



Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

The effect of low-dose radiation spillage during stereotactic radiosurgery for brain metastases on the development of de novo metastases



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ARTICLE INFO

Article history:

Received 3 January 2021

Revised 7 March 2021

Accepted 13 March 2021

Available online 29 March 2021

ABSTRACT

Purpose/Objective(s): Stereotactic radiosurgery (SRS) for metastatic disease to the brain is associated with higher in-brain failures compared to whole brain radiation therapy (WBRT). Here we investigated the relationship between low-dose fall off during SRS and location of new brain lesions.

Materials and Methods: One hundred sixty-seven patients treated with single fraction or fractionated SRS for intact or resected brain metastases at our institution from January 2016 to June 2018 were reviewed. Patients with imaging findings of new brain metastases after the initial SRS were included. Patients with WBRT before SRS were excluded. MRI scans for repeat treatments were fused with initial SRS plan. New lesions were outlined on the initial SRS planning CT. The mean dose that the site of new lesions received from initial SRS was tabulated.

Results: Thirty-eight patients met inclusion criteria. 165 new lesions were evaluated. There was a lower propensity to develop new brain lesions with increasing dose received by the regions from prior SRS, with 66%, 34%, 19%, 13%, 6%, 5%, 2% and 1% of new lesions appearing in regions that received less than 1 Gy, greater than or equal to 1, 2, 3, 4, 5, 6, and 7 Gy, respectively. Higher doses are received by smaller brain volumes during SRS. After accounting for volume, 14, 14, 11, 7, 2, 1 and 1 new lesions appeared per 100 cm³ of brain in regions that received doses of less than 1 Gy, greater than or equal to 1, 2, 3, 4, 5, 6, and 7 Gy, respectively, from prior SRS.

Conclusions: We identified low dose spillage during SRS to be associated with lower incidence of new brain metastases. Validation in larger dataset or prospective study of the combination of SRS with low dose WBRT would be crucial in order to establish causality of these findings.

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Introduction

Whole brain radiation therapy (WBRT) and surgery have historically been the most common modalities to treat brain metastases. WBRT treats the metastatic lesions and potential microscopic disease within the brain. Stereotactic radiosurgery (SRS), introduced in 1951 [1], has since then been used to treat only the metastases to a high dose in a single fraction. Several studies have looked into comparing the efficacy of SRS with WBRT in the definitive and post-operative setting, as well as boosting either one form of radiation treatment with the other. The addition of WBRT to SRS or surgery was found to decrease

intracranial relapses at initial sites and the incidence of new lesions but did not improve overall survival compared to SRS or surgery alone [2–5]. Importantly, there was higher risk of cognitive deterioration and decline in memory and learning at 6 months in patients receiving adjuvant WBRT compared to those treated with SRS or with the addition of WBRT to SRS or surgery [4,6]. Given the drawbacks of WBRT, SRS followed by close clinical monitoring for new brain recurrences has evolved as the treatment of choice for most brain metastases in an increasing proportion of patients.

In the present study we investigated the spatial distribution of low dose regions from prior SRS treatments and identified the dose shells in which subsequent new brain lesions appeared. The aim of the study was to evaluate which low dose levels resulting from prior SRS, if any, were associated with a lower incidence of in-brain recurrences.

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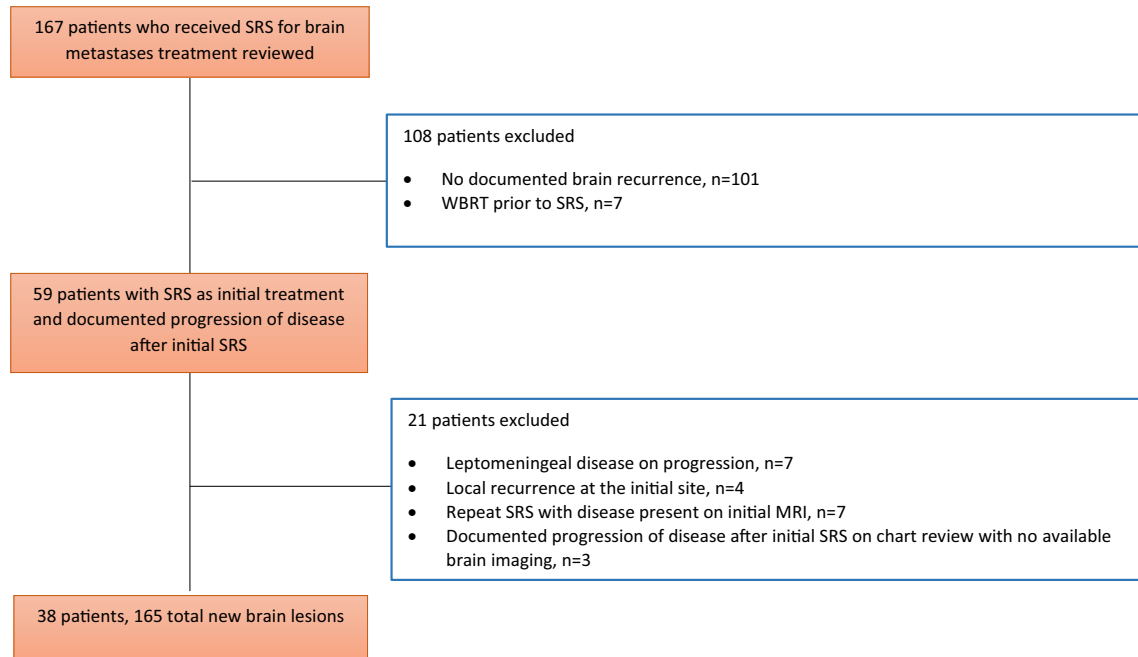


Fig. 1. Patients evaluated for the study with the exclusions.

Table 1
Patient and tumor characteristics for initially treated lesions and new brain lesions.

Median age, year (IQR)	64 (56–73)
Gender	
Male	23 (61%)
Female	15 (39%)
Histology	
Lung	28 (73%)
Adenocarcinoma	21
Squamous cell carcinoma	4
Other (including poorly differentiated)	3
Breast	5 (13%)
Renal cell carcinoma	2 (5%)
Melanoma	1 (3%)
Esophagus	1 (3%)
Unknown primary	1 (3%)
Patients receiving any chemotherapy after initial SRS	24 (63%)
Patients receiving any immunotherapy after initial SRS	20 (53%)
Total initial number of brain metastases	90
Median initial number of brain metastases (IQR) per patient	1 (1–3)
Number of initial lesions treated with post-operative SRS	11
Number of initial lesions treated with fractionated SRS	3
Number of initial lesions treated with single fraction SRS	87
Median dose for fractionated SRS, Gy (IQR) in 5 fractions	30 (30–35)
Median dose for single fraction SRS, Gy (IQR)	21(21–23)
Total number of new brain metastases	165
Total number of first brain recurrences	123
Median number of first brain recurrences per patient (IQR)	1 (1–4)
Total number of second brain recurrences in 10 patients	42
Median number of second brain recurrences per patient (IQR)	3 (2–5)
Time to progression, median months (IQR)	
– After first SRS	6.0 (3.0–10.2)
– After second SRS	4.7 (4.3–5.7)

Materials and Methods

Patient selection

We reviewed clinical data of 167 consecutive patients treated at our institution with single fraction or fractionated SRS for brain metastases from January 2016 through June 2018. Treatments

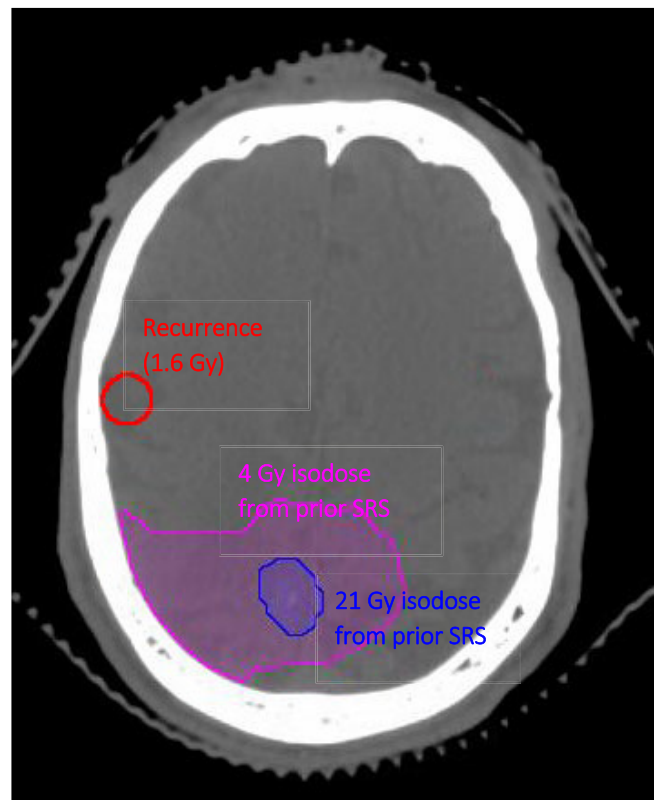


Fig. 2. Representative initial SRS planning scan from a patient where the new lesion was contoured based on the fused recurrence MRI scan. The high isodose line of 21 Gy as well as the low dose falloff of 4 Gy is shown here as an example. The region of recurrence received a mean dose of 1.6 Gy from prior SRS.

were delivered using a Varian TrueBeam™ STx equipped with the Novalis® Radiosurgery System. Patients with MRI findings of in-brain recurrence after the initial SRS were included while those

who had no diagnosis of recurrence due to stable disease or absence of repeat brain imaging with short term follow-up were excluded. Patients treated with WBRT prior to initial SRS were excluded. Local recurrence at the initial site of disease was not included for further analysis, as this study was focused on new brain lesions. Leptomeningeal spread on first recurrence was an exclusion as regions of recurrence were not possible to specify.

Data collection and statistical analyses

The cranial MRI revealing recurrence(s) after SRS was fused with the initial SRS planning computed tomography (CT) scan on each patient, and the new lesions were contoured. These contours were evaluated on the fused initial planning CT to determine the mean dose to this region of recurrence from the original SRS treatment plan (cf. Fig. 2). The number of new brain lesions in the low dose shells and the volume of these shells were recorded, ranging from 1 Gy to 7 Gy in increments of 1 Gy. Seven Gray was chosen as the upper limit of low dose shells as only approximately 1% of recurrences occurred in regions receiving more than 7 Gy. Other clinical aspects of recurrences including time to first and subsequent recurrences were tabulated. Descriptive statistics were used to summarize patient, tumor and dosimetric characteristics.

Results

Thirty-eight patients met the inclusion criteria, out of the 167 patients reviewed. Patients were excluded for the following reasons: 101 patients had no documented recurrence due to stable disease or absence of repeat brain imaging with short term follow-up, 7 had WBRT prior to SRS, 7 had leptomeningeal disease on progression after initial SRS, 4 had only one recurrence which was a local recurrence at the initial treatment site, 7 had repeat SRS for disease present on the initial MRI, and 3 had progression of disease based on chart review with no available brain images (cf. Fig. 1).

Median follow-up from initial SRS was 16.6 months (interquartile range, IQR 10.5 to 26.2). Patient characteristics are summarized in Table 1. Seventy-three percent of the patients had primary lung cancer, 75% of which were adenocarcinoma and 14% squamous cell carcinoma (SCC). Thirteen percent of total patients had breast cancer as their primary, 5% with renal cell carcinoma (RCC) and 3% each with melanoma, esophagus and unknown primary. The initial total number of lesions treated

with SRS were 90. Median number of initial lesions was one per patient (IQR 1 to 3). Eleven lesions received post-operative SRS as their initial treatment, 2 of them receiving fractionated SRS. In total, three lesions received fractionated SRS with 30–35 Gy in 5 fractions. The remaining 87 lesions or post-operative cavities were treated with single fraction SRS at a median dose of 21 Gy (IQR 21 to 23 Gy). One hundred twenty-three new lesions in 38 patients were noted on first recurrence and 42 new lesions in 10 patients on second recurrence. Median time to progression from initial treatment to first brain recurrence was 6.0 months while median time from first to second recurrence was shorter at 4.7 months. The median dose received by the areas that developed new lesions in all patients was 0.4 Gy (IQR 0.1–1.5 Gy). Fig. 2 shows a representative planning scan of a patient with the recurrence contoured, and the corresponding dose shells (area receiving at least the stated dose) from prior SRS plan.

When the new lesions were evaluated according to the various isodose levels, it was found that 66% occurred in regions receiving less than 1 Gy (Fig. 3a). This analysis showed that there was a lower propensity of new lesions with increasing dose received by the region from prior SRS, with 34%, 19%, 13%, 6%, 5%, 2% and 1% new lesions developing in regions that received greater than or equal to 1, 2, 3, 4, 5, 6 and 7 Gy, respectively.

As the low dose increases from 1 Gy to 7 Gy or higher, the volume of the brain receiving these doses decreases. The follow-up time is also not uniform across the patients. In order to account for the difference in volumes and follow-up time, the number of lesions in a unit volume and the number of lesions in a unit volume per year that received a specific dose were calculated. Accounting for volume only, there were 14, 14, 11, 7, 2, 2, 1 and 1 new lesions per 100 cm³ of brain volume that received less than 1 Gy, greater than or equal to 1, 2, 3, 4, 5, 6, and 7 Gy, respectively, from prior SRS (cf. Fig. 3b). Accounting for both volume and follow-up period, there were 17, 17, 11, 7, 3, 3, 2, and 2 new lesions per 100 cm³ of the brain per year. Thus, the regions that received doses of 4 Gy or more from previous SRS had 3 or fewer new lesions compared to 17 new lesions per 100 cm³ brain per year in regions that received 1 Gy or less in our cohort.

Fig. 4 shows the dose received by the regions of recurrence and the time interval to recurrence for different primary histologies. The majority of the 165 recurrences were in patients with lung adenocarcinoma (41%) and breast cancer (21%), followed by lung SCC (13%) and RCC (13%). Although RCC comprised only 13% of

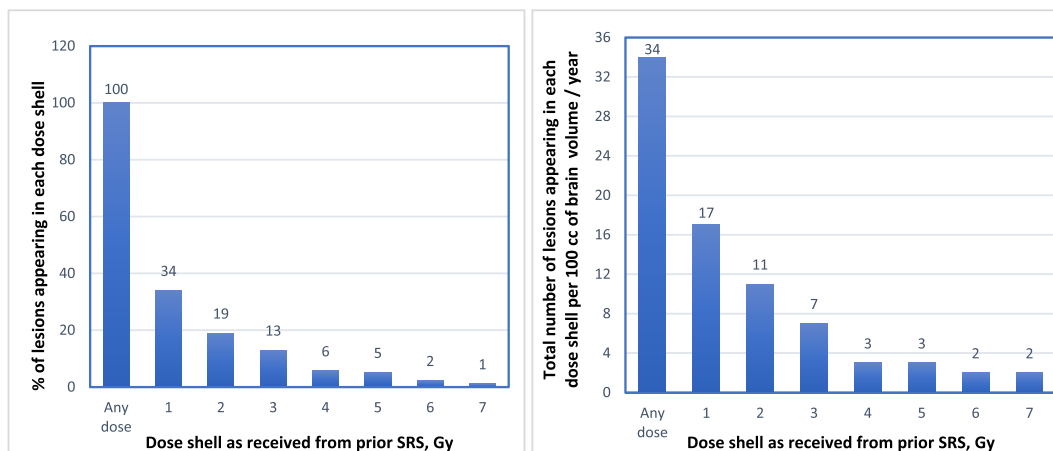


Fig. 3. a. Percentage of new lesions appearing in regions that received doses in each dose shell from prior SRS. b. Total number of lesions per 100 cm³ of brain volume per year appearing in regions that received doses in each dose shell from prior SRS.

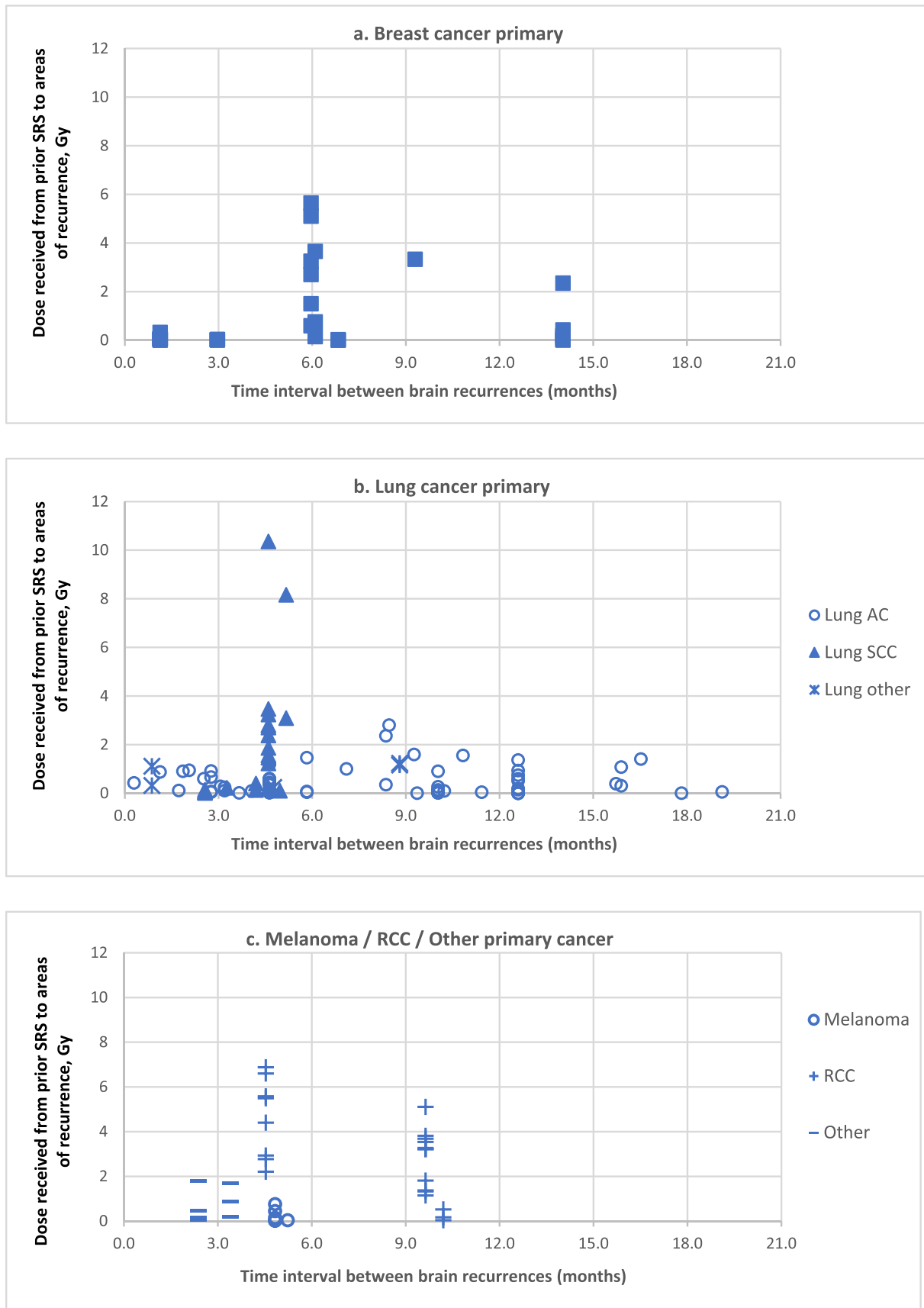


Fig. 4. Scatter plot showing the dose received by the regions of recurrence and the time interval to recurrence for different primary histologies a. Breast b. Lung c. Melanoma / RCC / other primary cancer.

new brain metastases observed, 6 out of the 10 recurrences in regions that received greater than 4 Gy from previous SRS were from primary RCC.

Discussion:

In this study we found that regions of the brain that received approximately 4 Gy or more from previous SRS had a lower incidence of new brain lesions compared to regions that received none or negligible doses. This suggests that low doses to the brain may be protective against the development of new metastases.

SRS for brain metastases offers a 12-month local control of 70–85% with a high proportion of distant brain failure of 50% or more [2,7–9]. In highly conformal treatments, such as SBRT and SRS, steep dose gradients are used to constrain the therapeutic dose to the target to limit doses to normal tissues; this may reduce the dose to microscopic disease not included in the clinical target volume (CTV). WBRT given along with SRS to targeted lesions may help ensure adequate coverage of microscopic disease in the brain parenchyma. The addition of WBRT to SRS in several randomized studies showed a 12-month relative reduction of any new distant brain metastases from 30% to 74% [2–4,10,11]. In our study we observed a reduction from 17 lesions to 3 lesions per 100 cm³ of brain and year of follow-up in regions where the brain is receiving low doses of radiation from previous SRS. This decrease in new metastases cannot be directly compared to the above-mentioned results of the randomized trials of WBRT + SRS versus SRS alone since all patients included in our study had new distant brain metastases. However, our observation concurs with the role of radiation in addressing possible microscopic disease in the brain. The WBRT dose delivered with SRS in these randomized trials was 30 Gy in 10–12 fractions. This dose fractionation was established by early studies based on assessment of neurological and functional status and local tumor control when WBRT was delivered with no SRS [12–14]. The relationship between WBRT dose and the magnitude of benefit with respect to reducing new brain metastasis risk remains unclear. In our cohort of patients, we observed that only 6% or fewer new lesions occurred in regions receiving ≥ 4 Gy, suggesting that perhaps lower doses of WBRT can be used when combined with SRS. Treatment with WBRT to doses of 4 to 7 Gy along with SRS would need to be validated in a larger dataset and investigated in the setting of a prospective clinical trial. The effects of radiation dose volume constraints associated with lower risk of cognitive impairment is evolving. It has been shown that limiting the dose to 100% of hippocampus to 9 Gy and a maximal hippocampal dose of 16 Gy in 10 fractions are associated with lower rates of neurocognitive impairment. So improved distant tumor control with whole brain doses as low as 4 Gy along with SRS as seen here may provide an advantage in terms of neurocognition. In addition, hippocampal sparing [15] and skin sparing intensity modulated radiation treatment techniques [16] can also be integrated with these low-dose WBRT treatments to further minimize side effect risk and severity. Routine follow up after SRS and WBRT with MRI brain should still remain the standard.

It is possible that the protective effects of the low dose falloff from SRS are not solely due to irradiating microscopic disease. Low radiation doses can modulate the stromal microenvironment and promote immune cell infiltration. The brain has traditionally been considered an immunoprivileged site. However, recent data show that the brain interacts with the immune system and is influenced by the proinflammatory and immunosuppressive actors [17,18]. T cells are present at the interface between brain parenchyma and metastases and in the stroma surrounding the metastases [19]. A recent preclinical study by Savage *et al* [20] looked into

post-ablation modulation with a dose of radiotherapy of 2 Gy given over 4 daily fractions to metastases-prone lung after treating the primary tumor with ablative doses in a 4 T1 breast cancer model. Post-ablation modulation radiotherapy with low doses to metastases-prone lung resulted in decreasing immunosuppressive regulatory T cell (Treg) population, activating macrophages to inflammatory phenotype and increasing CD8⁺ T cell infiltration to the lungs. There was increased survival with less lung metastases seen in these animals compared to the ones that received radiotherapy to the primary tumor alone. Furthermore, the group from MD Anderson Cancer Center has reported better response to immunotherapy in lesions that received low-dose fall-off from SBRT to lung primaries and liver and lung metastases without a corresponding response in those that did not receive any low dose radiation [21,22].

Limitations of our current study include a relatively small number of patients, which precludes a meaningful detailed evaluation of results based on clinical parameters such as age, performance status, systemic treatments, histology or fractionation. With regard to histology, it should be noted that RCC has been historically considered relatively radioresistant [23]. Interestingly, in our cohort of two patients with RCC, 6 of 22 total regions of recurrences (29%) had received greater than 4 Gy from prior SRS while in the entire cohort only 6% of the regions developed recurrence if they received greater than 4 Gy. Also, while only 3 patients (8%) in the cohort underwent fractionated SRS, their total dose in the fall-off regions likely has different implications than in those who received single fraction SRS. Leptomeningeal recurrences were not included in the present study as identification of definite dose shells for such recurrences is less meaningful when the disease is widespread in the brain, and thus the influence of low dose fall-off in this population cannot be analyzed. More recent management of brain metastases includes immunotherapy, whose role may be revealed with evaluation of a larger patient cohort. Also, anatomical changes of the brain parenchyma after the radiation treatment could occur as a result of tumor shrinkage, radiation necrosis and edema changes. Precise evaluation of the dose gradient associated with these brain changes is a limitation of this study. Deformable registration-based approaches could be implemented to address this issue in the future, but this was beyond the scope of this initial exploratory analysis.

Despite these limitations, the present study promotes an interesting hypothesis of reduced incidence of new brain lesions in areas that have received radiation doses larger than or equal to 4 to 7 Gy from previous SRS. Therefore, the addition of a low dose bath to the whole brain following or concurrent with SRS should be investigated. A combination of WBRT with SRS reduces local recurrence based on the literature, however no clear recommendation on the overall dose for the treatments exist when WBRT is given with SRS. With the observational data from this study as well as preclinical studies favoring low dose radiotherapy for immune modulation, clinical trials to further establish the efficacy of SRS plus low-dose WBRT may contribute to clinically important improvements in the field of brain metastases management.

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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