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Review article

Early tumor-related hemorrhage after stereotactic radiosurgery of brain metastases: Systematic review of reported cases☆

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ABSTRACT

Objective: Early (within 72 h) tumor-related hemorrhage (TRH) after stereotactic radiosurgery (SRS) of brain metastases (BM) has been reported only occasionally. Systematic review of such cases was done.
Methods: Literature search was performed through PubMed according to PRISMA guidelines using combination of the following medical subject headings: "hemorrhage," "stereotactic radiosurgery," and "brain metastasis."
Results: In total, 7 case reports and 8 clinical series, which noted early TRH after SRS of BM were identified. Scarce and inconsistent data precluded their precise synthesis and statistical analysis. BM of renal cell carcinoma comprised around one-third of reported cases. In 4 patients with multiple BM, TRH after SRS was noted simultaneously in several irradiated tumors. Considering 17 reported cases overall, in 3 patients TRH occurred during SRS session itself, in 4 within several minutes upon completion of treatment, in 7 within several hours thereafter, and in 3 on the third posttreatment day. Out of 11 reported cases providing detailed outcome, 6 patients died shortly after the ictus, 2 others were severely disabled at discharge, and 3 demonstrated good-to-moderate recovery. Overall, among evaluated series the median rates of early TRH after SRS for BM were 0.8% per patient (range, 0.4 – 1.9%) and 0.3% per tumor (range, 0.05 – 0.8%).
Conclusion: Early TRH is very rare, but potentially life-threatening complication of SRS for BM; thus, its risk (while extremely low) and possible consequences should be discussed at the time of obtaining informed consent.

1. Introduction

Brain metastases (BM) are one of the most devastating neurological complications of cancer. They occur in 10–30% of adults and in 6–10% of children with systemic malignancies, and identified in 10–26% of patients who die of cancer [1]. With such high incidence, BM are accounting for more than one-half of all intracranial neoplasms in adults. Nowadays, stereotactic radiosurgery (SRS) has become a standard option for their management, which is applied either as "stand-alone" technique or in combination with other treatment modalities (surgery, whole-brain radiation therapy [WBRT], chemotherapy, immunotherapy, molecular targeted therapy).

SRS for BM is considered a very safe treatment. Early complications and side effects are usually mild and transient, and limited to fatigue, headache, dizziness, nausea/vomiting, and seizures. The most common late complications include tumor pseudoprogression, radiation-induced necrosis, and brain edema [2,3]. Delayed tumor-related hemorrhage (TRH) after SRS of BM is not uncommon, but it was mainly noted in neoplasms prone for spontaneous bleeding (e.g., in cases of metastatic melanoma or renal cell carcinoma [RCC]), and frequently considered unrelated to high-dose irradiation and reflecting natural biological characteristics of the disease [4–7]. In contrast, early (within 72 h) TRH into BM as a direct consequence of SRS have been reported only occasionally. Herein we present systematic review of such cases and discuss rate of this complication, possible pathophysiological mechanisms, outcomes, and preventive measures.

2. Materials and methods

Literature search was done by 2 authors (RM, MFC) through PubMed according to PRISMA guidelines using the combination of the following medical subject headings (MeSH): "hemorrhage," "stereotactic

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radiosurgery," and "brain metastasis." Reports on cases of early (within 72 h) TRH (either intratumoral or peritumoral) after SRS of BM were targeted, as well as clinical series, which noted such complication, even without providing its detailed description. The following data were extracted: age and gender of the patient, primary cancer, presence of extracranial metastases, number of brain lesions treated during SRS session which was complicated by TRH, modality of SRS, presence of arterial hypertension or coagulopathy, previous brain irradiation, characteristics of the hemorrhagic tumor (location, volume, peritumoral edema, TRH before SRS, marginal and maximal radiation doses, prescription isodose), time from SRS to TRH, clinical manifestations of TRH, treatment, and outcome. Data from clinical series, which noted early TRH after SRS for BM with or without its detailed description were mainly used for assessment of the timing and rate of this complication. In selected case reports not only texts, but tables, figures and figure legends were carefully checked for possible extraction of relevant information. In cases of discrepancy between the text of the selected article and its accompanying abstract, the preference was given to the former. In addition, reference lists in the selected articles were reviewed for possible identification of additional relevant publications.

3. Results

In total, as of January 17, 2023, we were able to identify 7 case reports [8–14] describing 10 cases of early TRH after SRS of BM, and 8 clinical series [4,15–21], which noted such complication. In 2 of these series [4,19], the exact number of patients with early TRH could not be established, since only time range from SRS to TRH was provided (the lower limit of which preceded 72 h); thus, it was assumed that they contain one case of this complication each. One case was reported as a case report [8] and included in the clinical series [16]; all related information was extracted from the former. One case of early TRH was described with some detail in the clinical series of Fukuoka et al. [15]; other clinical series did not provide detailed description of this complication. On the other hand, 2 case reports [12,13] provided detailed information on parameters of practice in respective radiosurgical centers at the time when targeted complication was noted. Therefore, in total 11 reported cases were considered for extraction of individual data on early TRH after SRS of BM (Supplementary Table 1), and 10 series were used for evaluation of the incidence of this complication (Supplementary Table 2). Scarce and inconsistent data presentation in individual articles precluded their precise synthesis and statistical analysis. Therefore, only descriptive information is provided herein.

3.1. Demographics

Early TRH after SRS for BM was reported in 6 men and 4 women; their age varied from 44 to 79 years (median, 67 years). In one additional case neither gender, nor age were reported. In these patients, BM originated from RCC (5 cases), lung cancer (3 cases), and breast cancer (2 cases); in one patient two different cancers were diagnosed, cervical cancer and non-small cell lung cancer. Extracranial metastases were noted at least in 5 patients. From 1 to 9 BM (median, 4) were irradiated during SRS session, which was complicated by early TRH; in one case this information was not provided. Treatment was performed by means of Leksell Gamma Knife (LGK; 9 cases) or dedicated linear accelerator (LINAC; 2 cases). Arterial hypertension was reported in 2 patients, absent in 4 and in 5 cases the information on its presence was not provided. Coagulopathy was reported in 1 patient, absent in 4 and was not highlighted in 5 cases; in one additional patient the authors were concerned about possible local or systemic disturbances of blood coagulation, since SRS was done soon (on postoperative day 4) after microsurgical excision of another intracranial metastasis. Three patients underwent previous cranial irradiation by means of either WBRT (2 cases) or SRS (1 case); in one case this information was not provided.

3.2. Characteristics of hemorrhagic tumors

In 4 patients with multiple BM, TRH after SRS was noted simultaneously in several irradiated tumors [11,13,14]. Hemorrhagic BM were located in cerebral lobes (8 patients), cerebellar hemisphere (1 patient), and pons (1 patient); in one case this information was not provided. Among tumors which volume was reported, it varied from 0.2 to 50.5 cc (median, 3.5 cc). Peritumoral edema was presented in all but one (smallest) tumor, while in one case this information was not provided. In 3 patients, which had early TRH after SRS, TRH before SRS in the treated tumors was also noted on neuroimaging. Marginal irradiation dose varied from 10 to 30 Gy (median, 20 Gy). Maximal dose varied from 20 to 40 Gy (median, 31.9 Gy), but it was not reported in 6 patients and could not be re-calculated because of absent information on the prescription isodose percentage.

3.3. Early tumor-related hemorrhage after radiosurgery

Considering 11 reported cases on early TRH and 6 clinical series, which noted this complication without its detailed description, in 3 patients it occurred during SRS session itself [11,13,14] in 4 patients within several (up to 30) minutes upon completion of treatment [10,12–14], in 7 within several hours thereafter during the first posttreatment day [9,13,17–21], and in 3 on the third posttreatment day [4,8,15]. It typically manifested with sudden headache, nausea, vomiting, hemiparesis or hemiplagia, alteration of mental status, or coma. Surgical treatment directed at the evacuation of intracerebral hematoma and tumor resection was done at least in 4 patients. Out of 11 case reports providing detailed characterization of the outcome, 6 patients died shortly after the ictus, 2 were severely disabled at discharge, and 3 demonstrated good-to-moderate recovery.

3.4. Incidence of early tumor-related hemorrhage after radiosurgery

The authors of 2 presented case reports on early TRH after SRS of BM assessed rate of this complication in their own practice. Kalfas et al. [12] reported that in 2000–2009 they performed LINAC-based SRS in 950 patients with 2578 intracranial lesions, among which there were 2190 BM; in total, 93 patients had BM of RCC. Therefore, their single case of early TRH after SRS for BM of RCC translates into the rate of 1.1% per patient with BM of RCC, and of 0.05% per BM undergoing SRS [12]. Between 2009 and 2011, Yomo and Hayashi [13] treated 582 consecutive patients with BM of various cancers, and the total number of lesions was 3728. Therefore, their 3 cases of fatal early TRH after SRS translate into the rate of 0.5% per patient, and of 0.08% per tumor [13].

In their cohort of 31 patients with single BM of various cancers amenable for surgical resection and treated with SRS, Muacevic et al. [20] encountered 1 case of early TRH in 3 h after irradiation, which translates into excessively high rate of this complication (3.2%). Considering all other reports [4,12,13,15–19,21], the median rates of early TRH after SRS for BM were 0.8% per patient (range, 0.4 – 1.9%) and 0.3% per tumor (range, 0.05 – 0.8%).

4. Discussion

In their seminal report on multi-institutional experience with SRS for solitary BM published in 1994, Flickinger et al. [22] noted TRH after treatment in 3 of 116 cases, defined its actuarial rate of 7.6% at both 1- and 2-year follow-up, noticed that some of these patients required surgical intervention, but did not provide any other information, particularly with regard to timing of the complication. The same year Motozaki et al. [23] published the first detailed case report on TRH in large BM of breast carcinoma at 6 weeks after SRS, which necessitated emergency craniotomy. In the series of Fukuoka et al. [15] published in 1996, out of 130 patients with BM treated by means of LGK, there were 2 cases of posttreatment clinical deterioration caused by TRH, one of which

developed 3 days after irradiation.

Available evidence indicates that TRH during prolonged follow-up after SRS is not uncommon, especially in BM with known propensity for spontaneous hemorrhage, although reported incidence of this complication varies widely. Particularly, it was noted in 6 – 49% of metastatic melanomas [4–7,19,21,22,24–26] and in 0 – 12% of RCC [17,19,22,27,28], while in many series, cases of bleeding in irradiated and newly developed BM were evaluated together. Comparable rates of TRH in BM before and after SRS were considered by many as an indication that this complication is unrelated to high-dose irradiation and reflects natural biological characteristics of the disease [4–7,18]. In the retrospective study of Horstman et al. [29] directed at evaluation of risk factors for intracerebral hemorrhage (ICH) in heterogenous cohort of patients with BM, who underwent various treatments with and without concurrent anticoagulant therapy (ACT), this complication was noted relatively more often in those individuals, who underwent combined WBRT and SRS (26.7% vs. 8.3% in all treated patients), but according to authors it did not differ significantly in comparison with other treatment strategies. Different studies reported contradictory results on impact of TRH after SRS of BM on the local tumor control [18,26], but seemingly this complication does not influence the overall survival of patients [5,26,30].

Previously suggested factors associated with TRH after SRS for BM include female gender [18], melanoma histology [19,21,30], greater size of the tumor [18], greater size of the largest tumor and greater total volume of treated tumors in cases of multiple BM [4], treatment with larger number of isocenters [18], greater maximum dose [18], greater maximum biologically effective dose [26], and prior therapy with immune checkpoint inhibitors [26].

Pretreatment TRH, concurrent ACT, and early tumor response to irradiation have been discussed as possible predisposing factors for TRH after SRS as well, but related data are a bit controversial. Patients with hemorrhagic BM may be effectively treated with SRS without complications [4,5,31]. However, recently, Ehret et al. [30] in the cohort of 97 BM in 41 patients who were on ACT at the time of SRS revealed that bleeding event before treatment was significantly associated with TRH thereafter ($P = 0.02$); in such cases a hazard ratio for this complication was 4.2 and its actuarial cumulative rate at both 12- and 18-month follow-up comprised 46.1%. In their series, 8 of 9 TRH after SRS originated from metastatic melanoma [30]. Several retrospective studies did not reveal negative impact of concurrent ACT on risk of ICH in patients treated for BM (including those treated by means of SRS) [29,30]. However, in their propensity score-matched cohort analysis, Wood et al. [32] found that ACT in patients treated for BM with brain irradiation was associated with significantly increased risk for ICH detected with gradient echo or susceptibility-weighted MR imaging, symptomatic ICH, and extralesional ICH, which was most prominent in cases with previous ICH and of metastatic melanoma. Development of radiation-induced tumor necrosis with breakdown of fragile neoplastic vessels have been also suggested as one of the possible mechanisms of TRH during late follow-up after SRS [18,23]. However, this complication occurred in BM demonstrating shrinkage, stabilization, or increase in size after irradiation [18,23].

Finally, delayed ICH after SRS may be related to radiation-induced telangiectasia or cavernoma [33,34], but it is extremely rare in patients with BM since their limited survival does not allow for development of such lesions.

4.1. *Early tumor-related hemorrhage after radiosurgery for brain metastases*

In contrast to delayed one, early (within 72 h) TRH after SRS for BM has been reported only occasionally. Our literature search revealed only 7 case reports [8–14] and 8 clinical series [4,15–21], which noted such complication, frequently without its detailed description. Nevertheless, it seems to be not underreported, but truly rare event, as can be confirmed by previous clinical and radiological studies [35–38]. In our systematic review presented herein, based on the available data in analyzed reports [4,12,13,15–21], median rates of early TRH after SRS for BM were found to be 0.8% per patient and 0.3% per tumor, while they may vary with regard to cancer histology and other predisposing factors. These data, however, are based only on series, which reported this complication, while in many others it was not noted at all.

Due to rarity of TRH during or immediately after SRS of BM, pure coincidence of this event with treatment was occasionally suggested. Indeed, reported rates of spontaneous macroscopic hemorrhage during natural history of BM are varying from 2.9% in different adenocarcinomas to 35.7% in malignant melanomas, and even to 66.7% in sarcomas [39]. It should be underlined, that all demographic parameters of patients affected by early TRH and included in our systematic review seem rather typical, and such well-defined risk factors for ICH as arterial hypertension and systemic coagulopathy were absent at least in 4 of 11 reported cases each. However, in 4 patients with multiple BM, TRH was noted simultaneously in several irradiated tumors [11,13,14], which strongly suggests its pathophysiological link with SRS. Moreover, since such treatment is generally considered as minimally invasive *neurosurgical* intervention, any deviation from the ideal postoperative course occurring within 30 days of the procedure should be considered as complication [40,41].

The cause of TRH during SRS of BM was identified, more or less clearly, only in a case reported by Anderson et al. [11], who treated 71-year-old man with multiple BM of RCC and ankylosing spondylitis in Trendelenburg position with 15 – 20 degrees of inclination. After 3-hour SRS, the patient initially suffered a focal seizure, then arterial hypertension, generalized seizure, and coma. CT revealed hemorrhage in all 3 irradiated BM, which was most probably caused by venous outflow congestion and intracranial hypertension during irradiation owed to suboptimal positioning [11]. In other reported cases, suggested mechanisms of early TRH after SRS of BM have been merely speculative. The most possible pathophysiological causes of this complication are necrosis of the vessel wall, either within the neoplasm or in the peritumoral brain, disruption of the blood–brain barrier, or vessel thrombosis with subsequent ischemia and hemorrhage. Acute effects of high-dose irradiation on cerebral vasculature may be observed within several hours [42–44], but development of early TRH may require not only realization of such alterations, but their combination with some other factors affecting hemodynamic in the neoplasm and/or adjacent brain tissue. Peritumoral brain edema and excessive vascularity of the lesion may be important related factors [9,10,12,13,23]. Of note, acute swelling of BM and/or aggravation of the peritumoral edema without obvious TRH, resulting in serious clinical deterioration and even death of the patient early after SRS have been well recognized for a long time (specifically, in cases of lesions located in the posterior cranial fossa) [15,45]. Metastases of RCC comprised around one-third of reported cases included in our systematic review, thus may be considered more prone for this complication [13]. In collected cases, the median volume of hemorrhagic tumor was 3.5 cc, whereas median marginal dose was 20 Gy, which may suggest that larger BM treated without reduction of the prescribed dose may be more apt to early TRH after SRS. In fact, recently, McKenzie et al. [26] found that in patients with metastatic melanoma without previous bleeding episode multisession SRS (3–5 fractions) is associated with significantly lower risk of post-treatment TRH in comparison with single-session irradiation (8.3% vs. 47.4%; $P = 0.01$).

Outcome of early TRH after SRS for BM is poor, and according to 11 more or less detailed case reports, 6 patients died shortly after the ictus and 2 others were severely disabled at discharge. Therefore, prevention of this complication is highly desirable. Although uncertain causes and pathophysiological mechanisms of early TRH after SRS presume absence of any proved prophylactic measures, some “common sense” recommendations can be done. Importance of the optimal head and neck positioning during prolonged radiosurgical treatment, in particular with

rigid head fixation, to facilitate venous outflow and to prevent aggravation of the brain edema and intracranial hypertension, is obvious [11]. Monitoring of the arterial blood pressure for control and timely management of its fluctuations during the entire treatment session seems optimal [10]. Too short interval between open surgical intervention for intracranial tumor and subsequent SRS is usually avoided, while there is no sufficient evidence to establish an optimal interval between both procedures. Multisession SRS may be considered in patients deemed to be of high risk for TRH after SRS, since it may be associated with somewhat diminished incidence of this complication (while it requires further evaluation in prospective studies) [26]. For patients with hemorrhagic BM, 2-week delay of treatment with SRS was suggested [31]. In such cases both targeting of the entire tumor core without hematoma [31] and exclusion of the oozing areas from the prescription isodose volume [13] were applied, but which of these strategies is more effective for prevention of early TRH remain unclear.

5. Conclusions

TRH within 72 h after SRS of BM is very rare, but potentially life-threatening complication, which has been encountered in different series with the median rates of 0.8% per patient and 0.3% per tumor. Metastases of RCC comprise around one-third of reported cases, thus may be considered more prone for this complication. It seems important to discuss the risk (while extremely low) of early TRH after irradiation and its possible consequences at the time of obtaining informed consent before SRS for BM.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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