the surrounding parenchyma are not easily reported and this could lead to variation in the data. It should be noted that not all studies detail treatment or lesion characteristics of BSM. It is also uncertain whether the reports that do include specific details are representative of the broader series. These data also might not be representative of the percentage of patients who develop toxicity after SRS to BSM, because many patients might not survive long enough for toxicities to develop. Further investigations might provide more insight into treatment preferences and why/if medulla toxicities are truly rare.

CONCLUSIONS

In conclusion, for BSM treated via SRS, the median prescription doses vary from 13 to 18 Gy, with a local control rate of 86.7 ± 5.9% and a rate of toxicity of 3.4 ± 2.9%. The most common site of BSM is the pons. The median time to toxicity is 3 months for BSM treated by SRS. The current literature reports that some BSM may be safely treated with a prescription dose of up to 18 Gy or more and that volume and location do not predict for toxicity. More research is needed to further clarify these trends. These data show that no recipe for safe treatment of BSM does (yet) exist, but in most cases local tumor control can be achieved with acceptable toxicity.

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