Turkish Journal of Oncology

Turk J Oncol 2023;38(1):9–14
doi: 10.5505/tjo.2022.3591

ORIGINAL ARTICLE

Stereotactic Radiosurgery to the Resection Cavity in Patients with Brain Metastases: Patterns of Failure and Prognostic Factors

Uğur YILMAZ,[1] Gökhan YAPRAK,[1] Evren AYDOĞMUŞ,[2] Naciye IŞIK[1]

[1]Department of Radiation Oncology, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul-*Türkiye*
[2]Department of Neurosurgery, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul-*Türkiye*

OBJECTIVE

The objective of this study was to extensively analyze failure patterns of patients who received single or multi-fraction stereotactic radiosurgery (SRS) to the surgical cavity and to identify prognostic factors for recurrence and survival metrics.

METHODS

Patients with brain metastases who underwent surgical resection and then had SRS to the surgical cavity, between 2010 and 2021, at our department were identified. Local failure (LF), distant failure (DF), leptomeningeal disease (LMD), overall survival (OS), and salvage whole brain radiotherapy (WBRT) rates were calculated. Patient or treatment-related variables were evaluated for association with LF, DF, LMD, and OS.

RESULTS

Fifty-three patients with total of 54 operated metastases were identified. The median follow-up period was 13 months. Cumulative incidence rates of LF, LMD, and DF were 15%, 11%, and 37% at 1 year, respectively. Salvage WBRT was employed in 13 (26%) patients. DF was less frequent in patients with breast cancer primary compared to patients with other primaries (p=0.048, Hazard ratio [HR]:0.28) on univariate analysis. One-year OS rate was 54%. Median survival was 17 months. Eastern cooperative oncology group (ECOG) 0 performance status (p=0.0113; HR:0.328), being without active extracranial metastasis at the time of brain SRS (p=0.0035; HR:0.321), and metachronous brain metastases (p=0.0191; HR:0.399) were determined as statistically significant prognostic factors of survival on multivariate analysis.

CONCLUSION

SRS to surgical cavity seems optimal treatment modality especially for the patients with one of the following factors including ECOG 0 performance status, not having an active extracranial metastasis at the time of SRS, and metachronous brain metastases.

Keywords: Brain metastases; stereotactic radiosurgery; surgical cavity.

Received: March 30, 2022
Accepted: September 13, 2022
Online: November 15, 2022

Accessible online at:
www.onkder.org

Dr. Uğur YILMAZ
Kartal Dr. Lütfi Kırdar Şehir Hastanesi,
Radyasyon Onkolojisi Kliniği,
İstanbul-Türkiye
E-mail: druguryilmaz@gmail.com

Turk J Oncol 2023;38(1):9–14
doi: 10.5505/tjo.2022.3591

INTRODUCTION

Surgical resection of brain metastases is usually indicated for the treatment of large lesions with mass effect that can consequentially cause serious neurological symptoms. However, despite advances in surgical techniques and adjuncts, local control rates after brain metastasis resections remain relatively low (freedom from local recurrence around 30% to 43% at 1 year) even in the setting of magnetic resonance imaging (MRI) verified gross total resection.[1,2] Whole brain radiotherapy (WBRT) after surgical resection improves local control at the surgical site and decreases the incidence of distant brain metastases.[2] Therefore, WBRT has traditionally been employed as a standard of care following surgical resection of brain metastases. However, due to the negative cognitive effects of WBRT, less toxic approaches which would provide adequate disease control was sought.

Stereotactic radiosurgery (SRS) to the surgical cavity has been more widely applied in recent years with the benefit of improved local control over surgery alone and decreased neurocognitive decline compared to WBRT.[1,3] Moreover, despite reduction in distant brain control, overall survival (OS) was similar with SRS to the surgical bed compared to WBRT.[3] Hence, administering SRS to the surgical cavity could be an effective strategy to reduce local recurrence and to delay or to avoid WBRT.

We, herein, reviewed and analyzed the data of our patients who received single or multi-fraction SRS to the surgical cavity following brain metastases surgery.

MATERIALS AND METHODS

Patients

Patients with brain metastases who underwent surgical resection and then had single or multi-fraction SRS to the surgical bed, between 2010 and 2021, at our department were identified from institutional database. Patients were excluded if they had prior WBRT or had WBRT just after SRS without any disease progression. The patient, tumor and treatment characteristics, and follow-up medical records were retrospectively reviewed. Brain metastases were defined according to the time of their detection as follows: Precocious metastases, identified before primary tumor diagnosis; synchronous metastases, identified within 2 months after the initial diagnosis of the primary cancer; and metachronous metastases, identified 2 months or more after the initial diagnosis of the primary cancer.[4]

SRS and Follow-up Evaluation

All patients had a pre-operative brain MRI with contrast and a pre-RT T1-weighted post-gadolinium MRI that was acquired with a slice thickness of 1 mm. Patients underwent immobilization with a five-point thermoplastic mask and planning computed tomography (CT) scan was obtained in the treatment position. Pre-RT MRI was fused to planning CT scan for quantifying the extent of resection and identifying target. Clinical target volume (CTV) and organs at risk were delineated. The planning target volume (PTV) was defined as CTV plus a 1 mm margin. The number of treatment fractions varied between one and five based on PTV volume. The total radiation dose between 15 Gy and 30 Gy was prescribed. Dose planning was performed with the Multiplan Software (Accuray Inc., Sunyvale, CA, USA). CyberKnife treatment was performed in an outpatient setting.

Follow-up after treatment consisted of clinical examination and brain MRI with contrast within 3 months of SRS and then at 3-month intervals, unless clinically indicated at an earlier time point.

Outcomes

All times to event were measured from the date of SRS. Event was defined as follows: For local failure (LF), as a new contrast-enhancing lesion, contiguous with or within the surgical cavity, that was depicted by MRI scan; for distant failure (DF), as occurrence of new brain parenchymal metastases apart from the surgical site; and for leptomeningeal disease (LMD), as occurrence of LMD that was determined by MRI scan and clinical signs. Patients without an event were censored at the last contact date or at the time of salvage WBRT for failure metrics. OS was calculated from the date of SRS to the date of death or censoring at last clinical follow-up.

Variables evaluated for association with LF, DF, LMD, or OS included age (as a continuous variable evaluated only for OS), gender, the Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1 to 2), the timing of brain metastases identification (metachronous versus precocious or synchronous), primary cancer (breast vs. others), active extracranial metastases, number of brain metastases (1 vs. 2 to 4), location of lesion (supratentorial vs. infratentorial), tumor maximal dimension before surgery (≤3 cm vs. >3 cm), dural contact, venous sinus contact, extent of surgery (total vs. subtotal excised), and number of SRS fractions (1 vs. 2 to 5).

Statistics

Rates of LF, DF, and LMD were calculated using cumulative incidence methodology, accounting for death as competing risk. OS rate was estimated using the Kaplan-Meier method.

Variables associated with LF, DF, and LMD were analyzed using the Gray's test for equality of cumulative incidence functions, with death considered a competing risk. Variables associated with OS were evaluated with Cox proportional hazards regression model on both univariate and multivariate analysis. Multivariate analysis was performed with the variables which were found statistically significant on the univariate analysis. Hazard ratios and 95% confidence intervals were calculated.

Statistical analysis was carried out with statistical software package 9.4 of the SAS system for Windows, 2002–2012 SAS Institute, Inc., Cary, NC. P<0.05 is considered statistically significant.

RESULTS

Patient and Tumor Characteristics

Fifty-three patients with total of 54 operated metastases from 2010 to 2021 were identified. Surgery was performed to 38 patients having only one metastasis. Fifteen patients had two to four metastases, and only one metastasis was operated for 14 of them and two metastases were removed only for one patient. Remaining unresected metastases were treated with SRS. Median age was 56 years for all patient cohort whereas 60 and 51 years for men and women, respectively. Baseline patient and tumor characteristics are showed in Tables 1 and 2.

Survival and Failures

At the time of medical records' review, 36 (67.9%) of 53 patients had died, and 17 (32.1%) of 53 patients were alive. The median follow-up period for all patients and alive patients were 13 months (range 1–143) and 20 months (range 5–143), respectively. Isolated LF, LMD and DF occurred in four (7.5%), two (3.8%), and 17 (32.1%) of 53 patients, respectively. Five (9.4%) of 53 patients had both LF and DF, two (3.8%) patients had both LF and LMD, and one (1.9%) patient had LF, DF, and LMD. All of five LMD events occurred within 1 year after SRS.

Cumulative incidence rates of LF, LMD, and DF were 15% (95% confidence interval [CI], 7–27), 11% (95% CI, 4–21), and 37% (95% CI, 23–50) at 1 year, respec-

Table 1 Baseline patient characteristics

Patient characteristics	n	%
Age, years, median (range)	56 (20–73)	
Gender		
Male	30	56.6
Female	23	43.4
ECOG performance status		
0	16	30.2
1–2	37	69.8
Primary cancer		
NSCLC	23	43.4
Breast	10	18.9
Others	20	37.7
Active extracranial metastases		
Yes	18	34
No		
Treated	3	5.7
Extracranial metastases not present	32	60.4
The timing of brain metastases identification		
Precocious	19	35.8
Synchronous	5	9.4
Metachronous	29	54.7
Number of brain metastases		
1	38	71.7
2–4	15	28.3

ECOG: Eastern cooperative oncology group; NSCLC: Non-small cell lung cancer

Table 2 Tumor characteristics

Tumor characteristics	n	%
Location of lesion		
Supratentorial	38	71.7
Infratentorial	15	28.3
Tumor maximal dimension before surgery, median (range), cm	3.5 (1.7–6.7)	
≤3 cm	16	34†
>3 cm	31	66†
Dural contact		
Yes	34	72.3†
No	13	27.7†
Venous sinus contact		
Yes	8	17†
No	39	83†
Extent of surgery		
Total excised	41	77.4
Subtotal excised	12	22.6
Volume of PTV (cc), median (range)	15.2 (3.2–67.7)	
Number of SRS fractions		
1	10	18.9
2–5	43	81.1

†: Valid percents, missing data excluded. PTV: Planning target volume; SRS: Stereotactic radiosurgery

Turk J Oncol 2023;38(1):9–14
doi: 10.5505/tjo.2022.3591

tively. There was not any factor that showed statistical significance for the association with LF or LMD. However, DF was low in patients with breast cancer primary compared to patients with other primaries (p=0.048, Hazard ratio [HR]:0.28) on univariate analysis.

One-year OS rate was 54% (Fig. 1). Median survival was 17 months (95% CI, 11–25). Univariate analysis revealed the following factors to be statistically significant predictors of improved survival: female gender (p=0.0214; HR:0.444), breast cancer primary (p=0.0325; HR:0.341), ECOG 0 performance status (p=0.0085; HR:0.322), being without active extracranial metastasis at the time of brain SRS (p=0.0003; HR:0.277), and metachronous brain metastases (p=0.0056; HR:0.357) (Table 3). Of them, ECOG 0 performance status (p=0.0113; HR:0.328), being without active extracranial metastasis at the time of brain SRS (p=0.0035; HR:0.321), and metachronous brain metastases (p=0.0191; HR:0.399) factors remained as statistically significant predictors of survival on multivariate analysis (Table 3).

Salvage WBRT

Salvage WBRT was employed in 13 (26%) patients. Of those patients, median time to salvage WBRT after SRS was 12 months (range 2–21).

DISCUSSION

Surgical spillage of tumor cells at the time of surgery is one of the causative factors for the development of LMD following resection of brain metastases, particularly those in the posterior fossa.[5] Thus, patients treated with SRS after surgery have increased risk of LMD development compared to those undergoing SRS to intact lesions.[6] However, although WBRT has a hypothetical advantage over SRS for sterilizing spilled tumor cells, LMD rate was not different between treatment arms consisting of SRS and WBRT after resection

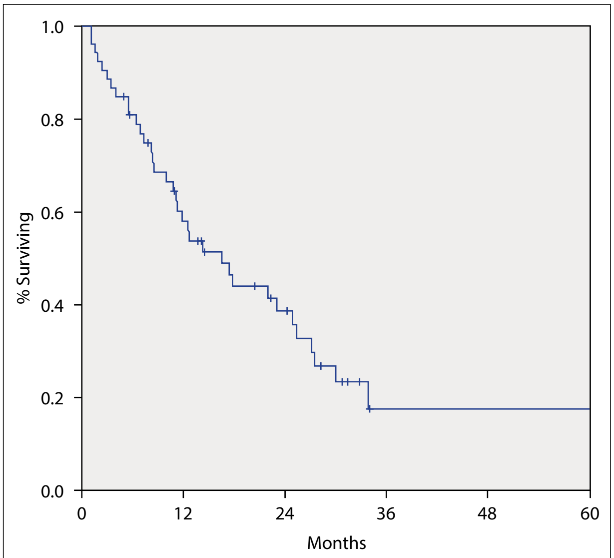

Fig. 1. Overall survival rate.

of metastatic brain disease in phase 3 NCCTG N107C/CEC3 trial.[3] Indeed, SRS to surgical cavity spares patients from the neurocognitive and quality of life side effects related with WBRT and provides similar OS despite reduction in distant brain control.[3]

Cumulative incidence rate of LMD was 11% at 1 year in our patient cohort, with death as a competing risk, respectively. Our result seems relatively similar to those reported in prior studies which were around 7% to 17%.[3,6,7] Cumulative incidence rate of DF was 37% at 1-year in our study and it was supported by the result of phase 3 NCCTG N107C/CEC3 trial in which DF rate was 35.3% at 1-year.[3] Cumulative incidence rate of LF was 15% at 1 year in our patient cohort. The diagnosis of LF was determined by MRI and was not confirmed by pathological evaluation. This could be a limitation of our study. However, although LF occurred in 12 (23%) of 53 patients, isolated LF was ob-

Table 3 Univarite and multivariate analysis of factors associated with overall survival

	Univariate analysis		Multivariate analysis	
Patient characteristics	**p**	**HR**	**p**	**HR**
Female gender	0.0214	0.444	0.0554	0.447
Breast cancer primary	0.0325	0.341	0.627	1.386
ECOG 0 performance status	0.0085	0.322	0.0113	0.328
Without active extracranial metastasis	0.0003	0.277	0.0035	0.321
Metachronous metastasis	0.0056	0.357	0.0191	0.399

ECOG: Eastern cooperative oncology group; HR: Hazard ratio served in only 4 (7.5%), relatively small percentage of, patients. Salvage WBRT was applied to approximately one-fourth of our patient cohort due to LF, LMD, or DF, and those patients underwent salvage WBRT with a median time interval of 1 year after SRS. These results demonstrated that cavity SRS seems to be an optimal treatment approach for operated brain metastases, despite the increased risk of higher LMD incidence and the reduction of distant brain control over WBRT.

Our analysis found that LF and LMD were not statistically significantly influenced by any factor. This could be due to the relatively small sample size of our patient cohort. However, patients with breast cancer primary had decreased DF (p=0.048, HR:0.28) on univariate analysis. Improved systemic therapies applied in breast cancer might lead to this outcome. Nonetheless, it is difficult to draw such conclusion due to the presence of small number of patients with breast cancer, 10 (18.9%) patients, in our study.

Fractionation was not same between studies; some used single fraction SRS, while others used multi-fraction SRS. Multi-fraction SRS could be favorable for avoiding potential enhanced clinical side effects resulted from single fraction SRS applied for large metastases. There also exist discrepancies in survival rates between studies. These inconsistent results seem due to the retrospective nature of the studies and existence of highly heterogeneous histologies in the studies. One-year OS rates were from 41.8% to 70% for post-operative SRS and from 58% to 81.9% for post-operative multi-fraction SRS in retrospective studies.[8] Median OS was 12.3 months for patients who underwent post-operative SRS in phase 3 NCCTG N107C/CEC3 trial.[3] Number of fraction varied from one to five in our study, and 1-year OS rate and median survival were 54% and 17 months, respectively. We found ECOG 0 performance status (p=0.0113; HR:0.328), being without active extracranial metastasis at the time of brain SRS (p=0.0035; HR:0.321), and metachronous brain metastases (p=0.0191; HR:0.399) to be predictive of improved OS on multivariate analysis. Therefore, these factors could pave a way for physicians to make the appropriate therapeutic decision.

Limitations of the Study

We acknowledge that our study has several limitations. Those include being retrospective, including fairly heterogeneous patient population, and small sample size. However, most of the studies on this subject have similar limitations.

CONCLUSION

WBRT could be avoided in three-quarter of patients with operated brain metastases and even could be delayed with a median time of 1 year in remaining one quarter. Thus, SRS to surgical cavity seems optimal treatment especially for the patients with one of the following factors including ECOG 0 performance status, not having an active extracranial metastasis at the time of brain SRS, and metachronous brain metastases.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (no: 2022/514/220/7, date: 22.02.2022).

Financial Support: None declared.

Authorship contributions: Concept – U.Y., G.Y., E.A., N.I.; Design – U.Y., G.Y., E.A., N.I.; Supervision – U.Y., G.Y., E.A., N.I.; Funding – U.Y.; Materials – U.Y., G.Y., E.A., N.I.; Data collection and/or processing – U.Y.; Data analysis and/or interpretation – U.Y.; Literature search – U.Y.; Writing – U.Y.; Critical review – U.Y., G.Y., E.A., N.I.

REFERENCES

1. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol 2017;18(8):1040–8.
2. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998;280(17):1485–9.
3. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 2017;18(8):1049–60.
4. Shibahara I, Kanamori M, Watanabe T, Utsunomiya A, Suzuki H, Saito R, et al. Clinical features of precocious, synchronous, and metachronous brain metastases and the role of tumor resection. World Neurosurg 2018;113:e1–e9.
5. Dankner M, Lam S, Degenhard T, Garzia L, Guiot MC, Petrecca K, et al. The underlying biology and therapeutic vulnerabilities of leptomeningeal metastases in adult solid cancers. Cancers (Basel) 2021;13(4):732.

Turk J Oncol 2023;38(1):9–14
doi: 10.5505/tjo.2022.3591

6. Johnson MD, Avkshtol V, Baschnagel AM, Meyer K, Ye H, Grills IS, et al. Surgical resection of brain metastases and the risk of leptomeningeal recurrence in patients treated with stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 2016;94(3):537–43.
7. Atalar B, Modlin LA, Choi CY, Adler JR, Gibbs IC, Chang SD, et al. Risk of leptomeningeal disease in patients treated with stereotactic radiosurgery targeting the postoperative resection cavity for brain metastases. Int J Radiat Oncol Biol Phys 2013;87(4):713–8.
8. Minniti G, Niyazi M, Andratschke N, Guckenberger M, Palmer JD, Shih HA, et al. Current status and recent advances in resection cavity irradiation of brain metastases. Radiat Oncol 2021;16(1):73.