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Radiosurgical Management of Brainstem Metastasis

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ET and US designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AK, NKD, SS and EYA managed the analyses of the study. Authors EDI, YB and BP managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Brainstem metastases account only for 3% to 5% of all intracranial metastasis. However, brainstem metastases undoubtedly represent a significant source of severe morbidity and mortality in affected patients with estimated average survival duration of only less than 6 months. Surgical resection is not suitable for most brainstem metastases due to the vital architectural structure of the brainstem. What's more, most conventional chemotherapeutics and targeted agents are ineffective on account of their low blood-brain-barrier penetration capacities. Accordingly, palliative short-course whole-brain radiotherapy stays to be the present standard of care for brainstem metastases. Nonetheless, the limited efficacy of WBRT and related neurocognitive toxicity concerns prompted eagerness on the utilization of stereotactic radiosurgery for brainstem metastases in like manner the cerebral and cerebellar metastases. In a shortage of reliable large series outcomes, the present review article

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meant to succinctly summarize the current stereotactic radiosurgery evidence on brainstem metastases with an explicit accentuation on the feasibility and efficacy of this novel sophisticated radiotherapy technique in such patients' groups of bleak prognoses.

Keywords: Brainstem metastases; stereotactic radiosurgery; local control; survival; complications.

1. INTRODUCTION

Brain metastases are most frequent intracranial tumors with an incidence range of 15% to 40% of adult patients [1]. Likely being related to the distinct bloodstream rates, 80% and 15% of all brain metastases are diagnosed in the cerebral hemispheres and cerebellum, individually [2]. Though the brainstem metastases (BSMs) constitute only 3% to 5% of all intracranial metastasis, yet this patient group has the worst prognosis with an average survival estimate of less than 6 months [3]. Despite perineural spread and direct invasion is conceivable; still, most BSMs are reported to result from the hematogenous systemic metastasis of index primary tumors [4]. Hypothetically, any tumor type may metastasize to the brainstem; however, Yen et al. indicated *that the tumors with the highest BSM were* lung-, breast-, renal cell-, and colon carcinomas [5].

The BSMs represents a significant cause of morbidity and mortality in patients presenting with this type of metastasis. Palliative short-course whole brain radiotherapy (WBRT) has long been considered to be the unique standard of care for BSMs [6]. Surgical resection is not suitable for most BSMs due to the special architectural traits of the brainstem, which constitutes dense concentrates of vital neural tracts and nuclei. Likewise, chemotherapy and targeted agents are of restricted viability because of their low blood-brain-barrier penetration capacities. In this respect, the limited efficacy of WBRT and related neurocognitive toxicity concerns led to enthusiasm on the use of stereotactic radiosurgery (SRS) for BSMs likewise the brain metastases with the expectations of similar excellent tumor control and severe toxicity rates [7].

Present review article aims to summarize the accessible BSM-SRS literature in terms of its viability in local control (LC), safety profile, and factors influencing these issues as well as the survival outcomes.

2. STUDIES EVALUATING BSM-SRS

Several researchers have investigated the usefulness of the SRS method in patients presenting with BSMs. However, most of these investigations were retrospective cohort analyses consolidating fewer than 50 patients (Table 1).

In a 1999 study, Huang et al. audited the results of 26 patients with 27 BSM who experienced BSM-SRS [8]. Most BSMs were located in the pons (N=21) followed by the medulla oblongata (N=6). The median tumor margin dose was 16 Gy (range: 12-20 Gy). At a median follow-up time of 9.5 months (range: 1-43 months), the LC for BSMs was 95% with a median overall survival (OS) of 9.0 months after the BSM-SRS. The authors reported that 18 of 24 deaths (75%) were owing to the extracranial disease progression with no BSM-related death in the remaining 6 cases.

In 2003, Shuto et al. reported the outcomes of retrospectively reviewed 25 patients with 31 BSMs who underwent gamma knife radiosurgery (GKRS) [9]. The mean BSM volume and prescription margin dose were 2.1 cm^3 and 13.0 Gy, respectively. Overall LC rate was 77.4% at a mean follow up of 5.2 months, with radiation-induced injury being experienced by only 2 (8%) patients.

In 2006, Fuentes et al. [10] and Yen et al. [11] reported the outcomes of 28 and 53 patients who underwent BSM-SRS, respectively. In the Fuentes's series the mean marginal GKRS dose was 19.6 Gy (range: 11-30 Gy). The maximum BSM diameter ranged between 10 to 30 mm with a mean of 17.2 mm. The median OS was 12.0 months and LC was achieved in 92% of patients with no GKRS-related morbidity [10]. The larger second series by Yen et al. [11] incorporated 53 patients treated with GKRS. Pons was the commonest BSM site (n=42) followed by the midbrain (n=8) and medulla oblongata (n=3). The mean GKRS prescription dose and mean BSM volume were 17.6 Gy (range: 9-25 Gy) and 2.8 cm^3 (range: 0.05-21 cm^3), respectively. In 37 patients who underwent an imaging follow-up evaluation at a mean of 9.8 months (range 1-25 months), the authors reported that the BSMs disappeared in 7 (18.9%), shrank in 22 (59.5), remained unchanged in 3 (6.3%), and grew in 5 (13.5%). Therefore, an overall objective response rate of 86.5% was achieved. In 35 patients with symptomatic BSMs, neurological

Table 1. Retrospective studies of stereotactic radiosurgery in brainstem metastasis

Study	Year	Patients (n)	BSMs(n)	Mean BSM volume (cm^3)	Mean MTD (Gy)	Local control (%)	Median survival (mo)	Toxicity rate (%)
Huang et al. [8]	1999	26	27	2.0	16.0	95	9.0	26.9
Shuto et al. [9]	2003	25	31	2.1	13.0	77	4.9	8.0
Fuentes et al. [10]	2006	28	NR	2.1	19.6	92	12.0	0
Yen et al. [11]	2006	53	NR	2.8	17.6	86.5	11.0	0
Hussain et al. [12]	2007	22	25	0.9	16.0	100	8.5	4.5
Kased et al. [13]	2008	42	44	0.26	16.0	85.0	9.0	9.5
Lorenzoni et al. [14]	2009	25	27	0.6	20.0	95.0	11.1	0
Koyfman et al. [15]	2010	43	43	0.3	15.0	85.0	5.8	7.0
Kelly et al. [16]	2011	24	NR	0.2	13.0	79.0	5.3	8.3
Yoo et al. [17]	2011	32	NR	1.5	15.9	87.0	7.7	3.1
Hatiboglu et al. [18]	2011	60	NR	1.0	15.0	76.0	4.2	20.0
Valery et al. [19]	2011	30	43	2.8	13.4	90.0	10.0	13.3
Kawabe et al. [20]	2012	200	222	1.3	18.0	81.8	6.0	0.5
Li et al. [21]	2012	28	32	0.78	16.0	90.6	9.0	3.1
Lin et al. [22]	2012	45	48	0.4	14.0	88.0	11.6	4.7
Jung et al. [23]	2013	32	34	0.71	13.0	87.5	5.2	0
Sengoz et al. [24]	2013	44	46	0.6	16.0	96.0	8.0	4.0
Peterson et al. [25]	2014	41	NR	0.66	17.0	91.0	4.4	2.4
Kilburn et al. [26]	2014	44	52	0.134	18.0	74.0	6.0	9.1
Trifiletti et al. [27]	2015	161	189	NR	18.0	87.3	5.5	1.8
Voong et al. [28]	2015	77	77	0.13	16.0	94.0	8.5	8.0
Liu et al. [29]	2016	54	NR	1.4	17.9	81.0	NR	NR
Joshi et al. [30]	2016	48	51	0.12	15.0	89.0	7.6	4.0
Nakamura et al. [31]	2017	20	26	0.33	18 - 30	90.0	17.0	25.0
Murray et al. [32]	2017	44	48	1.33	15.0	76.9	5.4	9.4
Emery et al. [33]	2017	43	43	0.4	20.0	NR	NR	NR
Patel et al. [34]	2018	14	19	0.04	17.5	87.5	NR	0
Sinclair et al. [35]	2019	8	9	0.1 – 3.5	25.3	89.9	13.0	44.4

Abbreviations: BSM: Brainstem metstasis; MTD: Marginal tumor dose

symptoms improved in 21 (60%) or remained stable in 11 (31.4% cases. The absence of active extracranial disease was reported to be the unique predictor of better survival outcomes.

Hussain et al. [12] published the results of GKRS in a retrospective review of 22 consecutive BSM patients in 2007. The median tumor margin dose and BSM volume were 0.9 mL (range: 0.1-3.3 mL) and 16 Gy (range: 14-23 Gy), respectively. Only 1 (4.5%) patient developed a new hemiparesis after GKRS and LC was achieved in all patients (100%). The median survival was 8.5 months from the GKRS.

In 2008, Kased et al. [13] reported the outcomes of 42 consecutive patients with 44 BSMs who underwent GKRS between 1991 and 2005 in *University of California, San Francisco.* The median BSM volume and prescribed dose were 0.26 cm^3 (range: 0.015-2.8 cm^3) and 16.0 Gy (range: 10.0-19.8 Gy). The authors reported that the superior OS times after GKRS were strongly associated with presentation with a single BSM, non-melanoma and non-renal cell histologies, BSM volume <1 cm^3, and controlled extracranial disease.

Lorenzoni et al. [14] treated 25 patients with 27 BSMs between 1999 and 2006. In this 2009 report, the mean BSM volume and marginal GKRS dose was 0.6 cm^3 (0.013-3.6 cm^3) and 20 Gy (15-24 Gy), respectively. TC rate was 95% with no GKRS related toxicity. In 2010 Koyfman et al. [15] reported the outcomes of 43 patients with single BSMs who underwent GKRS between 1997 and 2007 (15). The median marginal GKRS dose, conformity index, and heterogeneity index were 15 Gy (range, 9.6-24), 1.7 and 1.9, respectively. The 1-year actuarial LC rate was 85% with no grade 3 or 4 toxicities. Better performance status (P= 0.004), smaller tumor volume (P= 0.002), score index for radiosurgery (P= 0.004), and graded prognostic assessment score (P= 0.003) were the factors those demonstrated significant association with longer OS times on multivariate analysis.

In a 2011 study, Kelly et al. [16] reported the outcomes of 24 consecutive patients with BSMs after SRS. Of these patients, 21 had additional brain metastases and 23 had undergone prior WBRT. The median target volume was 0.2 cm^3 (range: 0.02-2.39 cm^3). The median dose was 13 Gy (range, 8-16) with only one patient who was treated with fractionated SRS of 25 Gy in 5 fractions. The absence of synchronous brain metastasis was reported to be the unique variable that trended toward statistical significance for OS at the 1-year time point (31% with versus 67% without synchronous brain metastasis; P = 0.11). The LC has achieved in 82% cases in the absence of grade 4-5 toxicities and only 2 cases of grade 3 toxicities. In the other studies by Yoo et al. [17], Hatiboglu et al. [18] and Valery et al. [19] reported similar efficacy and toxicity rates after BSM-SRS in the same year.

In 2012 Kawabe et al. [20], Li et al. [21], and Lin et al. [22] reported their retrospective experience of BSM-SRS, respectively. Kawabe et al. [20] identified 200 patients presenting with BSMs among 2553 patients with brain metastases from 1998 to 2011. A total of 222 BSMs were treated with GKRS. The mean median BSM volume and the median peripheral radiation dose were 0.2 cm^3 (range 0.005-10.7 cm^3) and 18.0 Gy (range 12.0-25.0 Gy), respectively. The median survival OS) was 6.0 months: 9.4 months in RPA Class I, 6.0 months in RPA Class II, and 1.9 months in RPA Class III, respectively. Better KPS, single BSM, and well-controlled primary tumor were significant predictors of longer OS. The qualitative survival rate was 90.8% and 89.2%, respectively, at 24 months of follow-up, with a 2-year TC of 81.8%. In Lin's study [22], the authors examined the outcomes of 45 patients with 48 BSMs treated with linear accelerator-based SRS. The median target volume and marginal prescription dose were 0.40 mL (range: 0.02-5.70 mL) and 14 Gy (range, 10-17 Gy) prescribed at 90% isodose curve, respectively. The 1-year LC rate was 92%. Univariate analysis demonstrated a significant relationship between LC and BSM volume (≤0.4 mL versus >0.4 mL, P= 0.023) and SRS mode (conventional circular arc versus dynamic conformal arc, P= 0.044), while there was a trend toward improved LC and prescription dose >14 Gy (P= 0.059). The 2-year overall brainstem complication rate was 4.7% with serious morbidities occurring doses beyond 17 Gy.

In 2013, Jung et al. [23] and Sengoz et al. [24] reported the outcomes of BSM-SRS in 32 and 44 patients treated for 44 and 46 BSMs, respectively. In Jung's study, the median BSM volume and tumor margin dose were 0.71 cm^3 and 13 Gy, respectively. The overall LC rate was 87.5% with no evidence of post SRS radiation necrosis [23]. The authors reported that the RTOG recursive partition analysis (RPA) class was a significant predictor of OS outcomes (19.2 months for RPA class I versus 8.4 months for RPA class II versus 1.9 months for RPA class III

(P<0.05). In the group treated with Sengoz and colleagues [24], the median BSM volume and marginal SRS dose were 0.6 cm^3 (range 0.34-7.3 cm^3) and 16 Gy (range 10-20 Gy), respectively. The authors utilized the basic score for brain metastases, graded prognostic assessment (GPA) score, and RPA classification for prediction of survival times after SRS. The LC and 1-year OS rates were 96.0% and 8.0 months, respectively. In this study, the female gender, Karnofsky Performance Score (KPS)>70, mesencephalic BSM location, and response to treatment were associated with longer survival; while the basic score for brain metastases and RPA classification were found to be associated with prognosis.

In 2014, Peterson et al. [25] and Kilburn et al. [26] reported the outcomes of GKRS in 41 and 44 patients presenting with 41 and 52 BSMs, respectively. In Peterson's study, LC was achieved in 91% of patients with a mean GKRS dose of 17 Gy [25]. Fatal brain hemorrhage after GKRS was reported in 1 patient. On multivariate analysis, the KPS 90-100 (P= 0.02) and the absence of prior WBRT (P= 0.02) were found to predict improved OS. In Kilburn's investigation, a median of 18 Gy (range: 10-22 Gy) GKRS dose was prescribed to the 50% isodose line [26]. Median BSM volume was 0.134 cc (range 0.013-6.6). The LC rate at 1-year was 74% (9% CI 52-87%). GKRS associated toxicity was reported in 4 (9.1%) patients. BSM volume >1.0 cc was found to predict post-GKRS toxicity.

In 2015, Trifiletti et al reported the outcomes of a relatively large study incorporating 189 BSMs from 161 patients treated with SRS between 1992 and 2014 [27]. Pre-SRS was utilized in 52% of patients. The median tumor margin dose was 18 Gy (50% isodose line). The LC was achieved in 87.3% BSMs with a grade 3-5 toxicity rate of only 1.8%. Results of multivariate analysis demonstrated that a margin dose of ≥16 Gy and greater KPS scores were associated with significantly improved LC (P= 0.049) and OS (P= 0.024) rates, respectively. In the same year, Voong et al. reported the post-SRS outcomes of 77 patients presenting with single BSMs [28]. Median BSM volume and SRS dose were 0.13 cm^3 (range: 0.003-5.58) and 16 Gy (range: 10-20), respectively. LC control was achieved in 72 (94%) patients. Symptomatic lesions (P= 0.05) and lesions ≥2 cm^3 (P < .001) were associated with worse LC and OS (P= 0.02 and P= 0.008), respectively. Midbrain BSM location was found as a significant predictor of higher disease progression rates (P= 0.03). Although the SRS-related toxicity rate was relatively low (8%), larger BSM size (P=0.05) and midbrain BSM location (P = 0.045) were identified as the significant associates of increased toxicity risk.

Two consecutive studies evaluating the efficacy, toxicity of SRS, and related prognostic factors for BSMs were published in 2016 [29,30]. In the first study, Liu et al. [29] reported the cyberknife SRS outcomes in BSM patients. Fifty-four patients within respective RPA Class II (N=35) and Class III (N=19) were included. Median tumor volume and marginal tumor dose were 17.9 Gy and 0.14 cm^3, respectively. Median OS was 5 months for the entire study populations: 8 and 2 months for Class II and III, respectively. With an overall LC rate of 80%, symptoms were improved in 86% of patients after the SRS procedure. The higher KPS, lower RPA class, and effective extracranial disease control were found to be the significant predictors of improved OS. Similarly, Joshi et al [30] assessed the prognostic utility of GPA tool in 48 patients treated with SRS for 51 BSMs. Median BSM volume was 0.12 cm^3 (range: 0.01-3.67 cm). The 1-year LC rate was 89% and only 2 (4%) patients experienced SRS-related grade 3 motor toxicity. Symptoms were improved in 6% of cases presented with BSM-related symptoms. Results of the multivariate analysis revealed significant associations between the improved OS and presentation with GPA score >2 (P<0.01), and diminished OS and prior chemotherapy usage (P=0.049), respectively.

In 2017, Nakamura et al. [31], Murray et al. [32], and Emery et al. [33] reported their experience on SRS for BSMs. Nakamura's study was a small study of fractionated SRS administered in 3 to 5 fractions as detailed in Table 1 [31]. In Murray's retrospective review 44 patients with 48 BSMs underwent SRS of whom 33 (75 %) also received WBRT somewhere during the course of the disease [32]. A median marginal dose of 15 Gy (range: 10-22) was prescribed to a median BSM volume of 1.33 cc (range 0.04-12.17). The 1-year LC rate was 76.9% with a median OS of 5.4 months for the whole study cohort. Four (9.6%) cases of radionecrosis were reported of which 2 (4.8%) were symptomatic. Although further studies are required to reliably comment on the issue, interestingly, the absence of WBRT trended towards improved OS in this study. In another study, because the number of brain metastases was mostly utilized parameter for evaluation of the toxicity and LC outcomes in patients presenting with brain metastases, Emery

et al investigated the impact of tumor location and relative tumor volume on OS in a large cohort 300 patients with 817 brain metastases. As expected, the commonest locations were the cerebral hemispheres (75%) followed by the cerebellum (19%). BSMs constituted only 5% of all cases. The results of this study confirmed the poor faith of BSM even after SRS as BSM patients demonstrated significantly inferior OS durations compared to either of the cerebral or cerebellar metastases.

In 2018, only one small BSM-SRS study was reported. In this report, Patel et al. [34] presented the Indiana University Health Center experience in 14 patients with 19 BSMs treated with GKRS from 2008 to 2016. Median BSM volume and marginal dose were 0.04 cc (range: 0.01-2.0 cc) and 17.5 Gy (range: 14-22 Gy), respectively. The 1-year LC rate was 87.5% with no grade ≥3 toxicity attributed to the GKRS procedure.

In 2019, to date, only one published study evaluated the clinical outcomes of SRS in BSM patients. In this small retrospective review, Sinclair et al. [35] investigated the feasibility of a so-called dose-adaptive GKRS procedure coined as Rapid Rescue Radiosurgery (3R) in the treatment of life-threatening intrinsic BSMs. Patients who were unsuitable for a single fraction GKRS due to either of V10 >1 cm^3 (volume receiving 10 Gy outside the tumor bed) with prior WBRT or V10 >3 cm^3 without prior WBRT history for a prescribed marginal BSM dose of 16-18 Gy were included. A total of 8 patients with 9 BSMs underwent 3 separate dose-adapted GKRS procedures (every 60-72 hours) over 7 days. Mean GKRS-1, GKRS-2, and GKRS-3 marginal doses at 35-50% isodose lines were 7.4, 7.7 and 8.2 Gy, respectively. The BSM volume reduction between GKRS 1 and GKRS 3 was 15% and 56% at first follow-up based on MRI-based measurements. Radiologic signs of adverse radiation effects were reported in 4 patients, yet all were asymptomatic.

3. DISCUSSION

As shown in Table 1, it is difficult to synthesize the accessible data and achieve remarkable conclusions on the safety and efficacy of SRS in the management of BSMs with regards to the small cohort sizes together with the heterogeneities across the patients. Owing to the difficulties in a reliable interpretation of the outcomes, two recent studies focused on these issues to provide more robust evidence by performing systematic literature reviews [36,37].

In one such recent commendable effort, Patel et al. [36] reviewed all available BSM-SRS studies to reveal the relationship between the tumor location in the brainstem and the incidence and severity of radiation-induced toxicity after SRS, as the potential life-threatening toxicities cause hesitance to perform BSM-SRS. A total of 29 retrospective studies published between 1999 to 2017 with 1878 patients and 2037 BSMs were analyzed. Only the grade ≥3 toxicities were reviewed. The BSM locations were specified clearly in 1945 lesions in 26 of 29 reports. The most common location was the pons (62.8%) trailed by the midbrain (22.4%), medulla (9.6%), and other structures (5.2%). WBRT before or after SRS was administered in 48.4% cases (range: .6.5% - 96.4%). The marginal BSM dose ranged between 13 and 18 Gy. The 1-year LC was achieved in 74% to 100% (mean: 86.7%) patients with a median OS ranging between 3.9 to 17.2 months. Of 1979 potential cases, 79 patients experienced SRS-induced toxicity with a rate varying between 0% and 9.5% (per report mean: 3.4%). The SRS-related grade ≥3 toxicity rates were 2.8%, 3.0%, and 0.8% (1/131) for the midbrain, pons, and medulla BSMs, separately. The median time to the emergence of toxic events was 3.0 months, and all toxicities occurred within 18 months with > 90% being occurred at the first 9 months of follow up period. Basing on these results, the authors proposed that the BSM location in brainstem substructures and BSM volume had no prescient incentive on the anticipation of toxicity outcomes.

Nonetheless, the results of Patel's retrospective analysis ought to be interpreted with caution, given the inherent impediments related to the nature of the reports included. First, just one instance of post-SRS lethality in BSMs situated in the medulla, most likely mirroring the uncommonness of the medullary BSMs as opposed to inherent radioresistance. Second, the prescription dose was commonly reported as the "marginal dose," with no reference to the isodose line. Therefore, it is difficult to assume the doses received by the surrounding normal brainstem parenchyma. What's more, third, as the authors remarked, patients probably won't survive long enough for toxicities to build up, this data also might not be representative for the true percentage of patients who develop toxicity after BSM-SRS.

In another study, Trifiletti et al. [37] published the outcomes of pooled GKRS data across multiple institutions internationally, incorporating a total of

596 BSMs in 547 patients. As expected, the majority of BSMs were located in the pons (58%) followed by the midbrain (21%) and medulla oblongata (8%). Of these 547 patients, 370 (68%) had additional extracranial metastases also. Prior WBRT was administered in 266 (49%) cases. The median BSM volume and marginal tumor dose were 0.8 cc (range 0.01 - 21.0) and 16 Gy (range: 8.0 - 25.0), individually. The 1-year LC after GKRS was 81.8%. The age <65 years (versus <65 years; P= 0.007), margin dose of > 20 Gy (versus 16 Gy; P= 0.039), and maximum dose >32 Gy (versus <32 Gy; P= 0.02) was shown to be associated with higher LC rates. The median, 1-, 2-, and 3-year OS were 5.6 months, 32.7%, 16.7%, and 10.9%, separately, with only 0.7% deaths being connected with post-GKRS BSM progression. Longer OS was found to be associated with younger age (P<.001), non-melanoma histology (P=0 .039), and single BSM-only metastases (P< 0.001). Grade 3 to 4 toxicity as a result of BSM GKRS was accounted for 44 patients (7.4%), with only 2 (0.3%) of them being grade 4. No toxic GKRS death was reported. Two additional vital discoveries of this international effort were the exhibit of critical connections between increased risks for severe GKRS toxicity and prior WBRT (P<0.001) and an interim <4.5 months between the WBRT and BSM GKRS.

Albeit still a lot of work is required to be done before reaching a reliable consensus on the ideal SRS of BSMs, available literature provides some useful proposals for future studies (Table 1). Recommending the careful selection of SRS candidates, it has been over and over reported that the better survival outcomes after BSM-SRS was firmly connected with the absence of extracranial disease, single BSM status, absence of further intracranial metastases, higher performance status (KPS>70), lower RPA class (I and II), smaller tumor volume (<1.0 cm^3), higher marginal SRS dose (>14-18 Gy), and non-radioresistant histology (particularly non-melanoma and non-renal cell). Therefore, as underscored above, BSM volume and marginal SRS dose seem to be the most pertinent SRS-related factors to influence the LC and OS outcomes.

In general, <12.0 - 12.5 Gy maximum point dose range is recommended to be safe for BSM-SRS as per the results of the studies by Sharma et al. [38] and Mayo et al. [39] for single-fraction SRS. Albeit different investigations recommending higher radiation resistance of the brainstem are additionally accessible, yet to be at the safe side, it might be reasonable to keep the brainstem doses below 12 Gy regarding the life-threatening characteristics of the severe toxicities in this organ of critical importance with many vital nuclei. Notwithstanding, it ought to likewise be remembered that untreated BSM patients have a median survival of nearly one month with plausible critical reductions in quality of life measures, which mandates well-adjusted treatment decisions in these patients' group [40]. In select patients, higher marginal BSM doses might confer higher LC and resultant better survival outcomes according to some investigators [14,18]. In this regard, although debated, single fraction doses beyond 14 to 18 Gy appear to be profoundly successful with resultant >90% LC rates at 1-year [14,18]. Therefore, despite Valery et al. [19] suggested that the lower marginal doses can achieve comparable LC and OS rates with those >14 Gy, yet available BSM-SRS literature overwhelmingly recommends higher marginal doses to accomplish better clinical results in carefully selected cases. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) report proposed that the maximum brainstem point doses <12.5 Gy of single-fraction SRS as the dose level associated with <5% severe toxicity [41]. In any case, the QUANTEC creators additionally underlined that the occurrence of serious toxicities was still moderately low for the dosages in the range of 15 to 20 Gy in limited patients gathering with longer survival durations where 14.2 Gy was cited as the dose for 3% isocomplication rate. However, in spite of its convenience in routine BSM-SRS practice, it ought to be perceived that the dosages proposed by the QUANTEC were just the maximum point doses with no accentuation on more subtle dose-volume impacts after single- or multi-fraction SRS. Moreover, albeit flawed, the brainstem was considered as a uniform neural structure as opposed to being a composite organ with differential dose-toxicity relationships at individual subsites.

Lastly, fractionated or adaptive SRS might be a proper option in cases esteemed to be at higher toxicity risk after SRS. As shown in a recent study by Sinclair et al. [42], such a methodology (rapid rescue SRS) may reveal rapid and significant BSM volume reductions up to 10% and 48% after the 1- and 3-week follow-up time points after the last fraction of SRS, which may demonstrate useful in rescue/preservation or even improvement of neurological functions.

4. CONCLUSIONS

Accessible retrospective series of BSM-RS cumulatively demonstrated that most BSMs may be securely treated with a prescription dose of up to ≥18 Gy with resultant LC and grade ≥3 SRS-related toxicity rates of >85% and <5%, separately. Even though most of the announced series consolidated the pontine BSMs <1 cc, yet, there exists no strong proof of whether the BSM volume or location might have influential impacts on the LC, OS, or severe toxicity rates. Since most BSM patients present with significant metastasis-related neurological deficits, which may even be life-threatening in some cases, it is reasonable to recommend the fractionated or single-fraction BSM-SRS for the routine management of fittingly chose patients. Such an approach may demonstrate valuable in quick alleviation of the neurological deformities by lessening the BSM volume and provision of relatively longer OS durations in such a patients' group with an estimated survival of only a few weeks, if untreated.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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