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Clinical Investigation

Single-Fraction Versus Multifraction (3 × 9 Gy) Stereotactic Radiosurgery for Large (>2 cm) Brain Metastases: A Comparative Analysis of Local Control and Risk of Radiation-Induced Brain Necrosis

Giuseppe Minniti, MD, PhD,[*,†] Claudia Scaringi, MD,[*] Sergio Paolini, MD,[†] Gaetano Lanzetta, MD,[†] Andrea Romano, MD,[‡] Francesco Cicone, MD,[§] Mattia Osti, MD,[*] Riccardo Maurizi Enrici, MD,[*] and Vincenzo Esposito, MD[†]

**Unit of Radiation Oncology, [‡]Unit of Neuroradiology, and [§]Unit of Nuclear Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy; and [†]IRCCS Neuromed, Pozzilli, Italy*

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Summary

Stereotactic radiosurgery (SRS) is an effective treatment in patients with brain metastases, although worse local control and a higher risk of radiation-induced brain necrosis have been observed in patients with large lesions. For patients with brain metastases >2 cm, our study shows that multifraction SRS at doses of 27 Gy in 3 daily fractions is associated with better local control and a reduced risk of brain necrosis as compared with single-fraction SRS.

Purpose: To investigate the local control and radiation-induced brain necrosis in patients with brain metastases >2 cm in size who received single-fraction or multifraction stereotactic radiosurgery (SRS); factors associated with clinical outcomes and the development of brain radionecrosis were assessed.

Methods and Materials: Two hundred eighty-nine consecutive patients with brain metastases >2.0 cm who received SRS as primary treatment at Sant'Andrea Hospital, University of Rome Sapienza, Rome, Italy, were analyzed. Cumulative incidence analysis was used to compare local control and radiation-induced brain necrosis between groups from the time of SRS. To achieve a balanced distribution of baseline covariates between treatment groups, a propensity score analysis was used.

Results: The 1-year cumulative local control rates were 77% in the single-fraction SRS (SF-SRS) group and 91% in the multifraction SRS (MF-SRS) group ($P = .01$). Recurrences occurred in 25 and 11 patients who received SF-SRS or MF-SRS ($P = .03$), respectively. Thirty-one patients (20%) undergoing SF-SRS and 11 (8%) subjected to MF-SRS experienced brain radionecrosis ($P = .004$); the 1-year cumulative incidence rate of radionecrosis was 18% and 9% ($P = .01$), respectively. Significant differences between the 2 groups in terms of local control and risk of radionecrosis were maintained after propensity score adjustment.

Reprint requests to: Giuseppe Minniti, MD, PhD, Unit of Radiation Oncology, Sant'Andrea Hospital, Sapienza University of Rome, Via di Grottarossa 1035, 00189 Rome, Italy. Tel: (+39) 06-33776034; E-mail: gminniti@ospedalesantandrea.it

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Conclusions: Multifraction SRS at a dose of 27 Gy in 3 daily fractions seems to be an effective treatment modality for large brain metastases, associated with better local control and a reduced risk of radiation-induced radionecrosis as compared with SF-SRS.

Introduction

Stereotactic radiosurgery (SRS) alone has become an increasingly utilized treatment option in the initial management of patients with brain metastases. Its efficacy has been demonstrated in randomized trials that report a local control (LC) rate of approximately 75% at 1 year and a survival benefit similar to that observed with the use of SRS plus whole-brain radiation therapy (WBRT) (1-3).

The most common late-delayed radiation effect of SRS is the development of brain radionecrosis (RN), which is associated with the presence of different degrees of neurologic deficits in up to one-third of patients (4-6). Factors correlated with the development of RN are radiation dose, tumor volume, use of chemotherapy, and volume of normal brain irradiated at specific doses (5-10). Using the normal brain volume exposed to 12 Gy ($V_{12\text{-Gy}}$) during SRS to predict the risk of developing RN, a few studies have observed an occurrence of necrosis up to 60% for $V_{12\text{-Gy}} > 10$ cm^3 (4-7), and this is likely to happen when treating large lesions.

Multifraction SRS (MF-SRS, 2-5 fractions) has been used as an alternative to single-fraction SRS (SF-SRS), with the aim to reduce the incidence of late radiation-induced toxicity while maintaining high LC rates. Using doses of 24 to 35 Gy given in 3 to 5 fractions, a few retrospective studies have reported an LC rate of 70% to 90% at 1 year, with a variable risk of RN in the range of 2% to 15% (11-14).

In the present study we evaluated the LC and incidence of RN in patients who received SF-SRS or MF-SRS (3 × 9 Gy) for brain metastases >2 cm in size. Related factors associated with clinical outcomes and the development of RN were assessed.

Methods and Materials

Between September 2008 and October 2014, 354 consecutive patients aged ≥18 years with cerebral metastases >2 cm on contrast-enhanced magnetic resonance imaging (MRI) derived from a histologically confirmed systemic cancer, and who received SF-SRS or MF-SRS (3 × 9 Gy), were retrospectively evaluated. All radiographic, surgical, and pathologic information was drawn from a prospectively maintained database of patients with brain tumors treated at Sant'Andrea Hospital, University of Rome Sapienza. Sixty-five patients were excluded because of insufficient clinical information (n = 14), prior WBRT (n = 18), different radiation schedules used to treat brainstem metastases (3 × 7 Gy; n = 11), or skull base metastases involving the optic pathway (5 × 5 Gy; n = 22). Finally, a total of 289 patients remained in the final analysis. The Sant'Andrea Insitutional Review Board approved the study.

All metastatic tumors were treated with linear accelerator–based SRS using a commercial stereotactic mask fixation system in conjunction with the IPlan treatment planning system (BrainLab, Munich, Germany). In each patient the gross tumor volume (GTV) was delineated using postcontrast thin-slice (1-mm) gadolinium-enhanced T1-weighted axial MRI sequences fused with planning computed tomography (CT) scans. The clinical tumor volume (CTV) was a zero-margin-expansion of the GTV. A 2-mm margin was geometrically added to GTV/CTV to generate the planning target volume (PTV) in 165 metastases (2008-2011; SF-SRS, 88; MF-SRS, 77); subsequently, the margin was reduced to 1 mm (SF-SRS, 96; MF-SRS, 84). For patients who received SF-SRS, doses were 18 Gy for metastases of 2-3 cm in size and 15-16 Gy for metastases ≥3 cm. Multifraction SRS was most commonly used to treat brain metastases ≥3 cm in size or located in close proximity to critical areas. Using the linear-quadratic model for the estimation of dose-effect relationship adjusted for high doses (15), the biological effective dose (BED) of MF-SRS at doses of 27 Gy in 3 fractions was 40 Gy assuming an α/β of 12 Gy for brain metastases (BED_{12}), corresponding to a single dose of approximately 22 Gy. Doses were prescribed to the 80% to 90% isodose line to achieve a minimum 95% target coverage of the prescribed dose. Treatment volumes were achieved with 6-15 noncoplanar dynamic arcs or fixed beams. Computed tomographic imaging and the ExacTrac image-guided system (BrainLab; from 2012) were used for setup verification before each fraction.

Patients were examined clinically 1 month after SRS and then every 2 months. Magnetic resonance imaging was done every 2 months in the first year after the treatment and then every 3-4 months or as appropriate. Complete and partial responses were defined as total radiographic disappearance of lesion or decrease in tumor volume >50%. At each visit the neurologic status and the severity of complications were rated according to Radiation Therapy Oncology Group (RTOG) central nervous system toxicity criteria.

Diagnoses of tumor progression or RN were determined on the basis of histologic findings (in patients who underwent surgical resection) or by imaging using MRI and 3,4-dihydroxy-6-(18)F-fluoro-l-phenylalanine (F-DOPA) positron emission tomography (PET)-CT, with a sensitivity of 86.7% and 90% and a specificity of 68.2% and 92.3%,

respectively (16). In summary, tumor progression was defined as any increase of tumor on contrast-enhanced T1-weighted images in at least 2 subsequent MRI studies associated with (*1*) a cerebral blood volume (CBV) ratio >2.0 at dynamic susceptibility-weighted contrast-enhanced perfusion images (calculated for each lesion by dividing the tumor CBV by the mean CBV value of normal white matter); and (*2*) a maximum lesion to maximum background uptake ratio ($SUVL_{max}/Bkgr_{max}$) >1.59 at F-DOPA PET-CT. Stable or shrinking lesions over a 6-month period associated with (*1*) a CBV ratio <2.0 and (*2*) a $SUVL_{max}/Bkgr_{max}$ <1.59 were diagnosed as RN. Distant failure was defined by the presence of new brain metastases or leptomeningeal enhancement outside the PTV.

Overall survival (OS) was estimated using the Kaplan-Meier method from the date of SRS to the date of death from any cause or censored at the date of last follow-up for survivors. Because censoring patients at time of death with the Kaplan-Meier method would lead to biased probability of LC and occurrence of RN given the high rate of death in the patient population, cumulative incidence curves and Gray's test (17) were used to compare (*1*) the distant brain control rates accounting for death as competing risk; and (*2*) LC and RN rates accounting for either death or distant brain progression treated with WBRT as salvage therapy or local relapse (RN analysis) as competing risks. Patients who did not experience an event were censored at the time of the last follow-up. Chi-squared and nonparametric Mann-Whitney tests were used to examine between-group covariate differences, and the Cox proportional hazards model was used for univariate and multivariate analysis to assess the effects of clinical/treatment variables on clinical outcomes. Variables at a significance level of $P<.1$ were included in multivariate analysis. According to previous published risk prediction models of RN (5, 6, 14), we analyzed the correlation between $V_{12\text{-}Gy}$ (SF-SRS) or $V_{18\text{-}Gy}$ (MF-SRS) and the risk of RN.

To avoid the effects of confounding variables on LC and risk of RN due to the nonrandomized comparison of groups, propensity score matching was used to achieve a balanced distribution of baseline covariates (18). Using SRS as dependent variable (control condition, SF-SRS), patients and controls were matched one-to-one by the nearest-neighbor method, using a caliper distance of width equal to 0.2 of the standard deviation of the pooled propensity scores. Covariates presumed to influence LC and development of RN from univariate analysis were included in a propensity score–matched analysis as independent variables to allow more patients to be compared. The adjusted treatment groups were assessed for balance, using the overall χ^2 balance test and the relative multivariate imbalance measure (L1) (19, 20). In addition, significant differences in treatment characteristics were adjusted using the inverse-probability-of-treatment weighting propensity score method (21). Independent covariates included age at diagnosis, gender, histology, number of metastases, extracranial disease, and irradiated volumes. The discrimination and calibration abilities of each propensity score model were assessed using the C statistic and the Hosmer-Lemeshow statistic. The Cox proportional hazards model was applied using propensity score–based matching for estimating treatment effects. Gray's test was used to test for differences in the cumulative incidence of LC and RN between groups. Standard software was used for statistical analysis (SAS software, version 9.3 [SAS Institute, Cary, NC]; XLSTAT [Addinsoft, New York, NY]).

Results

Patient characteristics and survivals

A total of 289 consecutive patients with 343 metastases >2 cm in size were analyzed. Patient characteristics are shown in Table 1. One hundred fifty-one patients received SF-SRS, and 138 patients received MF-SRS. Two hundred sixty-one received 1 or 2 lines of therapy before SRS. There were no statistically significant differences between groups in terms of gender, age, histology, Karnofsky performance status (KPS) scores, the diagnosis-specific graded prognostic assessment score (22), site of tumor, and conformity index (as defined by the prescribed isodose volume/tumor volume encompassed by the prescription isodose volume). However, patients given SF-SRS were more likely to have smaller GTV and PTV. At the time of analysis (May 2015), 47 patients were still alive (SF-SRS, 16; MF-SRS, 31).

At a median follow-up study of 29 months, median and 1-year OS were 13.4 months and 54% (95% confidence interval [CI] 45%-62%), respectively (Fig. 1). The cumulative incidence rate of distant brain failure at 1 year was 40% (95% CI 34%-46%) (Fig. 2). One-year OS and distant brain failure did not differ significantly by group: SF-SRS, 53% (95% CI 36%-70%) and 41% (95% CI 34%-49%); MF-SRS, 56% (95% CI 39%-74%) and 39% (95% CI 31%-48%).

A clinical neurologic improvement of pre-SRS existing symptoms was recorded in 47 of 78 patients (60%), being similar between groups ($P=.15$). One hundred ninety-one patients succumbed to their extracranial disease, and 51 patients died of progressive intracranial disease. Salvage therapies for intracranial progression included surgery (n=21), WBRT (n=57), and SRS (n=68), given alone or in combination. For progressive disease, 178 patients received chemotherapy (n=104) and/or molecular targeted agents (n=74), including erlotinib (n=28), trastuzumab (n=6), bevacizumab (n=8), sunitinib (n=5), everolimus (n=7), lapatinib (n=6), ipilimumab (n=4), vemurafenib (n=2), pembrolizumab (n=3), or other agents (n=11).

In the multivariate analysis, stable extracranial disease, breast cancer histology, and KPS >70 emerged as significant indices of prolonged OS. According to the diagnosis-specific graded prognostic assessment score, median survival times were 7.6, 14, and 22.5 months in patients with scores of 0-1, 1-2.5, and 3-4 ($P=.001$), respectively. The presence of multiple metastases ($P=.04$) and

Table 1 Summary of patient characteristics and treatment parameters

Variable	Patients who received single-fraction SRS (n = 151)	Patients who received multifraction SRS (n = 138)	*P*
Sex (female/male)	77/74	69/69	.9
Age (y)			
Median	64	62	.9
Range	30-80	28-82	
Histology			.6
NSCLC	62 (41)	58 (42)	
Breast carcinoma	25 (17)	24 (17)	
Colon carcinoma	20 (13)	22 (16)	
Melanoma	22 (15)	18 (13)	
Renal cell carcinoma	11 (7)	9 (7)	
Other*	11 (7)	7 (5)	
KPS			.6
Median	80	80	
60-70	54 (36)	44 (32)	
80-100	97 (64)	94 (68)	
Extracranial disease			.5
Present	113 (75)	99 (72)	
Absent	38 (25)	39 (28)	
No. of metastases			.3
Single	86 (48)	81 (49)	
Multiple (2-4)	93 (52)	83 (51)	
DS-GPA score			
≤1.0	35 (23)	31 (22)	.6
1.5-2.5	76 (50)	71 (51)	
≥3	40 (37)	36 (27)	
Size of metastases (cm)			.15
2-3	99 (55)	78 (47)	
>3	80 (45)	86 (53)	
GTV (cm^3)			.005
Median	8.8	12.5	
Range	3.1-24.1	4.1-47.9	
PTV (cm^3)			.001
Median	12.2	17.9	
Range	4.4-32	5.6-54	
Conformity index†			.2
Median	1.62	1.69	
Range	1.31-2.1	1.38-2.2	

Abbreviations: DS-GPA = diagnosis-specific graded prognostic factors; GTV = gross target volume; KPS = Karnofsky performance status; NSCLC = non-small cell lung cancer; PTV = planning target volume; SRS = stereotactic radiosurgery.

Values are number (percentage) unless otherwise noted.

* Other histologies included 6 rectal, 2 sarcoma, 2 bladder, 4 ovarian, 2 esophageal, and 2 gastric carcinomas.

† Calculated as prescribed isodose volume/tumor volume encompassed by the prescription isodose volume.

melanoma histology ($P = .03$) were associated with an increased risk of distant failure.

Local control

After a median radiologic follow-up of 10 months, 25 lesions in the SF-SRS group and 11 lesions in the MF-SRS group recurred ($P = .03$), as suggested by imaging; median times to progression were 10 months (range, 6-42 months) and 12 months (range, 6-27 months), respectively. Diagnosis of recurrence/progression was made by imaging in 21 patients (MF-SRS, 6 of 11; SF-SRS, 14 of 25) and by histology in 15 patients (MF-SRS, 5 of 11; SF-SRS, 11 of 25) who underwent surgery. Other local salvage treatments included repeated SRS (n = 16) or WBRT (n = 5). Cumulative LC rates were 97% and 94% at 6 months, 92% and 85% at 9 months, and 90% and 77% at 12 months ($P = .01$) for the MF-SRS and SF-SRS groups, respectively (Fig. 3); for lesions ≥3 cm, 6-month and 12-month LC rates were 62% and 54% after SF-SRS and 81% and 73% after MF-SRS ($P = .02$), respectively. Complete and partial response occurred in 18 and 47 lesions after SF-SRS and 28 and 64 lesions after MF-SRS, respectively.

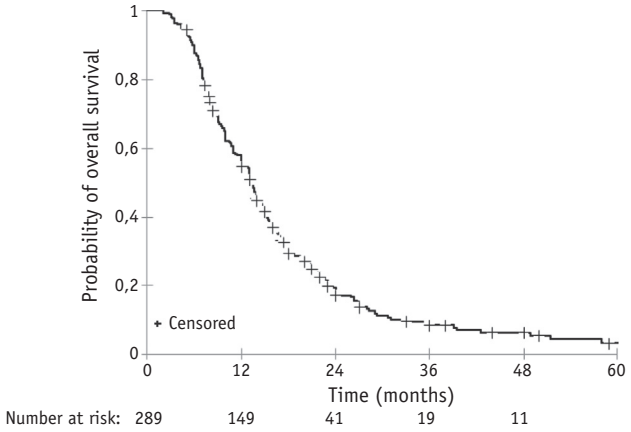

Fig. 1. Overall survival time for all patients after stereotactic radiosurgery.

Analysis of factors predictive of local failure showed that melanoma histology was associated with worse LC as compared with other histologies. Specifically, the 1-year local failure rates for melanoma metastases were 45% and 33% in SF-SRS and MF-SRS groups ($P = .1$), respectively. No other factors were predictive of local failure, although tumor size ≥3 cm was of borderline significance in patients receiving SF-SRS ($P = .07$).

Analysis of complications

Thirty-one patients (20%) undergoing SF-SRS and 11 (8%) subjected to MF-SRS experienced RN ($P = .004$), as suggested by MRI and PET-CT imaging; in 17 of 18 patients who underwent surgery, imaging results were confirmed by histology. Diagnosis of RN was made by imaging in 25 patients (MF-SRS, 7 of 11; SF-SRS, 18 of 31) and by histology in 17 patients (MF-SRS, 4 of 11; SF-SRS, 13 of 31) who underwent surgery. Median volumes of radionecrotic lesions were 12.7 cm^3 in the SF-SRS group and 18.0 cm^3 in the MF-SRS group ($P = .04$), with respective median times to RN of 10 months

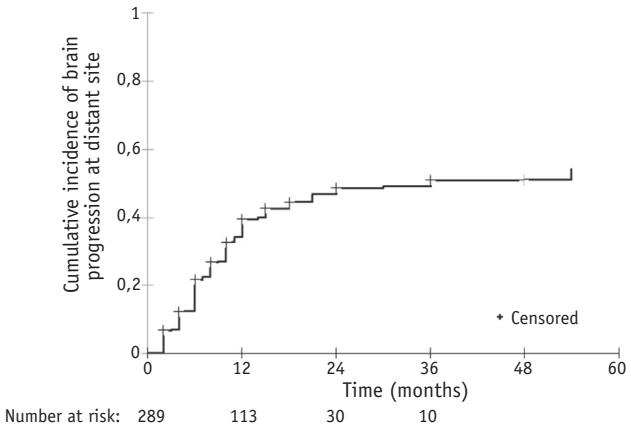

Fig. 2. Cumulative incidence of time to progression at distant brain sites for all patients after stereotactic radiosurgery.

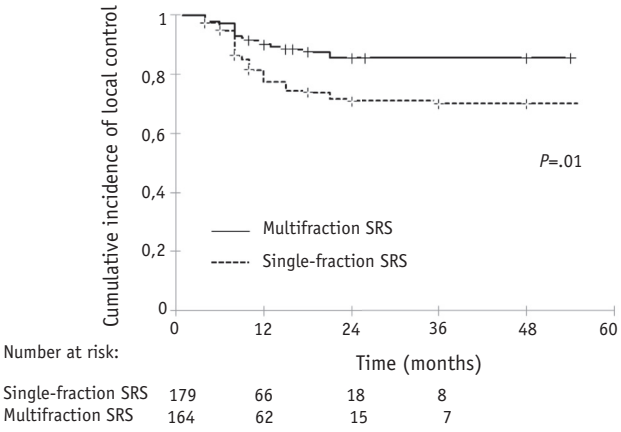

Fig. 3. Cumulative incidence of local control after single-fraction and multifraction stereotactic radiosurgery (SRS). Local control was significantly higher in the multifraction SRS group ($P = .01$).

(range, 4-32 months) and 12 months (6-24 months). The cumulative 1-year incidence of RN was 18% after SF-SRS and 9% after MF-SRS ($P = .01$) (Fig. 4); for lesions ≥3 cm, respective incidence rates of RN were 33% and 14% ($P = .01$). Radionecrosis was symptomatic in 13 of 151 and 4 of 138 patients after SF-SRS and MF-SRS, respectively ($P = .04$), requiring surgery or medical treatment. The RTOG grade 2 or 3 neurologic deficits included seizure (n = 5), motor deficits (n = 10), cognitive deficits (n = 3), and speech deficits (n = 3).

In the SF-SRS group, univariate analysis showed that tumor size, GTV, and volume of normal brain that received doses of 12-16 Gy were predictive of brain necrosis. The $V_{12\text{-}Gy}$ was the most significant variable associated with the development of RN; at a median radiologic follow-up of 10 months, the incidence of RN was 13% for $V_{12\text{-}Gy}$ ≤13.2 cm^3 and 28% for $V_{12\text{-}Gy}$ >13.2 cm^3 ($P = .02$). According to the $V_{12\text{-}Gy}$ quartile (Q1-Q4) distribution, the

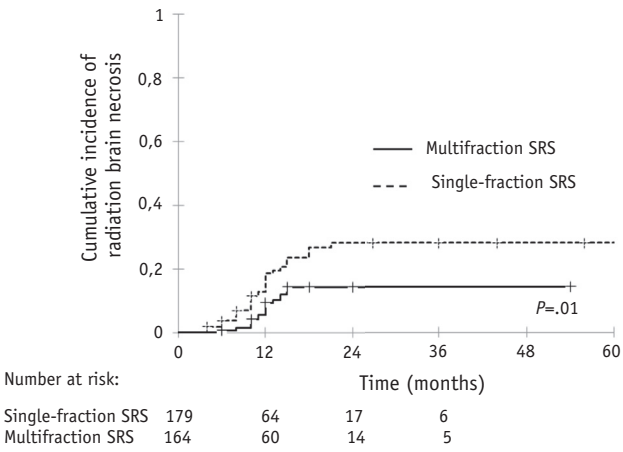

Fig. 4. Cumulative incidence of brain radionecrosis after stereotactic radiosurgery (SRS). The difference between the single-fraction and the multifraction SRS groups was significant ($P = .01$).

1-year risk of developing RN was 15%, 21%, 33%, and 49% for $V_{12\text{-Gy}}$ <10.5 cm^3 (Q1), 10.5-13.2 cm^3 (Q2), 13.3-18.2 cm^3 (Q3), and >18.2 cm^3 (Q4), respectively.

In the MF-SRS group, GTV and volume of normal brain receiving doses of 15-24 Gy were predictive of RN. The brain volume receiving 18 Gy ($V_{18\text{-Gy}}$) was the most significant prognostic factor for RN; the incidence of RN was 5% for $V_{18\text{-Gy}}$ ≤30.2 cm^3 and 14% for $V_{18\text{-Gy}}$ >30.2 cm^3 (P = .04). According to the quartile distribution, the 1-year risk of developing RN was 0%, 6%, 13%, and 24% for volumes <22.8 cm^3, 22.8-30.2 cm^3, 30.3-41.2 cm^3, and >41.2 cm^3, respectively. No other factors emerged as predictors of RN in both groups.

Propensity score matching analysis

Propensity score matching resulted in 102 matched pairs, for a total of 208 patients. Matched pairs were constructed for evaluation of LC and RN by matching by age, sex, histology, tumor size, and irradiated volumes (but not the presence of extracranial disease, number of metastases, or KPS, which did not seem to affect LC or RN to allow more patients included in the analysis). The overall χ^2 test for balance (P = .996) and the L1 index (0.84) suggested that the treatment groups were well balanced across all covariates. The 1-year cumulative LC rates were 91% and 76% (P = .01) (Fig. E1; available online at www.redjournal.org), respectively, and cumulative incidence rates of RN were 8% and 20% (P = .01) (Fig. E2; available online at www.redjournal.org), respectively. In Table 2, results of pair-matched and inverse-probability-of-treatment weighting propensity score analyses are shown. The adjusted Cox regression models confirmed significantly better LC and lower risk of RN in the MF-SRS group as compared with the SF-SRS group.

Table 2 Effect of single-fraction SRS and multifraction SRS on LC and RN risk

Outcome	HR	95% CI	P
LC			
Unadjusted cohort	0.43	0.21-0.9	.01
Propensity score matching	0.35	0.13-0.76	.01
IPTW propensity score	0.33	0.16-0.68	.007
RN risk			
No adjustment	0.42	0.21-0.83	.01
Propensity score matching	0.22	0.14-0.73	.005
IPTW propensity score	0.23	0.18-0.66	.001

Abbreviations: CI = confidence interval; HR = hazard ratio; IPTW = inverse-probability-of-treatment weighting; LC = local control; RN = radiation-induced brain necrosis; SRS = stereotactic radiosurgery. Other abbreviation as in Table 1.

Confounding variables on outcomes included in propensity scores were age at diagnosis, gender, histology, number of metastases, extracranial disease, and tumor volumes.

Discussion

The results of this study, in which either SF-SRS or MF-SRS was delivered to patients with brain metastases >2 cm in diameter, indicate that MF-SRS is superior in terms of LC and risk of RN. The above findings are strengthened by propensity score analyses, which address potential bias when retrospective data of two nonrandomized groups are compared.

Worse LC has been seen in patients with large lesions after SF-SRS (23-26). Using the RTOG recommended dose of 15 Gy for lesions >3 cm in diameter, Vogelbaum et al (24) reported a 12-month LC rate of 45%, as compared with 85% for lesions ≤2 cm that received 24 Gy. In 153 brain metastases treated with SF-SRS, Chang et al (23) reported a 12-month LC rate of 86% in tumors ≤1 cm in size and 56% in tumors >1 cm, and similar results have been observed in other studies (25, 26). In our study the most significant difference in LC between groups was observed for lesions ≥3 cm in size, being 54% and 73% at 1 year after SF- and MF-SRS (P = .02), respectively. Using the linear-quadratic model adjusted for high doses, Wiggenraad et al (27) compared the BED_{12} of different radiation schedules for the treatment of brain metastases. Analysis of published studies showed that a BED_{12} of at least 40 Gy, corresponding to 3 × 8.5 Gy or 20 Gy in a single fraction, was necessary to achieve a 1-year LC rate of ≥70%. Different BED_{12} values may explain, at least in part, the better LC reported in our series with 3 × 9 Gy as compared with single doses of 16-18 Gy, suggesting that MF-SRS may represent a better treatment option for large metastases.

RN represents the most important late toxicity reported after SRS. In the present study the development of radiologic changes suggestive of RN was significantly higher in patients who received SF-SRS as compared with those receiving MF-SRS, and this was associated with an increased risk of neurologic deficits. The $V_{12\text{-Gy}}$ and $V_{18\text{-Gy}}$ were the most significant predictors of RN for lesions treated with SF-SRS or MF-SRS, respectively; the 1-year risk of RN was up to 49% for $V_{12\text{-Gy}}$ >13.2 cm^3 and up to 24% for $V_{18\text{-Gy}}$ >30.2 cm^3, being consistent with previous published studies (5, 6, 10).

Using $V_{12\text{-Gy}}$ as a predictor of RN in 63 patients with a total of 173 brain metastases who received SF-SRS, Blonigen et al (5) reported a risk of RN up to 69% for volumes >10.8 cm^3. In another series of 198 intracranial tumors treated with Gamma Knife SRS, Korytko et al (10) confirmed the significant correlation between $V_{12\text{-Gy}}$ and the risk of symptomatic RN; the risk was 55.3% for $V_{12\text{-Gy}}$ >10 cm^3 versus 22.5% for $V_{12\text{-Gy}}$ <10 cm^3. A lower risk of RN has been reported after fractionated SRS (11-14, 28). In a series of 98 patients treated with either SRS or hypofractionated radiation therapy for brain metastases, Kim et al (28) observed a lower risk of toxicity in patients who received 6 × 6 Gy as compared with those who were given

20 Gy in a single fraction (5% and 17%, respectively; $P<.05$). Similarly, Fokas et al (13) found that the use of 5 × 5-Gy or 10 × 4-Gy schedules was associated with a lower rate of toxicity than SF-SRS in 260 patients with 1-3 brain metastases. In general, according to the linear-quadratic model, a risk of RN of 2-15% has been reported for BED values of 90-127 Gy3 ($\alpha/\beta = 3$ Gy) for late effects, corresponding to a radiation dose of 24-35 Gy given in 3-5 fractions (11, 12, 14). Overall, our data support the use of MF-SRS as an alternative to SF-SRS for large lesions, especially when located close to critical structures, to minimize the risk of long-term neurologic toxicity.

The major weakneses of the present study are the retrospective nature of the analysis and the clinical heterogeneity of patients with brain metastases. Moreover, the presence of unobserved confounding covariates may contribute to the observed differences in LC and risk of RN between groups, even when sophisticated statistical analysis are applied to reduce the impact of selection bias on outcomes. A randomized trial would be the ideal way to compare the 2 regimens used.

In conclusion, MF-SRS at a dose of 27 Gy in 3 consecutive fractions seems to be an effective treatment modality for brain metastases >2 cm in size, associated with improved LC and reduced risk of RN as compared with SF-SRS. The optimal dose/fractionation radiosurgical schedules need to be determined in future studies.

References

1. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. *JAMA* 2006;295:2483-2491.
2. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. *Lancet Oncol* 2009;10:1037-1044.
3. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 study. *J Clin Oncol* 2011;29:134-141.
4. Williams BJ, Suki D, Fox BD, et al. Stereotactic radiosurgery for metastatic brain tumors: A comprehensive review of complications. *J Neurosurg* 2009;111:439-448.
5. Blonigen BJ, Steinmetz RD, Levin L, et al. Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2010;77:996-1001.
6. Minniti G, Clarke E, Lanzetta G, et al. Stereotactic radiosurgery for brain metastases: Analysis of outcome and risk of brain radionecrosis. *Radiat Oncol* 2011;6:48.
7. Nedzi LA, Kooy H, Alexander E 3rd, et al. Variables associated with the development of complications from radiosurgery of intracranial tumors. *Int J Radiat Oncol Biol Phys* 1991;21:591-599.
8. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: Final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 2000;47:291-298.
9. Varlotto JM, Flickinger JC, Niranjan A, et al. Analysis of tumor control and toxicity in patients who have survived at least one year after radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys* 2003;57:452-464.
10. Korytko T, Radivoyevitch T, Colussi V, et al. 12 Gy Gamma Knife radiosurgical volume is a predictor for radiation necrosis in non-AVM intracranial tumors. *Int J Radiat Oncol Biol Phys* 2006;64:419-424.
11. Aoyama H, Shirato H, Onimaru R, et al. Hypofractionated stereotactic radiotherapy alone without whole brain irradiation for patients with solitary and oligo brain metastasis using noninvasive fixation of the skull. *Int J Radiat Oncol Biol Phys* 2003;56:793-800.
12. Ernst-Stecken A, Ganslandt O, Lambrecht U, et al. Phase II trial of hypofractionated stereotactic radiotherapy for brain metastases: Results and toxicity. *Radiother Oncol* 2006;8:18-24.
13. Fokas E, Henzel M, Surber G, et al. Stereotactic radiosurgery and fractionated stereotactic radiotherapy: Comparison of efficacy and toxicity in 260 patients with brain metastases. *J Neurooncol* 2012;109:91-98.
14. Minniti G, D'Angelillo RM, Scaringi C, et al. Fractionated stereotactic radiosurgery for patients with brain metastases. *J Neurooncol* 2014;117:295-301.
15. Joiner M. Quantifying cell kill and survival. In: Joiner M, Van der Kogel A, eds. *Basic Clinical Radiobiology.* 4th ed. London: Hodder Arnold; 2009:102-119.
16. Cicone F, Minniti G, Romano A, et al. Accuracy of F-DOPA PET and perfusion-MRI for differentiating radionecrotic from progressive brain metastases after radiosurgery. *Eur J Nucl Med Mol Imaging* 2015;42:103-111.
17. Gray RJ. A class of K-Sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141-1154.
18. Austin PC. Comparing paired vs non-paired statistical methods of analyses when making inference about absolute risk reduction in propensity score matched samples. *Stat Med* 2011;30:1292-1301.
19. Hansen B, Bowers J. Covariate balance in simple, stratified and clustered comparative studies. *Stat Sci* 2008;23:219-236.
20. Iacus SM, King G, Porro G. CEM: Coarsened exact matching software. *J Stat Softw* 2009;30:1-27.
21. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550-560.
22. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: An accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012;30:419-425.
23. Chang EL, Hassenbusch SJ 3rd, Shiu AS, et al. The role of tumor size in the radiosurgical management of patients with ambiguous brain metastases. *Neurosurgery* 2003;53:272-280.
24. Vogelbaum MA, Angelov L, Lee SY, et al. Local control of brain metastases by stereotactic radiosurgery in relation to dose to the tumor margin. *J Neurosurg* 2006;104:907-912.
25. Han JH, Kim DG, Chung HT, et al. Radiosurgery for large brain metastases. *Int J Radiat Oncol Biol Phys* 2012;83:113-120.
26. Yang HC, Kano H, Lunsford LD, et al. What factors predict the response of larger brain metastases to radiosurgery? *Neurosurgery* 2011;68:682-690.
27. Wiggenraad R, Verbeek-de Kanter A, Kal HB, et al. Dose-effect relation in stereotactic radiotherapy for brain metastases. A systematic review. *Radiother Oncol* 2011;98:292-297.
28. Kim YJ, Cho KH, Kim JY, et al. Single-dose versus fractionated stereotactic radiotherapy for brain metastases. *Int J Radiat Oncol Biol Phys* 2011;81:483-489.