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Implications for preserving neural stem cells in whole brain radiotherapy and prophylactic cranial irradiation: a review of 2270 metastases in 488 patients

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This study delineated the incidence of metastatic involvement of neural stem cell (NSC) regions and further aimed to explore the feasibility of selectively sparing the NSC compartments during whole brain radiotherapy (WBRT) and prophylactic cranial irradiation (PCI). A total of 2270 intracranial metastases in 488 patients were identified. Lesions were classified according to locations, including lesions in the NSC compartments (subventricular zone, SVZ, or hippocampus) and those in the rest of the brain/brainstem. The incidence of involvement of NSC regions was compared between oligometastatic patients (those with 1–4 lesions) and non-oligometastatic patients (those with 5 or more lesions) using a chi-square test. The volume of the NSC regions accounted for 2.23% of the whole brain, and the overall rate of metastatic lesions in NSC regions was 1.1% in 2270 metastases (25/2270), and 4.7% in 488 patients (23/488). Of the NSC region metastases, 7 (0.3%) involved the hippocampus and 18 (0.8%) occurred in the SVZ. Among the 7 hippocampal metastases identified in this study, 1/7 (14.3%) were found in oligometastatic patients, while 6/7 (85.7%) metastases were in non-oligometastatic patients. For metastases in the SVZ, all lesions occurred in non-oligometastatic patients with none in oligometastatic patients. Metastatic involvement of the NSC compartments was significantly lower in oligometastatic patients (0.15%, 1/670) than in non-oligometastatic patients (1.5%, 24/1600) ($P < 0.001$). Our retrospective review of 2270 metastases in 488 patients is that the volume of the compartments of NSC regions was 2.23% relative to the whole brain, but the incidence of involvement of the NSC compartments was 1.1%, and the vast majority of NSC lesions were found in non-oligometastatic patients. We believe our data supports selective reduction of doses for these aforementioned structures, when treating oligometastatic patients with WBRT and locally advanced-stage small-cell lung cancer patients with PCI.

Keywords: neural stem cells; hippocampus; subventricular zone; whole brain radiotherapy; prophylactic cranial irradiation

INTRODUCTION

It has been demonstrated that there are two main regions of human containing multipotent neural stem cells (NSCs): the subgranular zone (SGZ) within the dentate gyrus of the hippocampus, and the subventricular zone (SVZ) on the lateral aspect of the lateral ventricle [1, 2]. These NSCs are capable of replacing adult neuron loss caused by various

forms of harm (e.g. local ischemia, brain trauma, radiation exposure and neurodegenerative diseases) [3–5]. However, they are extremely sensitive to X-rays, and thus reduction of NSCs may play an important role in radiation-induced neurocognitive impairment [6, 7].

Whole brain radiation therapy (WBRT) is one of the main treatments for brain metastases. In addition, prophylactic cranial irradiation (PCI) has become a recommended treatment for patients with locally advanced-stage small-cell lung cancer (SCLC). In these two treatment plans, whole brain (down to C2) radiotherapy with a full dose is regularly adopted. However, over many years of clinical practice, we have observed a very low incidence of involvement of the NSC regions in metastases. We hypothesized that it would be beneficial to spare these two areas when treating patients with either WBRT or PCI, thus minimizing radiation-induced neurocognitive impairment without a significant increase in the number of metastases. In order to confirm this hypothesis, we conducted this study.

MATERIALS AND METHODS

To assess the incidence of brain metastases in the NSC regions, the postcontrast T1-weighted, axial MRI scans (1.5T or 3.0T, slice thickness of 6 mm) of 490 consecutive patients who were treated in Fudan University Shanghai Cancer Center from January 2010 to October 2011 were retrospectively reviewed. We excluded two patients with carcinomatous meningitis because of innumerable metastases in the brain. Therefore, outcomes of the present study are based on the analysis of 2270 lesions in 488 patients.

Currently, it is still technically difficult to accurately differentiate whether metastases in the hippocampus invade the SGZ of the dentate gyrus or not, so we defined metastases in the SGZ as including metastases in the hippocampus. The hippocampus was identified within the following anatomic boundaries: the anterior boundary includes the entire hippocampal head bound by the temporal horn; the lateral boundary is served by the cerebrospinal fluid (CSF) in the temporal horn. Similarly, the medial boundary extends to the CSF in the uncal and ambient cisterns. Posteriorly, the hippocampal tail was outlined to the crus of the fornix (Fig. 1) [8]. The SVZs were defined as the 5 mm of tissue immediately adjacent to the lateral aspect of the lateral ventricles (Fig. 2). The volumes of the NSC regions and of the whole brain in all 488 patients were evaluated. Metastases were identified as postcontrast-enhanced lesions with typical features of metastatic disease, such as surrounding brain edema and mass effect. We assessed total metastases in all 488 patients. All reported metastases were categorized into metastases within NSC regions (hippocampus vs. SVZ) or those within the rest of the brain/brainstem (the

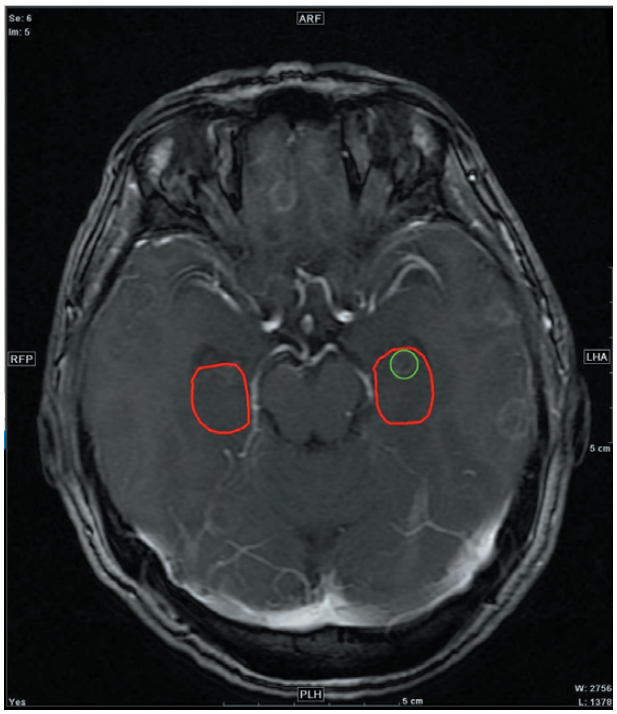

Fig. 1. Hippocampal metastasis. Contrast-enhanced T1 axial image of a patient who has a metastasis within the hippocampus. The red contour represents the hippocampal contour; the green contour represents the metastasis.

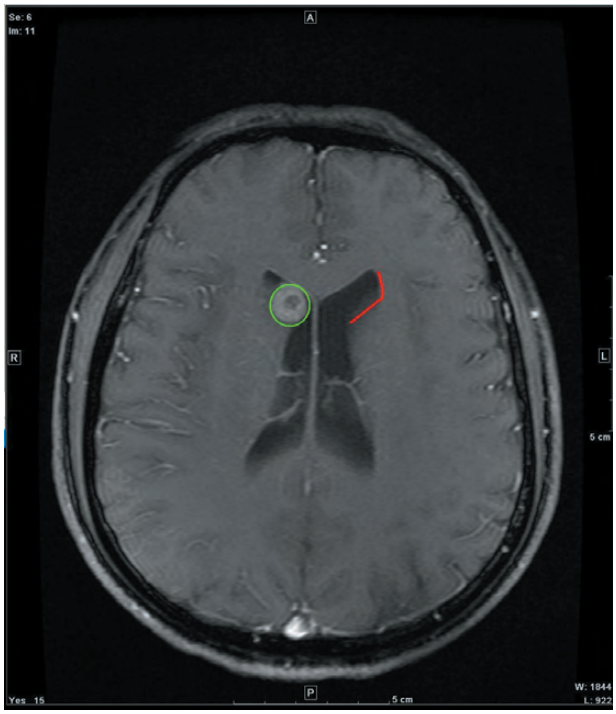

Fig. 2. SVZ metastasis. Contrast-enhanced T1 axial image of a patient who has a metastasis within the SVZ. The red contour represents the SVZ contour; the green contour represents the metastasis.

frontal lobe, temporal lobe, parietal lobe, occipital lobe, basal ganglia, cerebellum, and brainstem).

Individual patients were classified as patients with non-small-cell lung cancer (NSCLC), SCLC, breast cancer, and other cancers. Based on the primary cancer sites, other cancers of patients included prostate cancer, esophageal cancer, renal cancer, gynecological cancer, colon cancer, musculoskeletal cancer, melanoma, transitional cancer, and unknown cancer. Furthermore, patients were categorized as oligometastatic (1–4 metastases) and non-oligometastatic (5 or more metastases), and the corresponding incidence of NSC region metastases was assessed. The comparison of incidence between oligometastatic (1–4 lesions) and non-oligometastatic (5 or more lesions) patients was performed by Pearson's chi-square test. The statistical test was two-sided and $P < 0.05$ was considered statistically significant. PASW Statistics 13 (SPSS Inc., Chicago, USA) was used for the statistical analysis.

RESULTS

We analyzed postcontrast T1-weighted MRI scan outcomes of 488 patients with brain metastases in the radiotherapy clinic. Demographic and disease-specific data of 488 patients are presented in Table 1. The majority of patients were diagnosed with NSCLC (58.0%) and more than half were male. Of the whole study population, a total of 2270 metastases were identified and the average number of metastases was 4.7. The analysis based on histological subtypes indicated that average numbers of brain metastases in NSCLC, SCLC, breast cancer, and other cancers were 4.8, 5.1, 5.3 and 3.2, respectively. (Table 2). Most frequently distributed sites of metastases in the brain contained frontal lobe (580/2270, i.e. 25.6%), parietal lobe (429/2270, i.e. 18.9%), temporal lobe (324/2270, i.e. 14.3%), occipital lobe (379/2270, i.e. 16.7%), and cerebellum (424/2270, i.e. 18.7%). These data are shown in Table 3.

Additionally, a single metastasis was the major imaging manifestation, accounting for approximately 32.8% of all subjects. As shown in Table 4, 378 of 488 patients (77.5%) had 1–4 brain metastases, and 44 patients (9.0%) had more than 10 metastases.

The volumes of the NSC regions and the whole brain in all 488 patients were evaluated, and the two corresponding means ($\pm$ standard deviation) were $6.36 \pm 0.38\ cm^3$ and $284.77 \pm 19.34\ cm^3$, respectively. The proportion of the compartments of NSCs was 2.23% in the whole brain. Of a total of 2270 metastatic lesions, 25 cases (1.1%) involved NSC regions, among which 7/25 (28%) involved the hippocampus, while 18/25 (72%) involved the other NSC region known as the SVZ. The rate of involvement of the SVZ was 18/2270 (0.8%) of all intracranial metastases and 18/488 (3.7%) of all patients. The corresponding rates for the

Table 1. Patient characteristics ($n = 488$)

	Number	Percent (%)
Primary site		
NSCLC	283	58.0
SLCL	44	9.0
Breast	88	18.0
Others	73	15.0
Age		
<60	341	69.9
≥60	147	30.1
Gender		
Male	262	53.7
Female	226	46.3

NSCLC = non-small-cell lung cancer, SCLC = small-cell lung cancer.

Table 2. Number of brain metastases by histological subtypes

Cancer type	No. patients	Total no. of metastases	Median no. of metastases per patient
NSCLC	283	1 346	4.8
SLCL	44	225	5.1
Breast	88	462	5.3
Other	73	237	3.2
Total	488	2 270	4.7

NSCLC = non-small-cell lung cancer, SCLC = small-cell lung cancer.

Table 3. The distribution of metastases by location

Location	*n*	Percentage
Frontal lobe	580	25.6
Temporal lobe*	324	14.3
Parietal lobe	429	18.9
Occipital lobe	379	16.7
Cerebellum	424	18.7
Brainstem	39	1.7
Basal ganglia	70	3.1
Hippocampus	7	0.3
SVZ	18	0.8
Total	2 270	100.0

*Exclusion of metastases involved in hippocampus and SVZ, SVZ = subventricular zone.

hippocampus were 7/2270 (0.3%) and 7/488 (1.4%). In 18 patients with SVZ metastases, there were a total of 415 metastatic lesions and 23.1 metastases per patient. So, even among the patients with a heavy burden of metastases, SVZ lesions accounted for only 4.3% (18/415) of their total lesions. In 7 patients with hippocampus metastases, a total of 203 lesions and 32.9 metastases per patient was observed, and thus the rate was 3.4% (7/203). These results are presented in Table 5.

Table 4. Metastatic frequency distribution

No. metastases	No. patients
1	160
2	90
3	62
4	36
5	28
6	17
7	20
8	13
9	8
10	10
>10	44

Table 5. Pattern of involvement in patients with NSC region metastases

	SVZ	Hippocampus
Involvement of patients	18	7
No. of specific metastases in involved patients	18	7
Total metastases in involved patients	415	203
Median no. of metastases in involved patients	23.1	32.9
% of specific metastases (relative to total metastases) in involved patients	4.3%	3.4%

As shown in Table 6, of the 18 cases of SVZ metastases, none of them were observed in oligometastatic patients. In the case of metastases in the hippocampus, 1/7 (14.3%) of metastases occurred in oligometastatic patients, while 6/7 (85.7%) metastases occurred in non-oligometastatic patients. Also, 348 oligometastatic and 140 non-oligometastatic patients were respectively diagnosed with 670 and 1600 metastatic lesions. Hence, in oligometastatic patients, the rate of metastases in the SVZ was 0/670 (0%), while the rate was 1/670 (0.15%) for hippocampus metastases. Over all patients, the rate of involvement of the SVZ and hippocampus was 0.8% and 0.3%, respectively. Finally, statistical tests revealed that metastatic involvement of the NSC regions was significantly lower in oligometastatic patients (0.15%, 1/670) than that in non-oligometastatic patients (1.5%, 24/1600) ($P < 0.001$).

Table 7 demonstrated percentages of histological types in 25 lesions with NSC region metastases (NSCLC, 11; SCLC 6; breast cancer 6; others 2). Regions of NSC metastases accounted for 0.82% of all lesions in patients with NSCLC (hippocampus, 0.22%; SVZ, 0.6%), 2.7% of all lesions in patients with SCLC (hippocampus, 0.44%; SVZ, 2.2%), 1.3% of all lesions in patients with breast cancer (hippocampus, 0.22%; SVZ, 1.1%), and 0.84% of all lesions in patients with other histological types (hippocampus, 0.84%; SVZ, 0%).

DISCUSSION

The incidence of brain metastases in patients with malignant cancers has been reported as up to 30% [9] and varies among different cancer types. For some malignancies, the rate is even higher. For NSCLC, 55% of patients ultimately develop brain metastases during their clinical course [10]. Also, the cumulative incidence of two years' brain metastases in extensive SCLC patients is more than 50% [11]. Effective multimodality regimes which combine chemotherapy with radiation and/or surgery have improved overall patient survival and local control of primary site cancers, so the relative importance of brain metastases has increased [12–14].

Table 6. Incidence of NSC lesions in oligometastatic and non-oligometastatic patients

	SVZ	Hippocampus
No. of specific metastases	18	7
No. of specific metastases in oligometastatic patients	0	1
No. of specific metastases in non-oligometastatic patients	18	6
% of specific metastases (relative to total metastases) in oligometastatic patients	0% (0/670)	0.15% (1/670)
% of specific metastases (relative to total metastases) in non-oligometastatic patients	1.1% (18/1 600)	0.38% (6/1 600)
% of specific metastases (relative to total metastases) in all patients	0.8% (18/2 270)	0.3% (7/2 270)

Table 7. Incidence of involvement of NSC regions by histological subtypes

Histology	Total no. of metastases	NSC metastases (% of total)	Hippocampal metastases (% of total)	SVZ metastases (% of total)
NSCLC	1 346	11 (0.82)	3 (0.22)	8 (0.6)
SLCL	225	6 (2.7)	1 (0.44)	5 (2.2)
Breast	462	6 (1.3)	1 (0.22)	5 (1.1)
Other	237	2 (0.84)	2 (0.84)	0 (0)

NSCLC = non-small-cell lung cancer, SCLC = small-cell lung cancer.

WBRT, one of the main therapies, can be used to independently manage brain metastases, or may be combined with either surgical resection or stereotactic radiosurgery (SRS) [15–17]. Adjuvant WBRT after the resection of a single brain metastasis has been demonstrated to reduce the possibility of malignant recurrence at local and distant sites in the brain, and omission of WBRT probably increases the risk of recurrent brain metastases [16, 18–20]. Similarly for PCI, a randomized trial was conducted to evaluate the role of PCI in patients with extensive SCLC who had responded to chemotherapy. The results showed that PCI not only reduced the incidence of symptomatic brain metastases, but also prolonged disease-free and overall survival, consistent with a meta-analysis [11, 21].

The RTOG 9508 randomized trial showed that there was a survival benefit and advantage of Karnofsky Performance Status in the group being treated with a combination of WBRT and SRS, compared with monotherapy of WBRT. However, this clinical trial did not directly contrast the difference in neurocognition between the two plans [22]. Chang *et al*. assessed the decline of neurocognitive function among patients with brain metastases who were treated by radiosurgery or radiosurgery plus whole-brain irradiation. The trial was stopped because of clear results. Patients assigned to receive SRS plus WBRT were more likely to suffer from a significant decline in learning and memory function than patients treated with SRS alone [23].

A number of studies have investigated the effects of irradiation on the brain. NSCs have been well studied, because they are sensitive to irradiation. Studies have found that radiation-induced impairment of hippocampal neurogenesis is associated with hippocampal-dependent memory deficits in animal models, and radiation-induced loss of neural stem cells, resulting in the inability to repair damage, which might be linked to decline of executive function, consolidation of memory, and other late sequelae [6, 24–26].

Therefore, sparing these critical structures in WBRT and PCI may enable the brain to repair damage caused by cerebral irradiation, and help preserve neurocognitive function. The distribution of metastases is proportional to the blood flow in brain compartments, and about 80% of metastases are located in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem [27]. However, there is no accurate data to describe the distribution of brain metastases within the NSC regions.

Recently, two research groups have investigated the incidence of hippocampal metastases. Marsh *et al*. from Rush University Medical Center reviewed records of 697 metastatic lesions in 107 patients and found that only 16/697 metastases (2.29%) involved the hippocampus. The incidence of hippocampal metastases in oligometastatic patients (those with 1–3 metastases only) was 0.97% (1/103) and one of 53 oligometastatic patients (1.9%) had hippocampal metastases [28]. A safety profile for RTOG 0933 observed 1133 metastatic lesions in 371 consecutive patients from two separate institutions. They found that none of the metastases were within the hippocampus; metastases within 5 mm of the hippocampus were observed in 32/371 patients (8.6%) and 34/1133 brain metastases (3.0%) [8].

To the best of our knowledge, no other study has investigated the metastatic involvement of the other NSC compartment, the SVZ. In our retrospective review of 2270 brain metastases in 488 patients, we found that the rate of involvement of the SVZ was 18/2270 (0.8%) for all intracranial metastases, and 18/488 (3.7%) for all patients, while the rate for hippocampus was 7/2270 (0.3%) and 7/488 (1.4%), respectively. In 18 patients with SVZ metastases, there was a total 415 lesions with a mean of 23.1 metastases per patient. So, even among these patients with a heavy burden of metastases, SVZ lesions accounted for only 4.3% (18/415) of their total lesions. The corresponding rate in the hippocampus was 3.4% (7/203). Among the 18 patients with SVZ metastases identified in this study, none of the lesions occurred in oligometastatic patients and all of lesions occurred in non-oligometastatic patients. For metastases in the hippocampus, 1/7 metastases (14.3%) occurred in oligometastatic patients, while 6/7 metastases (85.7%) occurred in non-oligometastatic patients. Finally, we conclude that metastatic involvement of the SVZ and the hippocampus was 0.8% and 0.3% of all lesions, respectively, and involvement of the NSC regions was lower in oligometastatic patients (0.15%, 1/670) than in non-oligometastatic patients (1.5%, 24/1600) ($P < 0.001$). Above all, the volume of compartments of the NSCs was 2.23% relative to the whole

brain. However, the overall rate of metastases in the NSC regions was 1.1%. Thus, the occurrence of brain metastases per unit in the NSC regions is not equal to the whole brain and is relatively low in comparison to rest of the brain. Tomé *et al*. also revealed a relatively low incidence of brain metastases in the perihippocampal region [29].

The metastatic incidence of the NSC regions in patients with SCLC (2.7%) seemed to be higher than that of others (0.82% in SCLC, 1.3% in breast cancer, and 0.84% in other cancers). Because of the low morbidity of SCLC, we only collected 44 patients with SCLC with a total of 225 metastases in the present retrospective review. In order to obtain more accurate data, it is necessary for future studies to assess more cases with SCLC and brain metastases through a multi-cancer center database.

Barani *et al*. have shown the dosimetrical feasibility of NSC-preserving radiotherapy, even when the target was a periventricular lesion. They used inverse-planned intensity-modulated radiotherapy in two clinical scenarios—brain metastatic disease and primary high-grade glioma—to achieve cumulative dose reductions of 65% and 25% in the NSC compartments, respectively, compared with conventional radiotherapy [30]. Investigators at Rush University Medical Center also tested the feasibility of dosimetrically sparing the hippocampus and the SVZ (a 5-mm expansion around the lateral ventricle) during helical tomotherapy with WBRT and PCI. They found mean doses of 11.5 Gy in the PCI plan and 11.8 Gy in the WBRT plan for the hippocampus and SVZ, while treating the rest of the brain with 30 Gy in 15 fractions (PCI) or 35 Gy in 14 fractions (WBRT) with a V100 of 95%. They achieved the reduction in BED late effects of 73.8% in the hippocampus and 65.8% in the SVZ through a PCI study plan, compared with a standard plan. For the WBRT study plan, the reductions were 78.6% and 70.8% in the hippocampus and the SVZ, respectively [31]. Thus, to dosimetrically spare the NSC compartments has been proven to be feasible.

As a retrospective and single-institution study, our data has some inevitable limitations. However, our results are consistent with other studies [8, 28]. Thus, we believe that it is reasonable to selectively reduce doses to the two NSC compartments, while simultaneously treating other parts of the brain with full doses. The rate of involvement of NSC regions after conformal avoidance with WBRT and PCI needs to be elucidated in future clinical trials. Based on current findings of the NSC region involvement in oligometastatic patients, we are performing a study of dosimetric feasibility to examine the advantages and risks of sparing NSC-containing areas in oligometastatic patients (WBRT plan) and extensive SCLC patients with a response to chemotherapy (PCI plan). Plans will be conducted in two situations: PCI (25 Gy in 10 fractions) and standard WBRT (30 Gy in 10 fractions).

CONCLUSIONS

Our retrospective review of 2270 metastases in 488 patients found that the volume of the NSC regions accounted for 2.23% of the whole brain, but the incidence of involvement of the NSC compartments was 1.1%, and almost all of NSC lesions were limited in non-oligometastatic patients. We believe our data support the case for selective reduction of doses to these aforementioned structures when treating oligometastatic patients with WBRT, or locally advanced-stage SCLC patients with PCI.

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