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Risk Factors for Progression and Toxic Effects After Preoperative Stereotactic Radiosurgery for Patients With Resected Brain Metastases

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IMPORTANCE Preoperative stereotactic radiosurgery (SRS) has been demonstrated as a feasible alternative to postoperative SRS for resectable brain metastases (BMs) with potential benefits in adverse radiation effects (AREs) and meningeal disease (MD). However, mature large-cohort multicenter data are lacking.

OBJECTIVE To evaluate preoperative SRS outcomes and prognostic factors from a large international multicenter cohort (Preoperative Radiosurgery for Brain Metastases–PROPS-BM).

DESIGN, SETTING, AND PARTICIPANTS This multicenter cohort study included patients with BMs from solid cancers, of which at least 1 lesion received preoperative SRS and a planned resection, from 8 institutions. Radiosurgery to synchronous intact BMs was allowed. Exclusion criteria included prior or planned whole-brain radiotherapy and no cranial imaging follow-up. Patients were treated between 2005 and 2021, with most treated between 2017 and 2021.

EXPOSURES Preoperative SRS to a median dose to 15 Gy in 1 fraction or 24 Gy in 3 fractions delivered at a median (IQR) of 2 (1-4) days before resection.

MAIN OUTCOMES AND MEASURES The primary end points were cavity local recurrence (LR), MD, ARE, overall survival (OS), and multivariable analysis of prognostic factors associated with these outcomes.

RESULTS The study cohort included 404 patients (214 women [53%]; median [IQR] age, 60.6 [54.0-69.6] years) with 416 resected index lesions. The 2-year cavity LR rate was 13.7%. Systemic disease status, extent of resection, SRS fractionation, type of surgery (piecemeal vs en bloc), and primary tumor type were associated with cavity LR risk. The 2-year MD rate was 5.8%, with extent of resection, primary tumor type, and posterior fossa location being associated with MD risk. The 2-year any-grade ARE rate was 7.4%, with target margin expansion greater than 1 mm and melanoma primary being associated with ARE risk. Median OS was 17.2 months (95% CI, 14.1-21.3 months), with systemic disease status, extent of resection, and primary tumor type being the strongest prognostic factors associated with OS.

CONCLUSIONS AND RELEVANCE In this cohort study, the rates of cavity LR, ARE, and MD after preoperative SRS were found to be notably low. Several tumor and treatment factors were identified that are associated with risk of cavity LR, ARE, MD, and OS after treatment with preoperative SRS. A phase 3 randomized clinical trial of preoperative vs postoperative SRS (NRG BN012) has began enrolling (NCT05438212).

Invited Commentary

Supplemental content

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Postoperative stereotactic radiosurgery (SRS) is an established standard of care for patients with resected brain metastases based on 2 randomized phase 3 clinical trials that demonstrated improved cavity local control compared with gross total resection (GTR) alone and longer cognitive deterioration-free survival compared with postoperative whole-brain radiotherapy (WBRT).[1,2] Preoperative SRS is an alternative to postoperative SRS and has been shown to have potential advantages in uninvolved brain tissue radiation exposure, risk of adverse radiation effect (ARE), and meningeal disease (MD) occurrence compared with postoperative SRS.[3-9] Another potential advantage of preoperative SRS is less delineation uncertainty when targeting the preoperative intact lesion rather than the resection cavity, which generally requires a margin expansion of 1 to 2 mm into healthy brain tissue to reduce the risk of geographic miss.[10] Additionally, there is a lack of consensus as to what constitutes the postoperative volume to be treated with both aforementioned phase 3 trials of postoperative SRS that specifically target the surgical cavity with a 1 to 2 mm margin, but published contouring guidelines recommend additional inclusion of the entire surgical tract and a 1 to 10 mm expansion along the bone flap.[11]

The Preoperative Radiosurgery for Brain Metastases (PROPS-BM) collaboration was an international multicenter cohort of patients treated with preoperative SRS whose data were derived from retrospective and prospective registries. The goal of the current study was to determine risk factors for local and MD progression and toxic effects after preoperative SRS in an expanded multicenter cohort.

Key Points

Question What are the outcomes and prognostic factors after preoperative stereotactic radiosurgery (SRS) for patients with resected brain metastases?

Findings In this international multicenter cohort study of 404 patients with resected brain metastases, the cavity local recurrence, meningeal disease, and adverse radiation effect rates at 2 years were 13.7%, 5.8%, and 7.4%, respectively. Several novel prognostic tumor and treatment factors after preoperative SRS were identified, including extent of resection, type of resection, fractionation, target margin expansion, and primary tumor type.

Meaning The results of this cohort study suggest that preoperative SRS has a favorable risk-benefit profile.

Methods

Patients

The records of patients treated with preoperative SRS with a planned surgical resection from 8 institutions were included from separate institutional review board–approved retrospective or prospective databases. Patient consent was either waived due to the retrospective nature of the database or obtained based on the individual institution protocol and institutional review board determination. Patients with brain metastases from solid cancers who had at least 1 lesion treated with preoperative SRS and underwent planned resection were included. Stereotactic radiosurgery to other synchronous intact brain metastases was allowed. Exclusion criteria included classically radiosensitive or nonsolid cancers (eg, germinoma, small-cell cancer, lymphoma), planned WBRT, and/or no cranial imaging follow-up outside of immediate postoperative imaging. The decision for surgical resection and preoperative SRS was made within each respective center. Patients requiring immediate or urgent surgical decompression underwent initial resection and were considered for postoperative SRS and not included in this study cohort.

Treatments

The details of patient selection and preoperative SRS dosing, technique, and timing were previously published.[4] The SRS dose, fractionation, and size of planning target volume (PTV) margin expansion and interval between preoperative SRS and planned surgery were as per individual institutional protocol and not centrally mandated. In general, the single-fraction preoperative SRS dose was reduced by 10% to 20% compared with standard RTOG 90-05 dosing based on prior published studies of preoperative SRS.[3,12] The lesion to be resected was delineated on contrast-enhanced preoperative magnetic resonance imaging (MRI) of the brain and was defined as the index gross tumor volume (GTV). Postoperative follow-up was as per institutional practice, but in general, patients were evaluated with a clinical examination and MRI of the brain with and without contrast at 6 to 12 weeks after resection. Patients were then followed with regular clinical examinations and MRI brain imaging every 3 to 4 months thereafter.

Statistical Analyses

The details of the statistical analyses were previously published.[4] The date of resection was considered time 0. Intracranial event rates were estimated using the cumulative incidence with competing risk of death methods. Patients were censored at the time of last brain imaging or time of salvage WBRT (if performed for reasons other than the event of interest). For patients with multiple synchronous brain metastases, recurrence or progression at unresected sites was considered distant brain failure. Meningeal disease was classified as either classic or nodular based on MRI appearance.[13,14] Adverse radiation effects (AREs) were defined on the basis of 2 radiological criteria: (1) the development of a contrast-enhancing mass within previous radiation treatment fields and (2) conventional imaging features, such as a low lesion quotient.[15] If there was a question of the enhancement representing local recurrence (LR) or ARE, additional advanced imaging (eg, magnetic resonance perfusion, magnetic resonance spectroscopy, and/or brain positron emission tomography) was performed for further characterization. If the patient underwent surgery and the pathology results showed any viable cancer, the event was coded as an LR. The composite end point of cavity LR, any grade ARE, or nodular MD was evaluated as a measure of the overall efficacy and toxic effects of this therapy. This composite end point was the same as that of the primary end point in the phase 3 trial NRG BN012 (NCT05438212).[16] Active systemic disease was defined as a new diagnosis or evidence of systemic progression within 3 months

before preoperative SRS. Patient imaging was not centrally reviewed, and events were coded as per local investigator assessment. A multivariable analysis for cumulative incidence with competing risk of death events was performed using the Fine and Gray method.[17] Fine and Gray model assumptions were tested using goodness-of-fit procedures and were found to not be violated.[18] Variables with clinical relevance or with a *P* value less than or equal to .10 in univariable analyses were included, and backward stepwise variable selection was used to determine the final parsimonious model (eTable 1 in Supplement 1). Variable selection was complete when the type 3 *P* value for all remaining variables was less than .10. Overall survival (OS) was estimated using the Kaplan-Meier product limit method, and patients were censored at the time last known alive. A multivariable analysis for OS was performed using the Cox method. The Cox proportional hazards assumptions were tested using evaluation of Schoenfeld residuals and were found to not be violated.[19] The same variable selection method was used as described previously. Significance testing was 2-sided, with $P \leq .05$ considered statistically significant. Statistical analyses were conducted using R, version 4.2.0 (R Foundation), and SPSS, version 27 (IBM).

Results

Patients

A total of 404 patients with 416 preoperatively treated index lesions from 8 tertiary care centers were included in the cohort (**Table 1**). Preoperative SRS was initiated at a single institution in 2005, with most patients included in this cohort being treated between 2017 and 2021. Most patients had non–small-cell lung cancer (NSCLC; 192 [47.5%]), breast (62 [15.3%]), or melanoma (50 [12.4%]) primary cancer type. Most patients (249 [61.6%]) had a single brain metastasis. Most index lesions (397 [95.4%]) underwent GTR. Surgical resection was piecemeal, en bloc, and unknown for 229 (55%), 99 (23.8%), and 88 (21.2%), respectively. A total of 354 index lesions (85.1%) had a greater than 2 cm maximum diameter. No PTV margin expansion was used for 223 index lesions (53.6%), while a PTV margin expansion of 0.5 to 3 mm was used for 193 (46.4%). One, 3-, and 5-fraction preoperative SRS was used for 328 (78.8%), 80 (19.2%), and 8 (1.9%) index lesions, respectively. The median dose for single-fraction SRS was 15 Gy (IQR, 14-17 Gy) and 24 Gy (IQR, 24-24 Gy) for 3-fraction preoperative SRS. The median GTV volume was 10 cc (approximately equivalent to a 2.7-cm diameter sphere; IQR, 4.6-16.6 cc), the median interval between preoperative SRS completion and surgery was 2 days (IQR, 1-4 days), and the median cranial imaging follow-up period for patients who were alive was 18.1 months (IQR, 7.9-31.1 months).

Intracranial Outcomes

The 1-year and 2-year cumulative incidence of cavity LR was 11.9% (95% CI, 8.7%-15.5%) and 13.7% (95% CI, 10.3%-17.6%), respectively (**Figure 1**). Multivariable analysis demonstrated a significantly lower risk of cavity LR for patients with active systemic disease (vs no active systemic disease; hazard ratio

Table 1. Patient and Tumor Characteristics

Variable	No. (%) or median (IQR)
Patients	404 (100)
Index lesions	416 (100)
Institution	
Levine Cancer Institute	183 (45.3)
Cone Health	85 (21)
University of Texas Southwestern	20 (5)
Cleveland Clinic	8 (2)
University of Maryland	18 (4.5)
Ohio State University	64 (15.8)
Peter McCallum/Icon	26 (6.4)
Year of treatment	
2005-2007	31 (7.7)
2008-2010	19 (4.7)
2011-2013	29 (7.2)
2014-2016	96 (23.8)
2017-2019	128 (31.7)
2020-2021	101 (25)
Sex	
Female	214 (53)
Male	190 (47)
Primary site	
NSCLC	192 (47.5)
Breast	62 (15.3)
Melanoma	50 (12.4)
Kidney cell	29 (7.2)
Gastrointestinal	28 (6.9)
Other	43 (10.6)
Performance status at time of SRS	
0	114 (28.2)
1	211 (52.2)
2	68 (16.8)
3	11 (2.7)
Active systemic disease	
No	168 (41.6)
Yes	227 (56.2)
Unknown	9 (2.2)
RPA class	
1	68 (16.8)
2	311 (77)
3	25 (6.2)
Total No. of brain metastases including index lesion	
1	249 (61.6)
2	70 (17.3)
3	43 (10.6)
4	18 (4.5)
≥5	24 (5.9)
Age, y	60.6 (54.0-69.6)
GPA	2 (2-3)
Extent of resection	
Gross total	397 (95.4)
Subtotal	19 (4.6)

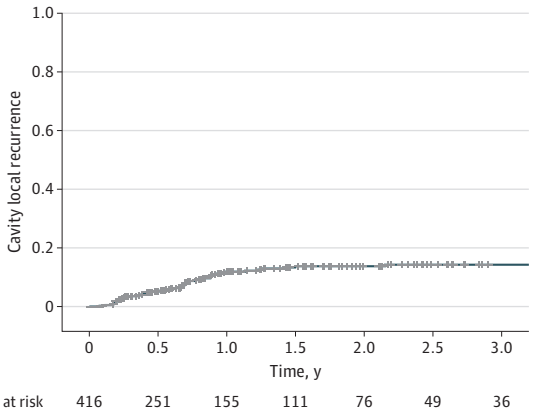
(continued)

Table 1. Patient and Tumor Characteristics (continued)

Variable	No. (%) or median (IQR)
Surgery type	
Piecemeal	229 (55)
En bloc	99 (23.8)
Unknown	88 (21.2)
Metastasis location	
Frontal	144 (34.6)
Parietal	71 (17.1)
Temporal	47 (11.3)
Occipital	49 (11.8)
Cerebellum	99 (23.8)
Other	6 (1.4)
SRS immobilization	
Framed	28 (6.7)
Frameless	388 (93.3)
SRS platform	
Gamma knife	34 (8.2)
Cyberknife	7 (1.7)
LINAC	375 (90.1)
No. of fractions	
1	328 (78.8)
3	80 (19.2)
5	8 (1.9)
Days between SRS and surgery	2 (1-4)
Prescribed dose, Gy	
1 fraction	15 (14-17)
3 fraction	24 (24-26)
5 fraction	30 (30-30)
GTV volume, cc	10 (4.6-16.6)
PTV margin, mm:	
0	223 (53.6)
0.5	7 (1.7)
1	130 (31.3)
2	2 (0.5)
3	54 (13)

Abbreviations: GPA, graded prognostic assessment; GTV, gross tumor volume; LINAC, linear accelerator; NSCLC, non–small-cell lung cancer; PTV, planning target volume; RPA, recursive portioning analysis; SRS, stereotactic radiosurgery.

Figure 1. Cavity Local Recurrence



Cumulative incidence of cavity local recurrence. Curve truncated at 3 years.

[HR], 0.33, 95% CI, 0.18-0.61; $P < .001$), GTR (vs subtotal resection [STR]; HR, 0.2; 95% CI, 0.08-0.53; $P = .001$), fractionated preoperative SRS (vs single fraction SRS; HR, 0.15; 95% CI, 0.04-0.62; $P = .01$), and en bloc tumor resection (vs piecemeal; HR, 0.34; 95% CI, 0.13-0.89; $P = .03$; **Table 2**). The 2-year rate of cavity LR after GTR (n = 397) and STR (n = 19) was 12.5% (95% CI, 9.1%-16.4%) and 36.8% (95% CI, 15.6%-58.4%), respectively ($P < .001$). There was a trend toward higher risk of cavity LR for gastrointestinal primary tumor type (vs NSCLC; HR, 3.0; 95% CI, 0.95-9.30; $P = .06$). Of note, GTV volume, PTV margin expansion, and time intervals between preoperative SRS and surgery were not associated with cavity LR risk.

The 1-year and 2-year cumulative incidence of distant brain failure was 33% (95% CI, 28.1%-37.8%) and 41.1% (95% CI, 35.8%-46.4%), respectively. Salvage WBRT was used in 52 patients overall (12.9%). The 1-year and 2-year rate of salvage WBRT use was 10.6% (95% CI, 7.7%-14.0%) and 13.5% (95% CI, 10.1%-17.4%), respectively. The primary indications for salvage WBRT were distant brain failure or classic MD.

The 1-year and 2-year cumulative incidence of MD was 4.8% (95% CI, 2.9%-7.4%) and 5.8% (95% CI, 3.5%-8.8%), respectively (eFigure 1 in Supplement 1). Most MD was classic MD (17 patients [70.8%]), with the remainder being nodular type (7 patients [29.2%]). The median interval from surgery to MD was 6.6 months (IQR, 3.2-21.5 months). Of the 17 patients with classic MD, 9 (53%) received salvage therapy, which comprised craniospinal radiotherapy (RT) (n = 1), spine RT only (n = 1), WBRT (n = 6), and systemic therapy only (n = 1). Of the 7 patients with nodular MD, 6 received salvage therapy, which comprised craniospinal RT (n = 1), SRS (n = 2), WBRT (n = 2), and spinal RT only (n = 1). Median OS from time of MD diagnosis for patients who received salvage therapy with nodular MD (n = 6) and classic MD (n = 9) was 11.3 months and 2.8 months, respectively ($P = .26$). The multivariable analysis demonstrated GTR (vs STR; HR, 0.18; 95% CI, 0.06-0.55; $P = .003$), breast primary (vs NSCLC; HR, 5.64; 95% CI, 1.63-19.6; $P = .01$), melanoma primary (vs NSCLC; HR, 7.9; 95% CI, 2.1-30.1; $P = .003$), other primary cancer type (vs NSCLC; HR, 4.6; 95% CI, 1.14-18.5; $P = .03$; **Table 3**) as being significantly associated with risk of MD. Posterior fossa location (vs supratentorial; HR, 2.4; 95% CI, 0.98-5.8; $P = .06$) had a trend toward higher risk of MD.

Toxic Effects

Postoperative complications occurred in 31 of 404 patients (7.7%). Eleven events were grade 1 or 2 (pneumocephalus, infection, delayed wound healing, intracranial hemorrhage, or hematoma). Twenty events (5%) were grade 3 to 5 complications (intracranial hemorrhage, stroke, wound infection/dehiscence, seizures, cerebrospinal fluid leak, or hydrocephalus). There were 2 grade 5 events. One event was postoperative hydrocephalus that required treatment with ventriculoperitoneal shunt placement. This patient then developed

Table 2. Multivariable Analysis for Cavity Local Recurrence via the Fine and Gray Method

Variable	Hazard ratio	95% CI	*P* value
Active systemic disease (vs no active systemic disease)	0.33	0.18-0.61	<.001
GTR (vs STR)	0.20	0.08-0.53	.001
Fractionated SRS (vs single fraction)	0.15	0.04-0.62	.01
Type of surgery			
Piecemeal	1 [Reference]	NA	NA
En bloc	0.34	0.13-0.89	.03
Unknown	0.46	0.21-1.05	.07
Primary site			
NSCLC	1 [Reference]	NA	NA
Breast	1.69	0.84-3.43	.14
Melanoma	1.13	0.44-2.92	.80
Kidney cell	3.19	0.04-2.43	.27
Gastrointestinal	2.97	0.95-9.32	.06
Other	1.66	0.64-4.35	.30

Abbreviations: GTR, gross total resection; NA, not applicable; NSCLC, non–small-cell lung cancer; SRS, stereotactic radiosurgery; STR, subtotal resection.

Table 3. Multivariable Analysis for Meningeal Disease via the Fine and Gray Method

Variable	Hazard ratio	95% CI	*P* value
GTR (vs STR)	0.18	0.06-0.55	.003
Primary site			
NSCLC	1 [Reference]	NA	NA
Breast	5.64	1.63-19.6	.01
Melanoma	7.89	2.07-30.1	.003
Kidney cell	4.33	0.64-39.4	.13
Gastrointestinal	2.26	0.24-21	.47
Other	4.60	1.14-18.5	.03
Posterior fossa (vs supratentorial)	2.38	0.98-5.78	.06
Type of surgery			
Piecemeal	1 [Reference]	NA	NA
En bloc	0.43	0.12-1.51	.19
Unknown	0.28	0.06-1.25	.10

Abbreviations: GTR, gross total resection; NA, not applicable; NSCLC, non–small-cell lung cancer; SRS, stereotactic radiosurgery; STR, subtotal resection.

ventriculoperitoneal shunt infection that required shunt removal and external ventricular drain placement, after which the patient continued to decline and then died. The other event was postoperative intracranial hemorrhage that was followed by the patient's death.

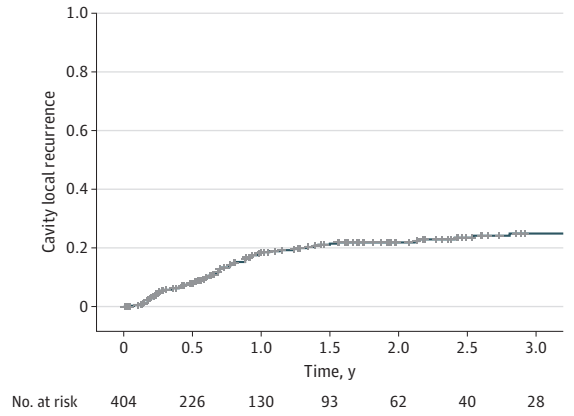
Adverse radiation effects (the imaging correlate of radiation necrosis)[20] occurred in 34 of 416 treated index lesions (8.2%), of which 21 (5%) were symptomatic. Thirteen events (3.2%) were grade 1, 18 (4.3%) were grade 2, and 3 (0.7%) were grade 3. The 3 grade 3 ARE events required surgical resection and were pathologically proven radiation necrosis. The 1-year and 2-year cumulative incidence of any grade ARE were 6% (95% CI, 3.9%-8.8%) and 7.4% (95% CI, 5.0%-10.5%), respectively. Multivariable analysis demonstrated a PTV margin expansion of more than 1 mm (vs ≤1 mm; HR, 2.93; 95% CI, 1.26-6.83; *P* = .01) and melanoma primary (vs NSCLC; HR, 2.59; 95% CI, 1.07-6.31; *P* = .04) as being significantly associated with risk of any grade ARE. The 2-year any grade ARE rate for PTV margin expansion of 1 mm or less (n = 359) vs >1 mm (n = 57) was 5.8% (95% CI, 3.6%-8.8%) and 20.5% (95% CI, 8.8%-35.5%), respectively (*P* = .004).

The 1-year and 2-year cumulative incidence of the composite end point of cavity LR, any grade ARE, or nodular MD was 18.5% (95% CI, 14.6%-22.8%) and 21.8% (95% CI, 17.5%-26.5%), respectively (**Figure 2**). Multivariable analysis demonstrated active systemic disease (vs no active systemic disease; HR, 0.49; 95% CI, 0.31-0.78; *P* = .002), GTR (vs STR; HR, 0.27; 95% CI 0.11-0.64; *P* = .003), and melanoma primary (vs NSCLC; HR, 1.94; 95% CI, 1.05-3.57; *P* = .03) as being significantly associated with risk of the composite end point. Breast primary (vs NSCLC; HR, 1.71; 95% CI, 0.95-3.06; *P* = .07) and GI primary (vs NSCLC; HR, 2.27; 95% CI, 0.9-5.72; *P* = .08) also had a trend toward higher risk of the composite end point (eTable 2 in Supplement 1).

Survival

With a median clinical follow-up period of 20.2 months for patients who were alive, the median OS for the overall cohort was 17.2 months (95% CI, 14.1-21.3 months). The 1-year and 2-year OS rate was 60% (95% CI, 54.9%-64.7%) and 41.7% (95% CI, 36.3%-46.9%), respectively (eFigure 2 in Supplement 1). A multivariable analysis demonstrated active systemic disease (vs

Figure 2. Composite End Point



Cumulative incidence of the composite end point of cavity local recurrence, adverse radiation effect, or nodular meningeal disease. Curve truncated at 3 years.

nonactive systemic disease; HR, 1.56; 95% CI, 1.17-2.07; $P = .003$), age (HR, 1.02; 95% CI, 1.01-1.03; $P = .001$), GTR (vs STR; HR, 0.35; 95% CI, 0.21-0.58; $P < .001$), graded prognostic assessment[21] (HR, 0.74; 95% CI, 0.61-0.9; $P = .003$), melanoma primary (vs NSCLC; HR, 0.55; 95% CI, 0.36 -0.86; $P = .01$), and kidney primary (vs NSCLC; HR, 0.57; 95% CI, 0.34-0.94; $P = .03$) were significantly associated with OS (eTable 3 in Supplement 1). Median OS for patients status post GTR (n = 385) was 19.6 months (95% CI, 15.3-22.6 months) compared with 6 months (95% CI, 3.5-10 months) for patients status post STR (n = 19, $P < .001$). Median OS for patients without active systemic disease was 28.5 months (95% CI, 22.1-37.5) compared with 12.6 months (95% CI, 9.8-16.8) for patients with active systemic disease at the time of preoperative SRS ($P < .001$). Overall survival based on primary tumor type for patients status post GTR is shown in eFigure 3 in Supplement 1.

Discussion

A previous publication by the PROPS-BM group included 242 patients with 253 preoperative SRS-treated index lesions derived from 5 institutions.[4] The current cohort includes substantially more patient-years of follow-up, with 404 patients with 416 treated index lesions derived from 8 institutions. The larger patient population and increased number of events allowed for a more detailed analysis of prognostic factors for intracranial outcomes, toxic effects, and survival for patients treated with preoperative SRS.

The study results found a 2-year cavity LR rate of approximately 14%. This compares favorably with published cavity LR rates of 22% to 39% after postoperative single-fraction SRS[1,2,22] and approximately 25% after postoperative fractionated SRS.[23,24] Active systemic disease was associated with a lower risk of cavity LR, likely due to an increased competing risk of death in that patient population. Newly identified prognostic factors for cavity LR after preoperative SRS included single-fraction vs fractionated SRS, type of surgery, and gastrointestinal primary. The association with type of surgery should be interpreted with caution given the high rate of missing/unknown data for this variable. Fractionated preoperative SRS (primarily 3 fractions) was associated with a lower risk of cavity LR compared with single fraction. The 3-fraction median dose of 24 Gy had a higher biologically effective dose of 43.2 Gy compared with 37.5 Gy for the single-fraction median dose of 15 Gy. The effect of fractionation for preoperative SRS is an area of ongoing investigation and will be reported in more detail in future studies.

The incidence of MD remains low, with a 2-year rate of 5.8%. This compared favorably with upfront surgery and postoperative SRS, for which the incidence of MD is approximately 16% to 21% based on recent multicenter studies.[14,23] Most MD was classic type, which is in contrast to the predominant pattern of MD being nodular type in the postoperative SRS setting.[14] This finding suggested that preoperative SRS is likely able to minimize the risk of nodular MD by sterilizing cells before surgical perturbation at the time of surgical resection. A multivariable analysis for MD showed that extent of resection, primary tumor type (breast, melanoma, and other), and posterior fossa location were prognostic. Several of these factors, such as breast histology and posterior fossa location, overlap with previously reported prognostic factors for MD after surgery and postoperative SRS.[25]

Incidence of AREs was also low after preoperative SRS, with a 5% rate of symptomatic AREs. We identified a PTV margin expansion of greater than 1 mm and melanoma primary as risk factors for ARE. An increased PTV margin expansion exposes larger volumes of healthy brain tissue to high-dose RT and is associated with increased risk of radiation necrosis.[26] The higher risk of ARE with melanoma may be due to increased use of immunotherapy and/or targeted therapy in this patient population, which has been shown to be potentially associated with increased rates of ARE.[27,28] We did not have access to data regarding the specific type or timing of systemic therapy compared with preoperative SRS in this cohort to be able to investigate this further.

There are 2 phase 3 randomized trials of preoperative vs postoperative SRS being conducted. A single-institution phase 3 trial is being conducted at the MD Anderson Cancer Center (Houston, Texas) with the primary end point of 1-year leptomeningeal disease-free rate (NCT03741673). The NRG BN012 trial (NCT05438212) is a multicenter phase 3 trial with the primary composite end point of cavity LR, ARE, or nodular MD. The study is powered to detect a reduction in the 1-year composite end point from 40% with postoperative SRS to 27% with preoperative SRS (HR, 0.57). In the current study, we found a 1-year composite end point rate of 18.5% after preoperative SRS. The 1-year composite end point rate for patients who received single-fraction preoperative SRS (n = 328), which is the fractionation used in NRG BN012, was 19.4%. We eagerly await the accrual, completion, and reporting of these trials.

Limitations

The limitations of this study are primarily due to its nonrandomized, retrospective nature. They include risk of selection bias for the use of preoperative SRS and resection, lack of central

imaging review for intracranial outcomes, the extended period (16 years) of the study interventions during which significant therapeutic advances were made, and a lack of standardization of preoperative SRS dosing and technique.

Conclusions

This international multicenter cohort study included patients treated with preoperative SRS. The demonstrated rates of cavity LR, any grade or symptomatic ARE, and MD were notably low. We identified several tumor and treatment factors that were associated with risk of cavity LR, ARE, MD, and OS after treatment with preoperative SRS. Extent of resection was shown to be a strong prognostic factor for multiple outcomes, and minimizing the likelihood of subtotal resection after preoperative SRS may be associated with improved outcomes, including OS. Fractionated preoperative SRS may be associated with improved cavity LR and will the subject of further study. A PTV margin expansion greater than 1 mm was found to be associated with higher risk of ARE.

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