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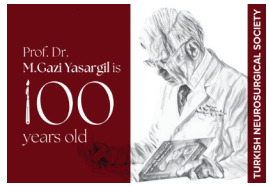

Preoperative Stereotactic Radiosurgery for Brain Metastases: A Single-Institution Experience

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ABSTRACT

AIM: To report a single center experience in preoperative SRS in patients with metastatic brain tumors.

MATERIAL and METHODS: We identified 18 patients who underwent preoperative stereotactic radiosurgery (SRS) in our clinic between 2015 and 2021. Two patients were lost to follow-up and therefore were excluded from clinical outcome analyses. SRS was administered using the CyberKnife system.

RESULTS: The median volume of index lesion was 14,19 mL (range 3,13-40,84). SRS was performed in median 1 fraction (range 1-2) to a median prescription dose of 15 Gy (range 12-17). Gross total resection was achieved in 14 (77.8%) patients. The median follow-up was 15 months (range 1-87). Median cancer specific survival (CSS) was 31 months. 6-, 12- and 24- months local control (LC) rates were 91%, 79% and 68%, respectively. Better gross tumor volume coverage was associated with better LC (p=0.01). 6-, 12- and 24- months distant brain control (DBC) rates were 82%, 58% and 47%, respectively. The infratentorial location of index lesion was associated with worse DBC (p=0.026). None of the failures were in the pattern of leptomeningeal dissemination (LMD). Grade IV symptomatic radionecrosis (RN) was reported in a single case. Three patients experienced fatal (grade V) post-operative complications.

CONCLUSION: Preoperative SRS approach, which provides the advantage of low rates of RN and LMD, is a meritorious alternative strategy in the treatment of brain metastasis. Care must be given to better assessment of surgical mortality and the selection of appropriate patients for this treatment approach.

KEYWORDS: Preoperative, Brain metastasis, Stereotactic radiotherapy

ABBREVIATIONS: BM: Brain metastases, **LR:** Local recurrence, **LC:** Local control, **DBC:** Distant brain control, **WBRT:** Whole-brain radiation therapy, **SRS:** Stereotactic radiosurgery, **OS:** Overall survival, **CTV:** Clinical target volume, **LMD:** Leptomeningeal dissemination, **RN:** Radionecrosis, **GTV:** Gross tumor volume, **RTOG:** Radiation therapy oncology group, **AAPM:** American Association of Physicists in Medicine, **CTCAE:** Common terminology criteria for adverse events, **RANO-BM:** Response assessment in neuro-oncology brain metastases, **CSS:** Cancer specific survival, **CSF:** Cerebrospinal fluid

INTRODUCTION

Brain metastases (BM) are one of the most common neurological complications of systemic malignancy, affecting approximately 20% of cancer patients (28), and leading to significant morbidity and mortality. In recent years, the incidence of BM has been further rising, possibly related to both the prolonged survival with the use of novel systemic therapy agents with limited intracranial efficacy and increased

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detection rates through more frequent surveillance with advanced and more widely accessible imaging modalities (13).

Management of brain metastases requires a multidisciplinary approach, including surgery, radiotherapy and, in certain cancers, novel systemic treatment options. Surgical removal should be considered especially in the presence of large BM causing a mass effect or when tissue diagnosis is required (35). In 1990, Patchell et al. reported the first landmark trial on the role of surgery in brain metastases and demonstrated the improvement in survival and quality of life in patients who underwent surgery (22). However, with an estimated local recurrence (LR) rates of up to 59%, surgery is not sufficient as the sole treatment method; hence postoperative radiotherapy, which has been shown in randomized controlled trials to increase both cavity local control (LC) and distant brain control (DBC), is recommended (11,21).

Historically, adjuvant whole-brain radiation therapy (WBRT) was applied after surgery of BM. However, due to the concerns about deterioration in neurocognitive function and quality of life following WBRT, this was replaced by postoperative cavity stereotactic radiosurgery (SRS) for limited brain metastases. A randomized controlled trial comparing postoperative radiotherapy modalities reported worse cavity LC and DBC, but better neurocognitive protection, preservation of quality of life, and functional independence with postoperative SRS compared to postoperative WBRT (6). Since there was no difference in terms of overall survival (OS) between the two groups, they recommended postoperative SRS as a better option in terms of neurocognitive protection (6). As a result, postoperative SRS has become the new treatment of choice.

However postoperative SRS planning has several challenges, such as difficulties in cavity delineation, the need for margin expansion and requirement for an even larger target volume in the presence of dural/venous sinus contact (18,31). Additionally, there are concerns about leptomeningeal dissemination (LMD) and radionecrosis (RN) in post-operative SRS setting, both of which are difficult to diagnose and manage.

To counter these challenges of postoperative SRS, preoperative SRS has been suggested by investigators as an alternative strategy. Preoperative SRS has several advantages both in treatment planning and potentially in treatment outcomes. Preoperative SRS reduces treatment volume by targeting only intact tumor with no need for wide margin expansion or inclusion of surgical tract, thus better preserves surrounding normal tissue and reduces the risk of RN. Additionally, tumor cells are exposed to radiation prior to surgery, therefore theoretically the risk of tumor spillage during surgery and LMD are diminished through preoperative sterilization of the surgical bed. Several retrospective studies and a recent meta-analysis offered preoperative SRS as a safe and effective treatment modality (3,15,20,25,32).

In the present study, we report our experience with preoperative SRS in patients with BM, with an example of an illustrative case.

MATERIAL and METHODS

Patients

The records of patients treated for brain metastases in our department were retrospectively reviewed. Data of 18 patients who underwent preoperative SRS and surgical resection between 2015 and 2021 were obtained.

Patients, who were deemed to require resection due to a large tumor with a mass effect by the neurosurgery team, were evaluated in a multidisciplinary manner in terms of eligibility for SRS before surgery. Patients considered suitable for this therapeutic approach were those over 18 years of age with good performance status (Karnofsky Performance Status Score ≥70), presenting with one to five brain metastases (one or two planned for preoperative SRS followed by resection and the remaining synchronous BM planned for definitive SRS), histologically confirmed or radiologically highly suspected metastatic disease, and no previous history of treatment for BM. Patients with BM greater than 5 cm in size or located within 5 mm of the optic chiasm, or those planned for resection of more than two BM, were not considered suitable for preoperative SRS. Following surgery, at least one month of radiological follow-up was required to evaluate the treatment results.

Informed consent was obtained from all patients. This retrospective study was approved by local ethical committee of our hospital (date:28.09.2022, register number: 2022/514/234/31) and was carried out in accordance with the declaration of Helsinki (34).

Radiotherapy technique and treatment planning

All patients were treated with a robotic linear accelerator-based SRT, CyberKnife system (AccurayInc, Sunnyvale, CA, USA). Patients were positioned supine on the 6D robotic couch and were immobilised using a non-invasive thermoplastic mask made at the time of the planning computerized tomography (CT) scan. CT and contrast-enhanced magnetic resonance imaging (MRI) studies with 1 mm-slice thickness were obtained. As part of our clinic's routine protocol, MR images taken within the last week were used for planning; however, the use of older MR images was also permitted at the discretion of the treating physician. Fusion of the MRI and CT images, contouring and planning were performed using dedicated inverse planning software using multiple isocenter, non-isocentric, and non-coplanar beams: Multiplan (Accuray®). The treatment plan of a representative patient is shown in Figure 1. During the treatment, real-time images were obtained through X-ray cameras and the skull-based tracking system was used.

The gross tumor volume (GTV) was defined as the contrast-enhanced area on T1-weighted images. A circumferential 1-mm margin was added to define the planning target volume (PTV). Similar to previous preoperative SRS studies, based on the rationale that the main objective in preoperative SRS is to control residual and microscopic disease after surgery, doses reduced by up to 10-20% from the standard dose definitions of Radiation Therapy Oncology Group (RTOG) 90-05 could be preferred (3,29). Most commonly, single-fraction SRS was applied, but two-fraction treatment was preferred in large tu-

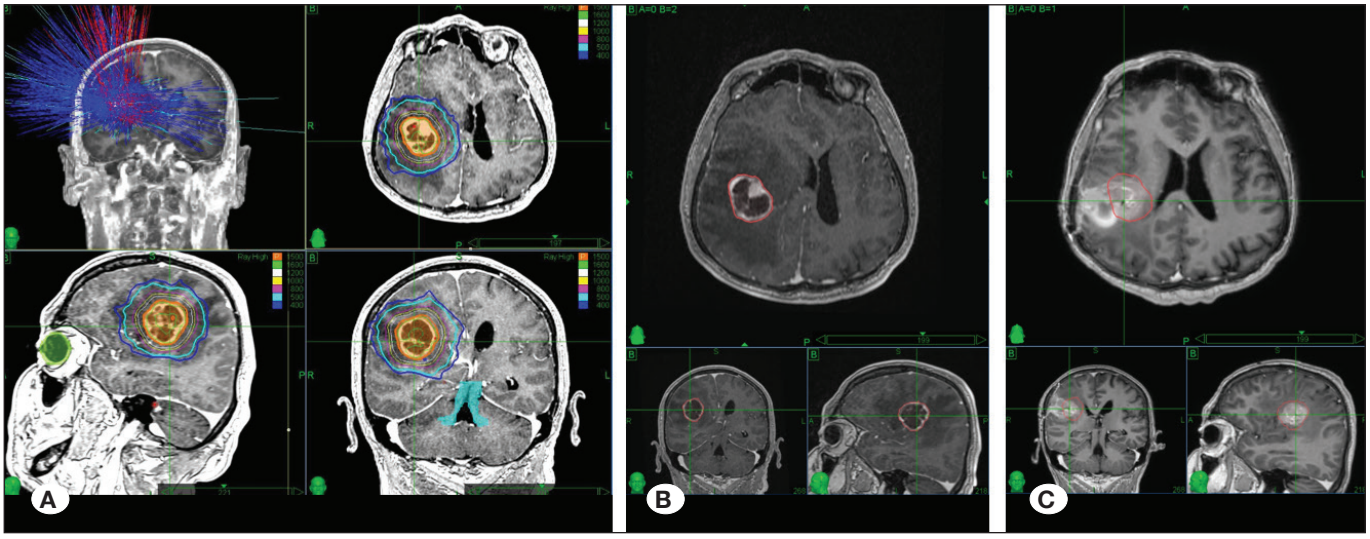

Figure 1: A) Preoperative stereotactic radiosurgery plan of an illustrative case. Single fraction of 15 Gy was prescribed to 84% isodose line. **B)** Preoperative MRI, red line: preoperative SRS gross tumor volume. **C)** Postoperative MRI showing extensive post-surgical changes, **red line:** preoperative SRS gross tumor volume.

mors (≥3 cm) if it would not delay the planned surgery. 95% of PTV and 99% of GTV are aimed to be covered by 100% of the prescription dose. However, by prioritizing normal tissue dose constraints, compromises could be made in coverage. American Association of Physicists in Medicine (AAPM) Task Group 101 report recommendations were utilized to evaluate all plans and normal tissue dose constraints (4).

All patients completed the planned treatment. Surgery was performed within one week after completion of radiotherapy.

Follow up

Initial evaluation was done by clinical examination and contrast-enhanced brain MRI at 4-8 weeks after surgery. Patients were then followed up regularly at three months intervals or as clinically indicated. During the follow-up visits, patients were evaluated clinically by history and physical examination and radiologically by contrast-enhanced brain MRI. Patient images were evaluated by an experienced neuroradiologist. In cases where tumor progression or RN distinction was uncertain, the diagnosis of RN was confirmed radiologically by advanced MRI studies (MR spectroscopy and MR perfusion) or pathologically by resection. Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 was used for adverse event reporting (33).

Statistics

LC was evaluated according to the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) radiologic criteria (16). Distant brain progression was defined as the detection of a new, non-contiguous enhancement beyond the 80% isodose line of preoperative radiation field on brain MRI.

Duration of LC and DBC, and cancer specific survival (CSS) were defined as the time from the first day of SRT to the date of detection of the recurrence in the cavity of preoperative SRS-applied (index) lesion, date of detection of the first distant brain failure and day of death from the cancer, respectively.

LC, DBC and CSS results were evaluated with the Kaplan-Meier method. Effects of the variables on outcomes were evaluated by performing univariate analyses using log-rank test. Multivariate analysis was not performed due to small sample size. A p-value of <0.05 was accepted as statistically significant. All statistical analyses were performed using the SPSS 20.0 software. (The Statistical Package for Social Sciences 20.)

RESULTS

We reviewed the records of patients treated for brain metastases in our department. Data of 18 patients who underwent preoperative SRS and surgical resection between 2015 and 2021 were obtained. The detailed individual patient information is summarized in Table I.

Patient, Tumor and Treatment Characteristics

Fifteen (83.3%) of the patients were male and three (16.7%) were female, and the median age at the time of SRS was 59 years. Median Karnofsky Performance Status score was 80 (range 70-100). The lung was the most common primary cancer site accounting for 66.7% of cases and other primary sites were colon, breast, skin, bladder. Median time from the diagnosis of cancer to the development of brain metastasis was 13.5 months (range 0-57). At the time of SRS, active extracranial disease was detected in 11 (61.1%) patients, and the brain was the sole active site in seven (38.9%) patients.

Majority (83.3%) of patients had a single brain metastasis, with only three (16.7%) patients having a second synchronous metastasis. In these three patients with two BM, the lesion other than the index lesion was treated with definitive SRS. In 13 (72.2%) patients, index lesion location was infratentorial. The median maximum diameter and volume of index le-

Table I: Detailed Individual Patient Information

Patient no	Sex	Age, years	Primary tumor	Active Extracranial disease	Number of brain metastases	Interval between preop-SRS and surgery, days	Time delay between MRI and preop-SRS delivery, days	Preop SRS dose fractionation scheme	Volume of preop-SRS applied lesion	BED_{10}/PTV value	Follow up, months	Radionecrosis	Intracranial Progression	Status	Cause of Death
1	Male	65	NSCLC	Yes	1	1	1	17/2	24,32	1,20	26	No	Local + Distant	Death	Cancer
2	Male	59	COLON	No	1	1	6	15/1	24,92	1,25	19	No	Local + Distant	Death	Cancer
3	Male	33	COLON	Yes	1	2	2	15	13,84	2,33	11	Yes	Local + Distant	Death	Cancer
4	Male	64	NSCLC	No	1	1	3	17/2	12,97	2,10	26	No	Distant	Alive	Alive
5	Female	46	BREAST	No	1	3	0	12	15,26	1,46	26	No	No	Alive	Alive
6	Male	50	LCNEC/SCLC	Yes	1	3	1	12	13,38	1,72	21	No	Distant	Death	Cancer
7	Male	63	NSCLC	Yes	1	2	4	15	18,21	1,81	4	No	No	Death	Cancer
8	Female	35	BREAST	Yes	2	2	12	16/2	21,14	0,99	87	No	Distant	Alive	Alive
9	Male	59	NSCLC	No	2	1	3	15	16,77	1,96	40	No	No	Alive	Alive
10	Female	67	NSCLC	No	1	1	4	15	10,15	3,34	6	No	No	Death	Hyponatraemic Seizure
11	Male	59	NSCLC	Yes	1	2	6	17/2	11,96	2,26	1	No	No	Death	Intracranial hemorrhage
12	Male	72	MELANOMA	Yes	1	1	12	15	14,54	2,27	1	No	No	Death	Pneumonia
13	Male	56	NSCLC	Yes	1	1	4	15	12,92	2,51	2	No	No	Death	Increased intracranial pressure
14	Male	73	NSCLC	Yes	1	1	4	15	19,86	1,66	1	No	No	Death	Intracranial hemorrhage, hydrocephalus
15	Male	59	NSCLC	No	1	0	4	15	40,84	0,84	1	No	No	Death	Pneumonia, Pulmonary thromboembolism
16	Male	66	NSCLC	No	2	2	6	15	6,82	4,62	31	No	No	Death	Cancer
17	Male	47	BLADDER	Yes	1	6	3	15	3,13	11,97	1	Lost to follow up	Lost to follow up	Lost to follow up	Lost to follow up
18	Male	49	NSCLC	Yes	1	1	6	15	13,13	2,50	1	Lost to follow up	Lost to follow up	Lost to follow up	Lost to follow up

sion were 33 mm (range 18-47, 5) and 14,19 mL (range 3,13-40,84), respectively.

Preoperative-SRS was delivered within a median of four days (range 0-12) after acquisition of the planning MRI. SRS was performed in median one fraction (range 1-2) to a median prescription dose of 15Gy (range 12-17), which is biologically equivalent to a dose of 37.5Gy (range 26.4-37.5). The SRS plan quality indices were as follows: median conformity index 1.18 (range 1.09–1.73), new conformity index 1.22 (range 1.13–1.73) and homogeneity index 1.19 (range 1.12–1.54). Median 96.46% (range 88.63-99.59) of the PTV and 98.54% (range 89.05-99.91) of the GTV were covered by the prescription dose. Median time interval between SRS and resection was one day (range 0-6). GTR was achieved in 14 (77.8%) patients. Four patients (22.2%) who underwent STR were followed-up; while local progression did not occur in three, one experienced both local and distant brain failure 3 months later. Both lesions resected surgically and subsequently, WBRT was applied.

The patient and tumor characteristics, and treatment parameters are summarized in Table II and III.

Clinical Outcomes

Two patients were lost to follow-up as they did not meet the minimum one-month radiological follow up criteria. Consequently, clinical outcome and toxicity analyses were performed based on the data of 16 patients. The median follow-up was 15 months (range 1-87). Median CSS was 31 months. Six-, 12- and 24- months CSS rates were 91%, 81% and 61%, respectively (Figure 2A).

Three (18.8%) patients had local failure, with one occurring at 3 months, another occurring at 8 months, and the third one occurring at 21 months after treatment. Six (37.5%) patients had distant brain failure. None of the failures were in the pattern of leptomeningeal dissemination. 6-, 12- and 24- months Kaplan-Meier LC rates were 91%, 79% and 68%, respectively (Figure 2B).6-, 12- and 24- months Kaplan-Meier DBC rates were 82%, 58% and 47%, respectively (Figure 2C).

Gender, lesion histology, maximum diameter, and volume of index lesion, PTV volume, SRS fractionation, BED10, BED10 / PTV, prescribed isodose line, SRS quality indices, dose coverages, extracranial disease control status, days between acquisition of planning MRI and SRS, days between SRS and resection and extent of resection were the variables investigated by univariate analyses to determine their effects on LC and DBC.

Better GTV coverage was associated with statistically significantly better LC (p=0.01) and infratentorial location of index lesion (p=0.026) was associated with statistically significantly worse DBC. None of the other investigated variables showed a statistically significant association with LC and DBC.

Ultimately, a total of four (25%) patients, two (12.5%) with both local and distant brain recurrence and two (12.5%) with distant brain recurrence alone, were treated with WBRT. One patient with distant brain recurrence alone was successfully treated with definitive SRS, no need for WBRT. In one patient

Table II: Patient and Tumor Characteristics

Patient Characteristics	
Number of patients	18
Age, years	59 (33-73)
Gender	
Female	3 (16.7%)
Male	15 (83.3%)
KPS score	80 (70-100)
SIR class	
1	2 (11.1%)
2	0 (0%)
3	15 (83.3%)
4	1 (5.6%)
GPA class	
1	0 (0%)
2	4 (22.2%)
3	11 (61.1%)
4	3 (16.7%)
RPA class	
1	6 (33.3%)
2	12 (66.7%)
3	0 (0%)
Primary site	
Lung	12 (66.7%)
Colon	2 (11.1%)
Breast	2 (11.1%)
Malign melanoma	1 (5.6%)
Bladder	1 (5.6%)
Active extracranial disease	
Yes	11 (61.1%)
No	7 (38.9%)
Tumor Characteristics	
Number of brain metastases	
1	15 (83.3%)
2	3 (16.7%)
Location of the index lesion	
Frontal	2 (11.1%)
Temporal	1 (5.6%)
Parietal	1 (5.6%)
Occipital	1 (5.6%)
Cerebellum	13 (72.2%)
Maximum diameter of the index lesion, mm	33 (18-47.5)
Volume of the index lesion, mL	14.19 (3.13-40.84)
Total intracranial tumor volume, mL	14.19 (3.13-40.84)

Values are presented as median(range) or number (%).
***KPS:** Karnofsky performance status, **SIR:** Score index for radiosurgery, **GPA:** Graded prognostic assessment, **RPA:** Recursive partitioning analysis.*

Table III: Treatment Characteristics

Treatment Characteristics	
Resection	
GTR	14 (77.8%)
STR	4 (22.2%)
PTV volume, mL	16.32 (3.13-44.91)
SRS dose, Gy	15 (12-17)
SRS fraction	
1	14 (77.8%)
2	4 (22.2%)
BED_{10}	37.5 (26.4-37.5)
BED_{10} / PTV	2.03 (0.84-11.97)
Prescribed isodose line	84 (65-89)
CI	1.18 (1.09-1.73)
nCI	1.22 (1.13-1.73)
HI	1.19 (1.12-1.54)
GTV coverage, %	98.54 (89.05-99.91)
PTV coverage, %	96.46 (88.63-99.59)

Values are presented as median(range) or number (%).
***GTR:** Gross total resection, **STR:** Subtotal resection, **PTV:** Planning target volume, **BED:** Biologically effective dose, **CI:** Conformity index, **nCI:** New conformity index, **HI:** Homogeneity index, **GTV:** Gross tumor volume.*

with both local and distant brain recurrence, sole surgery was performed, and adjuvant radiotherapy was not applied because the pathological examination also revealed RN.

Toxicity

Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 was used for adverse event reporting (33).

Grade IV symptomatic RN was reported in a single case after 8 months of follow up. Surgery was performed and pathological examination revealed combined tumor recurrence and RN.

Three (18.8%) patients experienced fatal (grade V) post-operative complications, namely intracranial haemorrhage and increased intracranial pressure.

DISCUSSION

In clinical studies for the treatment of BM, it has been shown that aggressive local treatment improves both OS and quality of life in patients with a limited number of lesions (2,22). In a seminal study investigating role of post-operative radiotherapy in the treatment of single BM by Patchell et al. reported 70% intracranial recurrence with surgery alone, compared to 18% with the addition of adjuvant WBRT (21). Other randomized studies have also proven that postoperative radiotherapy improves LC, but has no impact on OS (11,17). The radio-therapeutic approaches for resected brain metastases

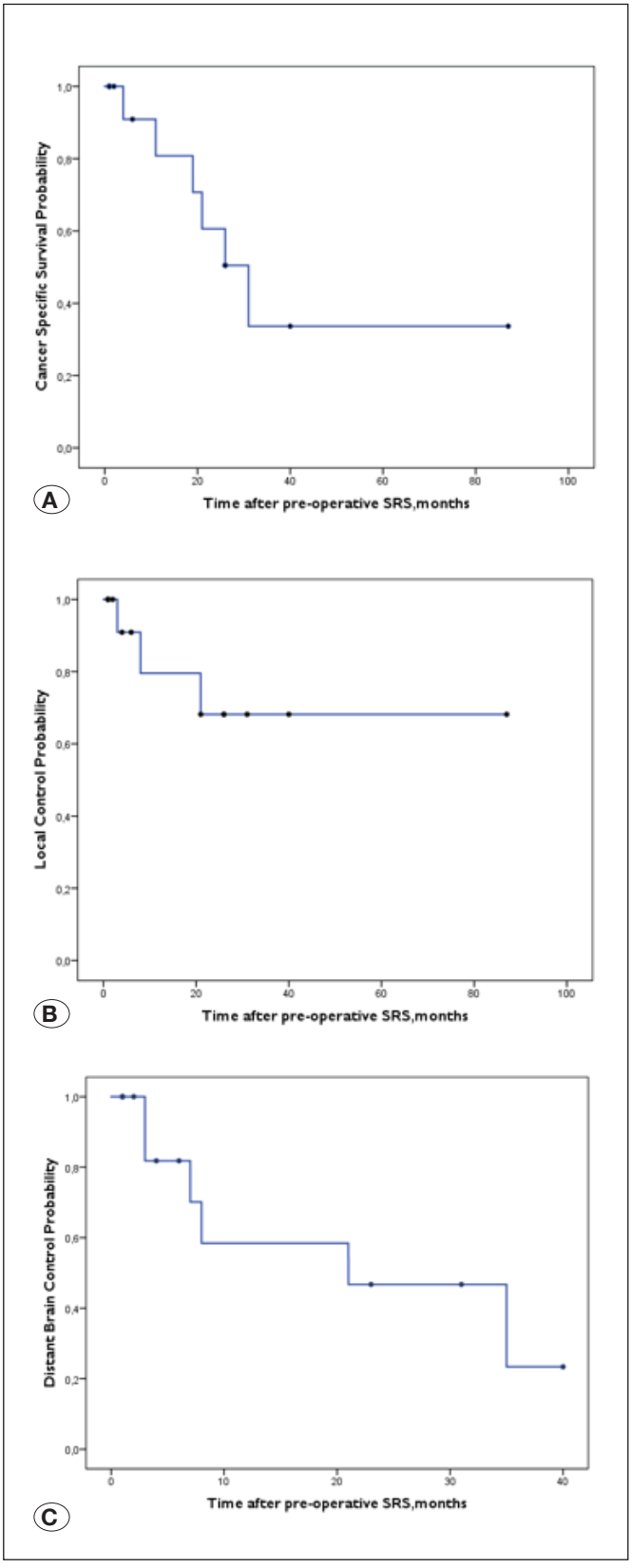

Figure 2: A) Cancer specific survival probability curve, **B)** Local control probability curve, **C)** Distant brain control probability curve.

have evolved significantly over the past decades. Over time, postoperative SRS has started to be investigated due to concerns about the deterioration of neurocognitive functions and quality of life with WBRT. Brown et al. conducted a landmark phase III study comparing postoperative WBRT with SRS in the treatment of single BM. After a median follow up of 11.1 months, SRS was reported to better preserve cognitive functions and quality of life as compared to WBRT without compromising OS (6). Six months after treatment, cognitive impairment was detected in 85% of patients receiving WBRT and 52% of patients receiving SRS ($p<0.001$) (6). Therefore, postoperative SRS is now widely accepted as the standard of care in patients with limited number of BM. However postoperative SRS also has several disadvantages. Delineating the tumor resection cavity for SRS can be challenging because of the irregular borders of the resection cavity, cavity dynamics, and other post-surgical changes on imaging (18). As well as the resection cavity, current guideline for clinical target volume (CTV) contouring recommends including the entire surgical tract and providing additional margins of up to 10 mm along the bone flap and up to 5 mm along the venous sinus, depending on the presence of preoperative dural/venous sinus contact (31). Although there is no clear recommendation for additional planning margin, it is frequently used in clinical practice and even margins up to 2 mm are used in randomized studies (6). Consequently, to achieve optimal target definition and thus adequate LC, they all result in a large target volume and an increase in normal brain tissue at risk for toxicity. Besides these concerns about planning, accumulating data on post-operative SRS has raised also questions about possible complications such as leptomeningeal spread and RN. Even resection itself is a risk factor for leptomeningeal spread due to tumor seeding in brain metastases (10). In a study of 465 patients treated with SRS, prior surgical resection is found as significant predictor of LMD on multivariate analysis ($p <0.01$) and the authors suggested that disruption of anatomical boundaries during surgery exposes meningeal surfaces to disease, resulting in a higher risk of LMD (9). Despite the attempt to overcome the shedding of tumor cells beyond cavity during surgery by a larger target delineation, there is still 3-fold increased risk of leptomeningeal dissemination with postoperative SRS as compared to WBRT (12). Furthermore, with postoperative SRS, the delivery of focused ablative radiation doses to hypoxic resection cavity led to concerns about RN. A meta-analysis on post-operative radiotherapy options revealed that post-operative SRS is associated with higher rates of RN with relative risk of 19.4 as compared to WBRT (12). Preoperative SRS is a new treatment paradigm that has emerged recently to overcome these disadvantages.

Preoperative SRS is an alternative treatment modality with many potential theoretical benefits. First, treating an intact brain metastasis allows for easy GTV delineation and does not require wide margin expansions to overcome target uncertainties. Second, preoperative SRS reduces the risk of intraoperative tumor seeding by sterilizing the tumor bed before surgery, thereby reducing the risk of LMD. Third, both irradiating smaller target volume and surgical resection of the surrounding irradiated healthy brain tissue reduces the risk of RN by reducing the release of cytokines that will catalyse RN. A dosimetric study of preoperative versus postoperative SRS on 24 patients revealed that despite smaller resection cavity volume than pre-operative lesion, target volume expansions end up with larger target volume and increased radiation dose exposure of healthy brain tissue in post-operative setting (7). Finally, irradiation of the tumor itself, rather than the postoperative hypoxic cavity, may provide a better response to radiotherapy. This theoretically rational concepts were supported by Patel et al. who published outcomes of 66 patients treated with preoperative SRS compared to 114 patients treated with postoperative SRS. They reported similar intracranial control and OS, but a lower risk of LMD (2 years: 3.2% vs 16.6%, $p=0.010$) and symptomatic RN (2 years: 4.9% vs 16.4%, $p=0.010$) with preoperative SRS compared to postoperative SRS (23).

The first report of pre-operative SRS in brain metastases was a series of 47 patients published in 2014 by Asher et al. They demonstrated that pre-SRS is effective and safe even in large tumors. They found LC rates to be 97.8%, 85.6%, and 71.8% at 6-, 12-, and 24-months follow-up, respectively (3). In the pooled analysis of 460 patients from seven studies investigating the preoperative SRS approach, the 1-year LC rate was 81% (20). In our study, LC rates at 6-, 12-, and 24- months are 91%, 79%, and 68%, respectively which is consistent with the literature. The most repetitively reported prognostic factor for LC in the literature was tumor volume of >10 mL (3,15,23). In our study, however, no significant relationship was found between tumor volume and LC. It should be noted that the tumor volume in our cohort was higher than those reported in other studies, and all but one of the patients included in analyses had an index tumor volume of >10 mL. Another factor reported in the literature to be associated with LC is the extent of resection. The PROPS-BM multicenter cohort study, published by Prabhu et al., which is the most comprehensive study on preoperative stereotactic radiosurgery (SRS) to date, identified subtotal resection (STR) as a strong independent predictor of LR (hazard ratio, 9.1; $p<.001$) (25). Nevertheless, in our study, no local progression was observed in follow-up for three out of the four patients with STR, and statistical analysis did not reveal a significant relationship between STR and LC. However, according to the results of univariate analyses in our study, the only factor that had a statistically significant effect on LC was better GTV coverage.

In our cohort, 6-, 12-, and 24- months DBC rates were 82%, 58% and 47%, respectively. In fact, DBC is a complex endpoint because, besides local disease and treatment characteristics, there are various confounders for DBC, such as extracranial disease control status and the use of systemic treatment agents. In our study, a significant relationship between extracranial disease control status and DBC could not be identified. However, we were unable to access information from the records regarding the systemic treatment agents used and whether these agents are active in the central nervous system; this is one of the limitations of our study. In our study, the only factor found to have an impact on DBC was the infratentorial location of the lesion. At the time of analysis, distant brain failure was detected in six (37.5%) patients, and

the index lesion was located infratentorial in all of them. To the best of our knowledge, our study is the first preoperative SRS study showing a relationship between infratentorial location and distant brain failure. There are studies reporting increased risk of distant brain failure following post-operative radiotherapy applied to the infratentorial lesion, which might be related to anatomically lesion proximity to the brain cisterns in infratentorial area and this proximity could also pave a way to leptomeningeal spread (5,30). However, in our cohort, none of the relapses were in the leptomeningeal pattern. Therefore, this finding needs to be confirmed in larger series and its pathophysiology needs to be further clarified. LMD is a rapidly progressive and fatal condition that develops as a result of metastatic disease spread through the leptomeninges and then the cerebrospinal fluid (CSF). In meta-analyses for preoperative SRS and postoperative SRS for BM, rates of LMD were reported to be 6% and 12.6%, respectively (1,20). In our recently published study, where we present our post-operative SRS results, the 1-year cumulative incidence of LMD was 11% (36). Consistent with the lower rates of LMD following preoperative SRS reported in the literature, none of the failures reported in our preoperative SRS cohort were of a leptomeningeal pattern.

RN is a well-known late side effect of SRS. In the meta-analysis of post-operative SRS for BM, the overall risk of radiation necrosis was reported as 6.9% (1). In comparison, in the meta-analysis of preoperative SRS for BM, actuarial rate of RN and symptomatic RN was found to be 6 % and 4% (20). In the study of Patel et al., the risk of symptomatic RN in the preoperative SRS cohort was reported as 4.9% (23). Consistent with the literature, RN was reported in a single case (6.3 %) in our study.

One of the major drawbacks about the preoperative SRS is the delivery of radiotherapy prior to the pathologic confirmation of metastatic disease. Historical randomized studies investigating the role of surgery in single BM reported up to 11% of non-BM histologies such as primary brain tumors or benign conditions (19,22). However, such an occurrence was not encountered in our study and pathological examination confirmed the diagnosis of BM in all patients.

One of the most striking finding of our study is the high surgical complication-related mortality. First publication on preoperative SRS by Asher et al. reported that there were no perioperative difficulties, complications or mortality; thus they offered surgical resection following preoperative SRS as a safe approach (3). In the PROPS-BM Multicenter Cohort Study, the postoperative surgical complication rate was reported as only 7% and was interpreted as similar to that expected in patients treated with upfront surgery (25). However, in our cohort, three (18.8%) patients experienced fatal post-operative surgical complications, namely intracranial haemorrhage and increased intracranial pressure. Most of the postoperative SRS data in the literature are also retrospective, and the presence or number of patients excluded for perioperative mortality were not stated in consort diagrams or study designs of prospective randomized studies. When we review the surgical series in the literature, although lower rates were reported, postoperative surgical mortality was mostly limited to 30 days (14,24). However, it should be noted that only one of our three postoperative surgical mortality cases died on the 30th day of surgery, while the others were even later. In conclusion, it is necessary to define better patient selection criteria for the preoperative SRS approach by making an appropriate pre-treatment evaluation in terms of surgical mortality, and also to better define and report postoperative surgical mortality.

The endpoints of neurocognitive functions and quality of life are crucial in terms of treatment options for brain metastases. Theoretically, preoperative SRS might be considered advantageous in these aspects due to smaller target volume definitions, and consequently, less exposure of healthy brain tissue to radiation. However, to the best of our knowledge, there are no studies in the literature reporting these endpoints in preoperative SRS. Due to the lack of detailed reporting on these endpoints in the patient records, our study could not contribute to the literature in this regard. This is one of the significant limitations of our study. The results of Phase III studies on these endpoints are eagerly awaited.

Although retrospective series have proven the potential benefits of preoperative SRS, ASCO-SNO-ASTRO consensus for management of BM states that no recommendation concerning the sequence of resection and radiotherapy can be made 35). Post-operative SRS still continues to be considered as the standard of care in clinical practice. Results from four ongoing randomized trials actively recruiting patients are expected to guide the timing of surgery and radiotherapy in BM with a stronger level of evidence (8,26,27,36).

The limitations of our study are its retrospective design, small sample size, inadequate documentation of systemic treatments and the lack of neurocognitive and quality of life assessments.

CONCLUSION

Preoperative SRS is a promising alternative strategy in the treatment of BM, with the advantage of lower RN and LMD rates as well as comparable local and intracranial control over postoperative SRS. The risk of surgical mortality should be better evaluated and strategies for selecting suitable patients for this treatment approach are needed.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: GY, NI, TH
Data collection: GY, MPV, NC
Analysis and interpretation of results: GY, MPV, NC, UY
Draft manuscript preparation: GY, MPV, NC
Critical revision of the article: GY, UY, NI, TH
Other (study supervision, fundings, materials, etc...): NI, TH
All authors (GY, MPV, NC, UY, NI, TH) reviewed the results and approved the final version of the manuscript.

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