Scientific Article

Outcomes in Patients with Intact and Resected Brain Metastasis Treated with 5-Fraction Stereotactic Radiosurgery

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Abstract

Purpose: Hypofractionated stereotactic radiosurgery (HF-SRS) with or without surgical resection is potentially a preferred treatment for larger or symptomatic brain metastases (BMs). Herein, we report clinical outcomes and predictive factors following HF-SRS.
Methods and Materials: Patients undergoing HF-SRS for intact (iHF-SRS) or resected (rHF-SRS) BMs from 2008 to 2018 were retrospectively identified. Linear accelerator-based image-guided HF-SRS consisted of 5 fractions at 5, 5.5, or 6 Gy per fraction. Time to local progression (LP), time to distant brain progression (DBP), and overall survival (OS) were calculated. Cox models assessed effect of clinical factors on OS. Fine and Gray's cumulative incidence model for competing events examined effect of factors on LP and DBP. The occurrence of leptomeningeal disease (LMD) was determined. Logistic regression examined predictors of LMD.
Results: Among 445 patients, median age was 63.5 years; 87% had Karnofsky performance status ≥70. Fifty-three % of patients underwent surgical resection, and 75% received 5 Gy per fraction. Patients with resected BMs had higher Karnofsky performance status (90-100, 41 vs 30%), less extracranial disease (absent, 25 vs 13%), and fewer BMs (multiple, 32 vs 67%). Median diameter of the dominant BM was 3.0 cm (interquartile range, 1.8-3.6 cm) for intact BMs and 4.6 cm (interquartile range, 3.9-5.5 cm) for resected BMs. Median OS was 5.1 months (95% confidence interval [CI], 4.3-6.0) following iHF-SRS and 12.8 months (95% CI, 10.8-16.2) following rHF-SRS ($P < .01$). Cumulative LP incidence was 14.5% at 18 months (95% CI, 11.4-18.0%), significantly associated with greater total GTV (hazard ratio, 1.12; 95% CI, 1.05-1.20) following iFR-SRS, and with recurrent versus newly diagnosed BMs across all patients (hazard ratio, 2.28; 95% CI, 1.01-5.15). Cumulative DBP incidence was significantly greater following rHF-SRS than iHF-SRS ($P = .01$), with respective 24-month rates of 50.0 (95% CI, 43.3-56.3) and 35.7 (95% CI, 29.2-42.2). LMD (57 events total; 33% nodular, 67% diffuse) was observed in 17.1% of rHF-SRS and 8.1% of iHF-SRS cases (odds ratio, 2.46; 95% CI, 1.34-4.53). Any radionecrosis and grade 2+ radionecrosis events were observed in 14 and 8% of cases, respectively.

Disclosures: 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.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: HF-SRS demonstrated favorable rates of LC and radionecrosis in postoperative and intact settings. Corresponding LMD and RN rates were comparable to those of other studies.

Introduction

Stereotactic radiosurgery (SRS) is the preferred local treatment for many patients with brain metastasis (BMs). Radiation Therapy Oncology Group 90-05 prospectively established a standardized single-fraction SRS (SF-SRS) dosing regimen based on lesion size;[1] however, for BMs greater than 2 cm, this regimen is associated with decreased local control (LC) and increased risk of radionecrosis (RN).[2-5] Alternatively, hypofractionated SRS (HF-SRS) with or without surgical resection may maximize the therapeutic ratio for larger BMs, reducing toxicity aor improving LC.[6] In the absence of randomized comparisons between SF- and HF-SRS, several series demonstrate equivocal rates of LC and decreased risk of RN following HF-SRS.[7-17]

Despite the emerging central role of HF-SRS for larger BMs, optimal target volumes and planning parameters remain a matter of debate. Moreover, within the evolving context of multidisciplinary BM management, associations of patient- and tumor-specific parameters to clinical outcomes following HF-SRS remain poorly understood. Herein, we report clinical outcomes, associated predictive factors, and toxicity rates following 5-fraction HF-SRS.

Methods and Materials

For this institutional review board−approved retrospective review, we identified all patients who completed an initial HF-SRS course for intact (iHF-SRS) and resected (rHF-SRS) brain metastases at our institution between 2008 and 2018. Prior SF-SRS, surgical resection, or whole brain radiation therapy were allowed. Demographic variables, clinical characteristics, and treatment parameters were obtained.

All patients underwent linear accelerator-based, image-guided HF-SRS, for which patients were simulated in the supine position with head immobilization using a frameless stereotactic mask. Gross tumor volume (GTV) was defined as contrast enhancing tumor on T1 contrast enhanced thin-sliced axial magnetic resonance image (MRI) (typically an axial 3-dimensional spoiled gradient with a 1-mm thickness), fused with treatment planning axial computed tomography (CT) images (- mm thickness).[18] Planning target volumes (PTVs) for iHF-SRS and rHF-SRS were created by expanding the contrast-enhancing GTV by 1 mm[19] and postoperative resection cavity including any dural attachment and residual enhancement by 2 mm, respectively.[20,21] The decision to hypofractionate SRS was at the discretion of the treating physician, according to tumor size (PTV > 3 cm in greatest dimension), volume of normal brain parenchyma that would receive a dose of ≥12 Gy if delivered in a single fraction (V12, >15 mL), and tumor location (eg, brain stem, motor strip, or other eloquent location).[1,3,4] All patients received 5, 5.5, or 6 Gy per fraction, prescribed to the 100% isodose line. The decision to treat to 5, 5.5, or 6 Gy per fraction was left to the discretion of the individual radiation oncologist, generally based on BM size, histology, and location. In general, for cases involving multiple BMs, HF-SRS was used across all BMs if indicated for ≥1 dominant lesions. HF-SRS was delivered using a Varian TrueBeam STx linear accelerator (Varian, Palo Alto, CA, USA) or, before 2011, a Novalis Tx (Varian, Palo Alto, CA, USA) with daily cone beam CT and 6° of freedom motion couch.

RN and LC were determined by multidisciplinary clinical consensus, which retrospectively incorporated findings from serial MRI brain scans, response to steroids, and, when available, histopathologic diagnosis. Where histopathologic diagnosis was not available, subsequent serial MRI was used to confirm initial RN/LC diagnoses, the latter defined per Response Assessment in Neuro-Oncology criteria.[22] Distant brain progression (DBP) was recorded independently from LC. RN events were graded using Common Terminology Criteria for Adverse Events v5.0 criteria.

Time to local progression (LP) (eg, LC), time to DBP, and overall survival (OS) were calculated. Univariate and multivariate Cox proportional hazard models assessed the effect of clinical factors on OS. Fine and Gray's cumulative incidence model for competing events examined the effect of clinical factors on LP and DBP. The occurrence of leptomeningeal disease (LMD) was determined, and multivariable logistic regression examined predictors of LMD. Analyses were performed using SAS version 9.4 (Cary, NC, USA).

Results

Across 445 patients, median follow-up was 39.4 months. The length of follow-up of patients alive at the time of analysis ranged between .23 and 87.8 months. Patients were predominantly female (53%) and Karnofsky performance status ≥70 (87%), with a median age of 63.5 years at time of HF-SRS. Common primary tumor sites were lung (43%), breast (16%), gastrointestinal

(11%), skin (11%), and genitourinary (11%), with evidence of extracranial metastatic disease in 77% of cases at time of HF-SRS (Table 1). rHF-SRS and iHF-SRS comprised 53 and 47% of cases, respectively, with ≥2 brain metastases present in 32% of rHF-SRS and 67% of iHF-SRS cases. Following HF-SRS, 70% of patients received immunotherapy, a small molecule inhibitor (IT/SMI).

Lesion-specific parameters are provided in Table E1 for 781 intact BMs (76%) and 249 resected BMs (24%). Nineteen percecnt of BMs had received local treatment before HF-SRS, primarily consisting of whole brain radiation therapy (16%) or SRS (5%). Dural contact was observed for 230 of 781 intact BMs (29%) and 191 of 249 resected BMs (77%). More than 99% of BMs received <6 Gy per fraction; 69% and 75% of intact and resected BMs received 5 Gy per fraction, respectively. Across all patients, maximum diameter of the dominant BM was 3.0 cm (interquartile range [IQR], 2.3-3.7) axially and 3.9 cm (IQR, 3.1-4.9) across any orientation. For all intact BMs, mean values included a maximum axial diameter of 1.33 cm (standard deviation [SD], 1.08), GTV of 3.31 cc (SD, 6.67), conformity index of 1.60 (SD, 0.68), and GTV maximum dose of 30.09 Gy (SD, 2.14), while the maximum diameter of the dominant BM was 3.0 cm (IQR, 1.8-3.6) across any orientation. For all resected BMs, mean values included a maximum axial diameter of 3.47 cm (SD, 1.09), GTV of 19.37 cc (SD, 14.88), conformity index of 1.14 (SD, 0.09), and GTV maximum dose of 29.22 Gy (SD, 1.95), while the maximum diameter of the dominant resection cavity was 4.6 cm (IQR, 3.9-5.5) across any orientation.

As shown in Figure 1A, median OS across all patients was 8.3 months (95% confidence interval [CI], 7.2-9.7). Median OS was 5.1 months (95% CI, 4.3-6.0) following iHF-SRS and 12.8 months (95% CI, 10.8-16.2) following rHF-SRS ($P < .01$). At 12, 24, and 60 months following rHF-SRS, OS was 52.1 (95% CI, 45.5-58.4), 34.2 (27.9-40.6%), and 19.7% (95% CI, 13.3-27.0), respectively (Figure 1B). At the same time points following iHF-SRS, OS was 20.4 (95% CI, 15.2-26.1), 10.3% (95% CI, 6.6-15.0), and 3.8% (95% CI, 1.4-8.1) at 12, 24, and 60 months, respectively. For patients completing iHF-SRS, clinical factors associated with OS on multivariate analysis included post-SRS receipt of IT/SMI (hazard ratio [HR], 0.48; 95% CI, 0.33-0.69) and ≥6 versus 1 brain metastases (HR, 1.71; 95% CI, 1.08-2.70; Table 2). For patients completing rHF-SRS, clinical factors associated with OS included post-SRS receipt of IT/SMI (HR, 0.42, 95% CI, 0.28-0.64), BM-related neurologic symptoms (HR, 1.95; 95% CI, 1.32-2.88) and dural contact (HR, 0.68; 95% CI, 0.44-0.99; Table 2).

Across all patients, cumulative incidence of LP was 7.4% (95% CI, 5.2-10.1) at 6 months, 13.6% (95% CI, 10.6-17.0) at 12 months, and 14.5% (95% CI, 11.4-18.0) at 18 months (Figure 1C). No significant differences in LP were observed across resected versus intact cases (Figure

1D; $P = .41$). On multivariable analyses for patients completing iHF-SRS, greater total GTV (cc) was significantly associated with greater LP risk (HR, 1.12; 95% CI, 1.05-1.20). No significant associations to LP were found among those completing rHF-SRS. Across all patients, LP was significantly associated with recurrent rather than newly diagnosed BMs (HR, 2.28; 95% CI, 1.01-5.15; Table 3).

Figure 1E provides cumulative incidence of DBP across all patients, which was significantly greater following rHF-SRS than iHF-SRS ($P = .01$). Cumulative incidence of DBP following rHF-SRS was 32.6% (95% CI, 26.7-38.7) at 6 months, 46.1% (95% CI, 39.5-52.4) at 12 months, and 50.0% (95% CI, 43.3-56.3) at 24 months (Figure 1F). Following iHF-SRS, cumulative incidence of DBP was 28.9% at 6 months (95% CI, 22.9-35.1), 33.7% at 12 months (95% CI, 27.3-40.1), and 35.7% at 24 months (95% CI, 29.2-42.2). On multivariable analysis, cumulative incidence of DBP was not associated with any patient- or tumor-specific factors aside from postoperative status (Table E2).

LMD was identified in 57 patients (33% nodular, 67% diffuse) following HF-SRS, including 40 patients treated with rHF-SRS (22% nodular, 78% diffuse) and 17 patients treated with iHF-SRS (59% nodular, 41% diffuse). LMD involvement was regional in 37 patients (65%); across all patients with LMD, involved sites included right hemisphere (33%), left hemisphere (26%), posterior fossa (28%), cistern (25%), lateral and/or third ventricles (11%), and fourth ventricle (21%). On multivariable analysis among all patients (Table 4), clinical factors associated with LMD included postoperative status (rHF-SRS, 17.1%, iHF-SRS, 8.1%; odds ratio [OR], 2.10; 95% CI, 1.03-4.27) and primary site (lung vs breast OR, 0.45; 95% CI, 0.22-0.93; other vs breast OR, 0.32; 95% CI, 0.15-0.68). The percentage of rHF-SRS and iHF-SRS patients who experienced LMD were 17.1% and 8.1%, respectively. Following iHF-SRS, presence of LMD was associated with lung vs breast (OR, 0.18; 95% CI, 0.05-0.68) and other vs breast (OR, 0.23; 95% CI, 0.07-0.79) primary sites, while no clinical factors were associated with LMD following rHF-SRS. On exploratory analysis, rates of LMD were proportionally greater following rHF-SRS than iHF-SRS within cases of lung and other primary sites origin in comparison to breast (Table E1). Similarly, rates of LMD were proportionally greater following rHF-SRS than iHF-SRS in cases without IT/SMI receipt (Table E3).

RN was identified in 63 patients (14%). The maximum RN grade experienced was grade 2 or higher in 37 patients (8%), 18 of whom underwent biopsy confirmation (Table 5). Grade 2 or higher RN was observed in 6% of patients completing iHF-SRS including a single grade 5 event (0.5%), as well as 11% of patients completing rHF-SRS including a single grade 4 event (0.4%). Among patients with documented RN, median time from SRS

Table 1   Demographic, clinical, and treatment parameters are provided for all patients by postoperative status

| | Postoperative status | | | |
| | No | | Yes | |
Characteristic	N	%	N	%
Sex				
Female	124	58.8	114	48.7
Male	87	41.2	120	51.3
Age at SRS (y)				
Mean (SD)	62.4 (11.8)	-	61.7 (11.9)	-
Range	22-87	-	25-84	-
White race				
No	41	19.4	58	24.8
Yes	170	80.6	176	75.2
KPS				
30	1	0.5	0	0.0
40	4	1.9	2	0.9
50	12	5.7	4	1.7
60	19	9.0	16	6.8
70	56	26.5	44	18.8
80	56	26.5	72	30.8
90	54	25.6	88	37.6
100	9	4.3	8	3.4
Primary site				
Breast	36	17.1	37	15.8
GI	18	8.5	32	13.7
GU	27	12.8	22	9.4
Lung	92	43.6	101	43.2
Other	16	7.6	14	6.0
Skin	22	10.4	28	12.0
Systemic burden				
Present	182	86.3	162	69.2
Absent	27	12.8	59	25.2
Unknown	2	1.0	13	5.6
Newly diagnosed or recurrent				
Newly diagnosed	163	77.3	195	83.3
Recurrent	48	22.8	39	16.7
Dural contact				
No	77	36.5	54	23.1
Yes	134	63.5	180	76.9
Location				
Frontal	21	10.0	67	28.6
Parietal	18	8.5	33	14.1
Cerebellum	34	16.1	66	28.2

Table 1 (*Continued*)

| | Postoperative status | | | |
| | No | | Yes | |
Characteristic	N	%	N	%
Brain stem	19	9.0	0	0.0
Temporal	6	2.8	26	11.1
Occipital	6	2.8	32	13.7
Cavernous sinus/BOS	13	6.2	0	0.0
Multiple	94	44.6	10	4.3
Number of metastases				
1	69	32.7	159	68.0
2	39	18.5	42	18.0
3-5	57	27.0	27	11.5
≥6	46	21.8	6	2.6
Receipt of immunotherapy or small molecule inhibitor				
No	145	68.7	165	70.5
Yes	66	31.3	69	29.5
Radiation therapy				
5 Gy	159	75.4	174	74.4
5.5 or 6 Gy/fraction*	52	24.6	60	25.6
Prior WBRT				
No	167	79.2	220	94.0
Yes	44	20.9	14	6.0

Treatment parameters	Median (IQR)		Median (IQR)	
Total planned target volume (cc)	13.99 (6.06-25.47)		28.45 (20.19-42.24)	
Total gross tumor volume (cc)	9.54 (17.6-62.7)		16.0 (24.0-99.5)	
Brain V24 (cc)	19.00 (7.52-30.96)		38.74 (27.83-55.52)	
Maximum lesion axial diameter (cm)	2.55 (1.70-3.27)		3.40 (2.70-4.10)	
Maximum lesion diameter, any axis (cm)	3.09 (1.96-3.73)		4.64 (3.92-5.49)	
Time between craniotomy and SRS (mo)	—		0.89 (0.76-1.08)	

Abbreviations: GI = gastrointestinal; GU = genitourinary; IQR = interquartile range; KPS = Karnofsky performance status; BOS = base of skull; SD = standard deviation; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

* A single patient received 6 Gy per fraction.

completion to any grade 1 to 5 RN event was 8.0 months (IQR, 5.3-19.1).

Discussion

HF-SRS is commonly used for BMs that are >2 cm, resected, or adjacent to critical organs at risk. For consecutive BM patients undergoing HF-SRS with or without surgical resection at a single institution between 2008 to 2018, we report rates of OS, time to LP, time to DBP, leptomeningeal progression, and RN. Clinical outcomes and toxicity rates of the present report compare favorably to prior HF-SRS series across intact[7,11-14,16,17,23] and postoperative[9,15] settings (Table E4),[24] despite greater proportions of recurrent disease, multiple BMs, and comparatively smaller RT doses (75% patients receiving 5 Gy per fraction).

The distribution of demographic and clinical parameters across iHF-SRS and rHF-SRS cases appears consistent with clinical criteria for surgical resection, many of which are associated with favorable OS: greater Karnofsky performance status, younger age, limited extracranial disease, and fewer brain metastases.[25-28] Accordingly, OS was
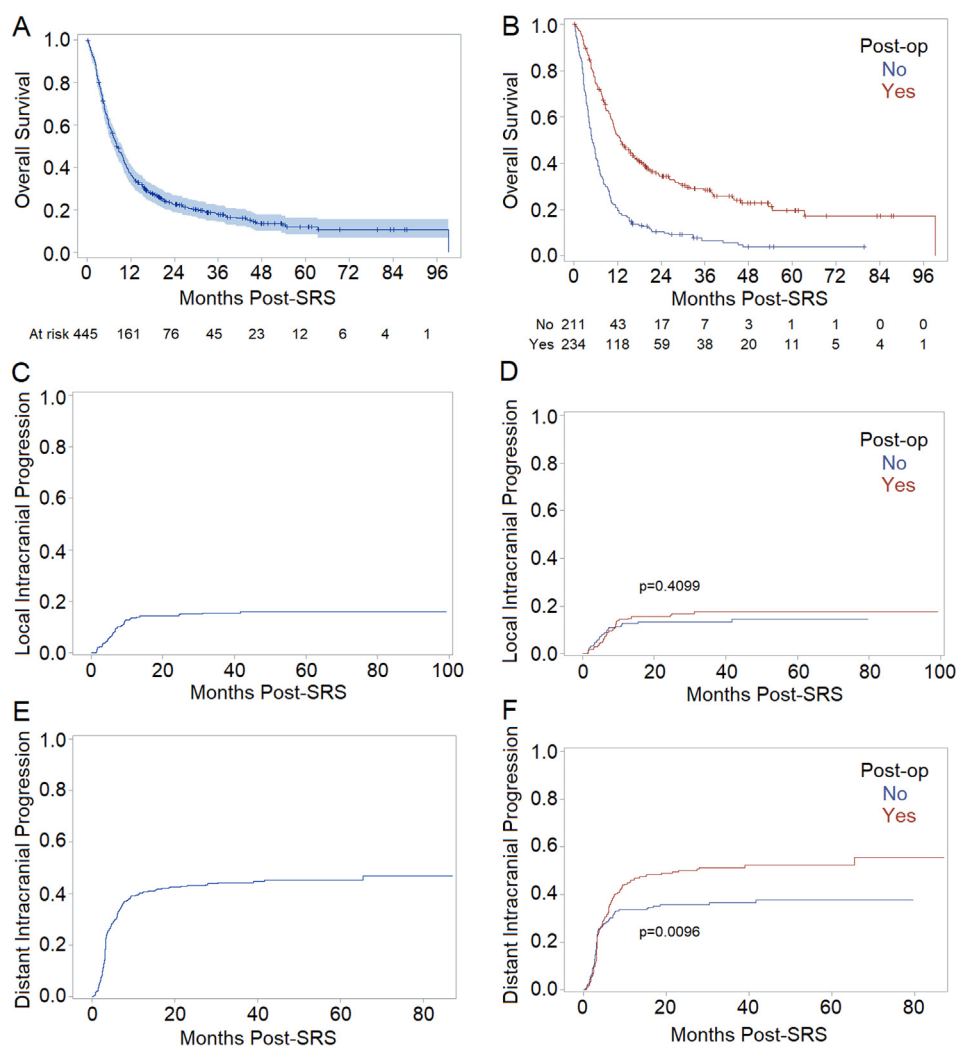
Figure 1   Kaplan-Meier plots are shown for A, B, overall survival; C, D, cumulative incidence of local intracranial progression; and E, F, cumulative incidence of distant brain progression across all patients and stratified by postoperative status, respectively. *Abbreviation:* post-op = postoperative; SRS = stereotactic radiosurgery.

greater following rHF-SRS than iHF-SRS, in line with prior reports.[15] Notably, our institutional series contained a relatively large proportion (32%) of patients treated with rHF-SRS with multiple BMs. For patients with multiple BMs, resection was considered in the presence of BM-related neurologic symptoms and otherwise favorable clinical characteristics.[29] Global determinants of OS for BM patients are largely independent of local intracranial therapy, and include overall performance status, extracranial disease burden, and receipt of post-SRS systemic therapy.[30]

As median OS continues to improve across BM populations, durable LC and late toxicity mitigation following SRS are increasingly important considerations. Time to LP (eg, LC) observed in this study compares favorably to those of prior HF-SRS reports, which typically range from 70 to 90% ≥12 months following SRS.[8,11,13,15-17,23,31] Prior HF-SRS series have demonstrated associations between

improved LC and smaller tumor size,[15,17] surgical resection,[15] and greater HF-SRS dose.[16,17,23,31] We similarly identified significant association between greater total GTV (cc) and LP; however, we found no association to SRS dose or surgical resection among a population with a larger number of BMs of similar size, with >99 and 69% BMs receiving 5-fraction HF-SRS total doses <30 and 25 Gy, respectively. Comparatively, in a recent 5-fraction HF-SRS series with just 38% patients who received <6 Gy per fraction, a total radiation therapy dose of ≥30 Gy prescribed to 99% PTV coverage was associated with superior LC.[23] Rates of RN were nearly identical to those observed following 6 to 6.5 Gy per fraction.[23] Notably, this series reported a median maximum lesion diameter of 1.9 versus 3.9 cm in the present data. Accordingly, these data may support the utility of 5-fraction HF-SRS at 5 to 5.5 Gy per fraction, particularly for cases where minimization of brain V24 or dose to adjacent normal structures is of

Table 2   Multivariable analyses of overall survival across all patients, intact cases, and postoperative cases

Parameter		All patients (n = 445)		Intact (n = 211)		Postoperative (n = 234)	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Postoperative	No	Reference		N/A		N/A	
	Yes	.42 (.31-.56)	<.0001				
KPS	≥70	Reference		Reference		Reference	
	<70	1.41 (1.02-1.94)	.0382	1.48 (.99-2.23)	.0583	1.45 (.79-2.68)	.2282
Age at SRS (y)	≤50	Reference		Reference		Reference	
	50-70	.96 (.70-1.31)	.7938	.95 (.61-1.48)	.8108	.99 (.62-1.58)	.9728
	≥70	1.10 (.78-1.57)	.5765	1.23 (.75-2.01)	.4105	.99 (.58-1.67)	.9643
Sex	Male	Reference		Reference		Reference	
	Female	.82 (.65-1.05)	.1241	.86 (.62-1.20)	.3811	.81 (.56-1.18)	.2656
Primary site	Breast	Reference		Reference		Reference	
	GI	1.47 (.96-2.25)	.0762	2.09 (1.10-3.96)	.0235	1.21 (.66-2.23)	.5443
	GU	1.03 (.64-1.65)	.9132	1.04 (.55-1.97)	.8983	.93 (.43-2.04)	.8644
	Lung	1.00 (.71-1.41)	.9987	.94 (.59-1.49)	.7937	1.05 (.62-1.80)	.8525
	Other	.98 (.59-1.63)	.9497	.89 (.46-1.73)	.7296	1.06 (.47-2.38)	.8933
	Skin	1.41 (.89-2.23)	.1390	1.47 (.79-2.76)	.2266	1.32 (.63-2.78)	.4667
Symptom burden	Absent	Reference		Reference		Reference	
	Present	1.74 (1.31-2.32)	.0002	1.36 (.84-2.21)	.2132	1.95 (1.32-2.88)	.0008
Immunotherapy or small molecule inhibitor	No	Reference		Reference		Reference	
	Yes	.45 (.34-.59)	<.0001	.48 (.33-.69)	<.0001	.42 (.28-.64)	<.0001
Dural contact	No	Reference		Reference		Reference	
	Yes	.74 (.58-.95)	.0173	.68 (.47-.99)	.0466	.68 (.47-.99)	.0437
GTV total	Per cc	1.01 (.98-1.03)	.5177	1.00 (.95-1.04)	.8877	1.01 (.98-1.05)	.5393
PTV total	Per cc	1.00 (.98-1.01)	.6529	1.00 (.96-1.03)	.808	.99 (.97-1.02)	.5330
Brain V24	Per cc	1.01 (.99-1.02)	.2893	1.01 (.99-1.04)	.2965	1.01 (.99-1.02)	.3155
Number of brain metastases	1	Reference		Reference		Reference	
	2	1.20 (.89-1.63)	.2229	1.02 (.66-1.57)	.919	1.39 (.89-2.16)	.1428
	3-5	1.46 (1.08-1.97)	.0125	1.30 (.88-1.92)	.1841	1.58 (.94-2.67)	.0851
	≥6	1.70 (1.16-2.49)	.0063	1.71 (1.08-2.70)	.0217	.92 (.31-2.74)	.8841
Prior WBRT	No	Reference		Reference		Reference	
	Yes	.99 (.71-1.38)	.9514	.92 (.62-1.38)	.6982	1.20 (.57-2.53)	.6325

Abbreviations: CI = confidence interval; KPS = Karnofsky performance status; GI = gastrointestinal; GTV = gross tumor volume; GU = genitourinary; HR = hazard ratio; N/A = not applicable; PTV = planned target volume; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

primary concern.[32] The discrepancy between medial lesion axial diameter (1.3 cm) and median maximum lesion diameter (3.9 cm) reflects both the high proportion of patients with multiple BMs and our institutional practice of treating all BMs with HF-SRS via single-isocenter multitarget technique where hypofractionation is indicated for a single dominant BM. Given the lack of significant association to LP across a comprehensive list of clinical and treatment parameters, future analyses of LP

may wish to examine radiomic and genomic parameters as predictors of clinical outcomes. To guide clinical management of patients undergoing resection of 1 to 3 BMs, the ongoing Alliance A071801 phase III trial (NCT04114981) compares LC rates following SF-SRS versus HF-SRS.[33]

The clinical significance of LMD risk is difficult to ascertain across studies, given that LMD subtype (ie, nodular versus diffuse) is often not reported despite its

Table 3 **Multivariable analyses of cumulative incidence of local progression across all patients, intact cases, and postoperative cases**

Parameter	All Patients (n = 445) HR (95% CI)	P value	Intact (n = 211) HR (95% CI)	P value	Postoperative (n = 234) HR (95% CI)	P value
Postoperative						
No	Reference		N/A		N/A	
Yes	1.00 (.50-2.02)	.9984				
Primary site						
Breast	Reference		Reference		Reference	
GI	.61 (.23-1.60)	.3144	.13 (.02-1.03)	.0537	1.35 (.44-4.20)	.6028
GU	.42 (.13-1.33)	.1397	.47 (.11-1.99)	.3023	.26 (.03-2.19)	.2166
Lung	.88 (.46-1.69)	.7028	.48 (.17-1.33)	.1557	1.27 (.53-3.01)	.5926
Other	.90 (.31-2.61)	.8419	.57 (.13-2.46)	.4520	.71 (.11-4.55)	.7211
Skin	.33 (.10-1.07)	.0647	.26 (.05-1.33)	.1053	.43 (.08-2.23)	.3142
Location						
Frontal	Reference		Reference		Reference	
Parietal	.43 (.15-1.21)	.1089	.27 (.03-2.94)	.2839	.45 (.14-1.48)	.1877
Cerebellum	.77 (.38-1.57)	.4690	1.02 (.27-3.90)	.9765	.77 (.33-1.80)	.54
Temporal	.91 (.34-2.42)	.8423	.42 (.05-3.58)	.4272	.84 (.33-2.14)	.7095
Occipital	.50 (.17-1.48)	.2077				
Cavernous sinus/BOS	.37 (.04-3.13)	.3577	.46 (.05-4.53)	.5068	*N/A	
Brain stem	.80 (.17-3.69)	.7736	.65 (.07-5.76)	.6993	*N/A	
Multiple	.91 (.38-2.19)	.8350	.90 (.28-2.91)	.8609	.46 (.05-3.90)	.4742
Newly diagnosed or recurrent						
Newly diagnosed	Reference		Reference		Reference	
Recurrent	2.28 (1.01-5.15)	.0472	1.91 (.62-5.94)	.2628	2.22 (.88-5.61)	.0906
SRS dose						
5 Gy	Reference		Reference		Reference	
5.5 or 6 Gy/fraction	.96 (.50-1.85)	.9027	2.18 (.78-6.08)	.1353	.36 (.12-1.07)	.0663
Immunotherapy or small molecule inhibitor						
No	Reference		Reference		Reference	
Yes	1.07 (.61-1.87)	.8202	1.59 (.68-3.75)	.2875	.9 (.40-2.02)	.8029
Dural contact						
No	Reference		Reference		Reference	
Yes	1.37 (.64-2.91)	.4148	1.32 (.41-4.25)	.6447	1.36 (.49-3.82)	.5555
Total GTV (cc)	1.04 (.99-1.10)	.1143	1.12 (1.05-1.20)	.0011	1.01 (.94-1.09)	.7720
Total PTV (cc)	.97 (.93-1.02)	.2128	.92 (.87-.97)	.0039	1.00 (.94-1.06)	.9146
Maximum lesion axial diameter (cm)	1.08 (.79-1.48)	.6352	.87 (.40-1.85)	.7112	1.17 (.83-1.65)	.3800
Maximum lesion diameter, any axis (cm)	1.1 (.78-1.56)	.5776	1.29 (.59-2.82)	.5230	.98 (.68-1.41)	.9165
Number of brain metastases						
1	Reference		N/A		N/A	
2	1.87 (.93-3.77)	.0811	N/A		N/A	
3-5	.86 (.38-1.91)	.7057	N/A		N/A	
≥6	.94 (.31-2.86)	.9094	N/A		N/A	
Prior WBRT						
No	Reference		Reference		Reference	
Yes	.46 (.15-1.37)	.1625	†N/A		.21 (.02-2.06)	.1795

Abbreviations: CI = confidence interval; KPS = Karnofsky performance status; GI = gastrointestinal; GTV = gross tumor volume; GU = genitourinary; HR = hazard ratio; N/A = not applicable; PTV = planned target volume; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

* There are no patients in this subgroup.

† Prior WBRT was not included in the model due to high collinearity with other variables in the model.

Table 4 Multivariate analyses of leptomeningeal disease across all patients, intact cases, and postoperative cases

Effect	All patients (n = 445)				Intact (n = 211)				Postoperative (n = 234)			
	OR	95% Wald CI		P value	OR	95% Wald CI		P value	OR	95% Wald CI		P value
Postoperative: yes vs no	1.977	0.942	4.318	0.0783	N/A				N/A			
Primary site: lung vs breast	0.451	0.219	0.933	0.0302	0.173	0.040	0.636	0.0107	0.173	0.040	0.636	0.0107
Primary site: other vs breast	0.314	0.144	0.676	0.0031	0.216	0.058	0.739	0.0164	0.216	0.058	0.739	0.0164
Number of brain metastases: >1 vs 1	0.749	0.379	1.458	0.3979	0.660	0.222	2.043	0.4554	0.66	0.222	2.043	0.4554
Dural contact: no vs yes	0.477	0.207	0.999	0.0627	0.477	0.112	1.708	0.2770	0.477	0.112	1.708	0.2770
Immunotherapy or small molecular inhibitor: yes vs no	0.903	0.455	1.721	0.7622	1.434	0.434	4.535	0.5400	1.434	0.434	4.535	0.5400
GTV (cc)	0.997	0.936	1.06	0.9210	1.049	0.878	1.211	0.5706	1.049	0.878	1.211	0.5706
PTV (cc)	1.000	0.955	1.044	0.9980	0.949	0.848	1.072	0.3971	0.949	0.848	1.072	0.3971
Prior WBRT	0.734	0.236	1.894	0.5539	0.858	0.175	3.193	0.8307	0.858	0.175	3.193	0.8307

Abbreviations: CI = confidence interval; GTV = gross tumor volume; N/A = not applicable; OR = odds ratio; PTV = planned target volume; WBRT = whole brain radiation therapy.

Table 5 Radionecrosis frequency by maximum event grade experienced by a patient

RN Grade	Intact (n = 211)		Postoperative (n = 234)	
	N	%	N	%
0	192	91.0	190	81.2
1	7	3.3	19	8.1
2	7	3.3	9	3.8
3	4	1.9	15	6.4
4	0	0.0	1	0.4
5	1	0.5	0	0.0
Any RN event	19	9.0	44	18.8
G2+ RN events	12	5.7	25	10.7

Abbreviation: RN = radionecrosis

prognostic and therapeutic implications.[34] Significant associations between LMD, surgical resection, and primary breast tumor origin were consistent with prior reports.[35,36] In contrast to a recent 5-fraction HF-SRS series, this study revealed no association between LMD and number of BMs.[23]

This report has several limitations. In a nonrandomized setting, utilization of HF-SRS and surgical resection both reflect significant selection bias. Patient inclusion from 2008 to 2018 may incorporate significant chronological bias consistent with improved clinical outcomes in recent years. Novel systemic agents confer superior central nervous system activity and OS,[37] as well as technological advances in both surgery and SRS. Generalizability of linear accelerator-based HF-SRS to patients completing CyberKnife or GammaKnife SRS may be limited. While multidisciplinary consensus regarding RN and LP were retrospectively confirmed through serial radiographic images, histopathologic confirmation was not available for the majority of RN cases. Furthermore, the relatively short OS following iHF-SRS in particular limits analysis of non-OS outcomes. Infrequent LMD events precluded analysis of potential interactions across parameters. Nevertheless, to our knowledge, this report provides the largest single institution 5-fraction HF-SRS series to date, with favorable rates of OS, LC, DBP, LMD, and RN across both rHF-SRS and iHF-SRS cases despite a patient population with a relatively advanced intracranial disease burden and relatively low HF-SRS doses.

Conclusions

Patients completing 5-fraction HF-SRS with and without surgical resection represent distinct subgroups within the BM population, with superior OS following rHF-SRS versus iHF-SRS despite higher rates of distant brain progression and LMD. Patient- and tumor-specific factors

associated with OS and LP varied across rHF-SRS and iHF-SRS cases. DBP incidence was greater following rHF-SRS than iHF-SRS. Across all patients, rates of LP, LMD, and RN compared favorably to those of other series despite a relatively advanced intracranial disease burden and slightly lower HF-SRS doses.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101166.

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