Scientific Article

Focal Management of Large Brain Metastases and Risk of Leptomeningeal Disease

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Abstract

Purpose: Surgery is often used for large or symptomatic brain metastases but is associated with risk of developing leptomeningeal dissemination. Emerging data suggest that fractionated stereotactic radiation therapy (FSRT) is an effective management strategy in large brain metastases. We sought to retrospectively compare leptomeningeal disease (LMD) and local control (LC) rates for patients treated with surgical resection followed by radiosurgery (S + SRS) versus FSRT alone.

Methods and Materials: We identified all patients with a brain metastasis ≥ 3 cm in diameter treated from 2004 to 2017 with S + SRS or FSRT alone (25 or 30 Gy in 5 fractions) who had follow-up imaging. LMD was defined as focal or diffuse leptomeningeal enhancement that was >5 mm from the index metastasis. Categorical baseline characteristics were compared with the χ^2 test. LMD and LC rates were evaluated by the Kaplan-Meier (KM) method, with the log-rank test used to compare subgroups.

Results: A total of 125 patients were identified, including 82 and 43 in the S + SRS and FSRT alone groups, respectively. Median pretreatment Graded Prognostic Assessment in the S + SRS and FSRT groups was 2.5 and 1.5, respectively ($P < .001$). Median follow-up was 7 months. The KM estimate of 12-month LMD rate in the S + SRS and FSRT groups was 45% and 19%, respectively ($P = .048$). The KM estimate of 12-month local control in the S + SRS and FSRT groups was 70% and 69%, respectively ($P = .753$). The 12-month KM estimate of grade ≥ 3 toxicity was 1.4% in S + SRS group versus 6.3% in the FSRT alone group ($P = .248$). After adjusting for graded prognostic assessment (GPA), no overall survival difference was observed between groups ($P = .257$).

Conclusions: Surgery is appropriate for certain brain metastases, but S + SRS may increase LMD risk compared with FSRT alone. Because S + SRS and FSRT seem to have similar LC, FSRT may be a viable alternative to S + SRS in select patients with large brain metastases.

Introduction

Advances in the efficacy of systemic therapies have led to improved survival in patients with brain metastases.[1] The improvements in survival have created a 2-fold challenge with regard to intracranial metastasis management, including the need for improved efficacy of brain-directed treatment and the need to minimize treatment-related morbidity. These challenges are important to address because patients are now more likely to live long enough to experience the sequela of either intracranial progression or central nervous system (CNS) toxicity associated with treatment.

Prospective data comparing stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT) have shown that SRS alone offers a relatively high rate of local tumor control.[2,3] WBRT has the benefit of decreasing distant brain failure, but the feasibility of salvage SRS after an initial course of radiosurgery has been demonstrated.[3,4] Moreover, WBRT does not offer a survival advantage over focal brain metastasis treatment,[2,5-7] and WBRT is more likely to induce cognitive decline in treated patients.[8,9]

Despite the advantages of treating patients with limited brain metastases with single-fraction radiosurgery, increasing tumor size is associated with decreased tumor control and increased CNS toxicity rates.[4] Additionally, owing to the mass effect of some tumors, upfront surgical resection is often necessary. Surgery involves the disruption of anatomic boundaries with the potential for cerebrospinal fluid (CSF) seeding of malignant cells and subsequent development of leptomeningeal disease (LMD). Patients with LMD often face rapid neurologic decline with short survival on the order of weeks to months.[10,11] Adjuvant WBRT may reduce the risk of LMD by treating the entire intracranial CSF space, but adjuvant radiosurgery would leave much of the CSF space untreated. Therefore, the management of large brain metastases remains a challenge. Radiobiologically, fractionating a course of radiation results in decreased normal tissue effects while maintaining tumor control; therefore, several authors have reported on the efficacy and safety of fractionated stereotactic radiation therapy (FSRT).[12,13] In fact, FSRT is a radiosurgery strategy that allows for treatment of larger tumors that are often susceptible to CNS toxicity and low tumor control with single-fraction radiosurgery.

Surgery is the historic standard in focal management of large or symptomatic brain metastases but is associated with a risk of developing leptomeningeal dissemination.[14] Emerging data suggest that FSRT is an effective management strategy in appropriately selected large brain metastases.[12,13] We sought to retrospectively compare LMD and local control (LC) rates at our institution for patients treated with surgical resection followed by radiosurgery (S + SRS) versus FSRT alone. We hypothesize that FSRT will result in a lower rate of LMD with acceptable LC compared with S + SRS.

Materials

Patients

Patients presenting with a previously untreated brain metastasis measuring ≥3 cm in maximal diameter that were treated with either surgical resection followed by radiosurgery (single or multiple fractions) or FSRT alone from 2004 to 2017, were eligible for inclusion. Exclusion criteria included: >1 tumor ≥3 cm in diameter, WBRT as a component of treatment, lack of follow-up magnetic resonance imaging (MRI), history of intracranial surgery for another brain metastasis, or tumors that appeared to predominantly arise from the meninges. Patients were eligible for inclusion if they had multiple brain metastases; however, patients were excluded if they had >1 brain metastasis that was ≥3 cm in diameter. Specific treatment decisions were based on the treating physicians' preference after consideration of relevant patient and tumor characteristics. Upon approval by our institutional review board, we retrospectively reviewed the medical records of all eligible patients.

Treatments

The decision to perform surgical resection of a given brain metastasis was made by the treating physicians with consideration of multiple factors, including tumor location, degree of mass effect and associated symptoms, medical urgency, and the need for definitive tissue analysis. In cases where surgical resection was deemed appropriate, a gross total resection (GTR) of each lesion was obtained whenever feasible. A GTR was defined as no evidence of residual tumor after surgical resection as reported by operative reports and postoperative MRI interpretations. Corticosteroid utilization was at the treating physicians' discretion. Commonly corticosteroids (typically dexamethasone 4-10 mg) were administered on the

days of radiosurgery treatment with additional corticosteroid administration driven by the patient's symptoms and other clinical factors.

All patients received either Gamma Knife radiosurgery (Elekta model B or C) or linear accelerator (LINAC) radiosurgery with a Volumetric Modulated Arc Therapy (VMAT) technique. The modality of choice at our institution transitioned gradually over time from initial utilization of Gamma Knife to sole utilization of LINAC VMAT radiosurgery. The postoperative decision to treat patients with a single fraction or a hypofractionated dose schedule was typically based upon maximum cavity diameter. Gamma Knife was delivered as a single dose of radiation with the dose typically being prescribed to the 50% isodose line. The target volume in all postoperative Gamma Knife cases was the cavity without an additional margin.

All patients treated with FSRT alone and some patients treated with postoperative radiosurgery were treated with linear accelerator based stereotactic radiosurgery. Patients who received LINAC-based radiosurgery were simulated in the supine position with a thermoplastic mask used for immobilization. A thin slice (≤2 mm slice thickness) MRI was obtained and registered with the simulation computed tomographic (CT) scan for improved target delineation and normal structure identification. For intact cases, the gross tumor volume was defined as the enhancing abnormality as identified on the T1 postcontrast MRI sequence and CT scan; the MRI defined cavity was the gross tumor volume in postoperative radiosurgery cases. An optional 1- to 3-mm planning target volume expansion was infrequently used at the discretion of the treating physician to account for setup inaccuracy before the installation of a couch capable of 6 degrees of freedom correction. For patients receiving adjuvant single-fraction radiosurgery, the median prescription dose was 16 Gy. In patients receiving FSRT, the total prescription dose was 25 or 30 Gy in 5 fractions. All LINAC-based radiosurgery treatments (definitive and adjuvant) were prescribed volumetrically according to our institutional protocol[12,15] such that the plans were normalized to where 99% to 100% of the planning target volume received at least the prescription dose delivered during a 5- to 14-day period. Thus, there was no set prescription isodose line for LINAC-based treatments because of the previously described normalization strategy, but these plans are typically heterogeneous in nature. Additionally, every day treatment delivery was allowed at the discretion of the treating physicians, but the majority of patients were not treated in 5 consecutive days.

Single isocenter treatment plans were generated in Varian Eclipse (Varian Medical Systems, Palo Alto, CA) following a standardized optimization protocol.[15] Institutionally defined treatment planning goals were used to assess the quality of the plans.[12,15] Linear accelerator based treatments were initially delivered with a Varian

2100iX via sliding window intensity modulated radiation therapy using 6X or 15X photons and later with a Varian TrueBeam or Varian EDGE via VMAT in flattening filter free mode with 10X photons (≤2400 MU/min). Daily patient alignment was confirmed with a combination of kV orthogonal radiographs and cone beam CT for precise positioning immediately before treatment.

Follow-up

In patients treated with surgical resection, follow-up consisted of a postoperative MRI that was typically obtained on postoperative day 1, which was used for determination of extent of resection. Also, patients were followed with a clinical examination and MRI approximately 1 month after radiosurgery treatment completion. Additional follow-up with clinical examinations and MRI was performed at 2- to 3-month intervals unless earlier evaluation was clinically indicated.

Endpoint definitions and statistical analysis

Local failure was defined as the development of new nodular contrast enhancement within 5 mm of the resection cavity in surgical patients or a 25% increase in tumor diameter on follow-up MRI in FSRT alone patients.[12,16] Subsequent interventions resulting in pathologic confirmation of tumor recurrence was considered a local failure in both groups. Diffuse tumor cavity or nodular enhancement that resolved on subsequent imaging was considered treatment effect. LMD was defined as focal or diffuse leptomeningeal enhancement of the brain, spinal cord, cauda equina, cranial nerves, or dura that was >5 mm from the index metastasis (Fig 1). Each case of LMD was confirmed by a neurosurgeon and radiation oncologist in collaboration with a neuroradiologist. Additionally, cytologic confirmation of malignant cells in the cerebrospinal fluid was also considered LMD. Grade 3 or higher toxicity events as defined by the RTOG 9005 CNS toxicity criteria were recorded.

Categorical baseline characteristics were compared with the χ^2 test, and continuous variables that were not normally distributed were compared via the Mann-Whitney nonparametric test. Overall survival, leptomeningeal disease rates, and CNS toxicity were estimated on a per-patient basis using the Kaplan-Meier method and measured from the initiation of treatment. Living patients were censored at the time of the most recent clinical encounter, and patients without evidence of toxicity were censored at the time of most recent MRI or time of death. Estimation of local tumor control was performed on a per-tumor basis. Locally controlled tumors and tumors without leptomeningeal failure were censored from the analysis at the time of death or most recent MRI; to reduce the chance of overestimating the
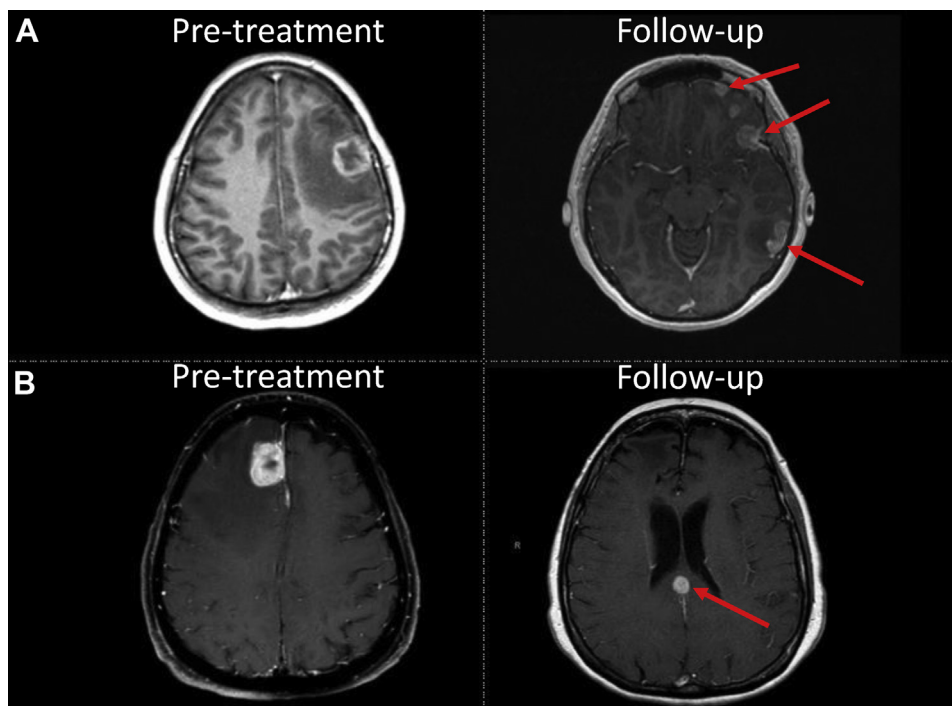
Figure 1   Pre-treatment and follow-up magnetic resonance images of patients with diffuse (A) or focal (B) leptomeningeal disease after their initial treatment.

effect of the initial intracranial treatment, tumors were also censored from the local control and leptomeningeal analysis if they underwent additional radiation therapy to this area for progressive disease not thought to represent local failure (for instance if a patient received salvage WBRT for distant brain progression). Kaplan-Meier estimates between groups were compared using the log-rank test. A multivariable model (Cox Proportional Hazards model) to evaluate the rate of LMD was constructed with surgery and other known predictors of LMD, namely tumor histology (breast vs nonbreast), total number of brain metastases, and tumor location (infratentorial vs supratentorial). All statistical tests were performed using SPSS software (IBM SPSS version 24.0, Chicago, IL).

Results

Patient and treatment characteristics

A total of 125 patients with 125 tumors meeting inclusion criteria were identified and included in this analysis. Baseline patient and tumor characteristics are shown in Table 1. The S + SRS group included 82 patients, and the FSRT alone group included 43 patients. Median imaging follow-up for all patients and for those still alive at the time of analysis was 7 (range, 1-110) and 7 (range, 1-110) months, respectively. The median clinical follow-up was 9 months (range, 1-110). No statistically significant difference was observed between treatment groups in the

baseline characteristics of breast histology ($P = .310$) or location (infratentorial vs supratentorial; $P = .064$). In the 82 patients with 82 resected tumors, a GTR was obtained in 60 (73%) and a subtotal resection was obtained in 22 (27%). In patients who received surgery and postoperative radiosurgery, the median time from surgery to radiosurgery was 36 days. Multiple treatment characteristics differed between the 2 groups, including median tumor diameter, median GPA, and diagnosis specific GPA (DS-GPA). The median tumor diameter in the S + SRS group was 4.0 cm compared with 3.5 cm in the FSRT alone group ($P = .004$). The median pretreatment GPA and DS-GPA was 1.5 and 2 in the FSRT group, and the median GPA and DS-GPA was 2.5 and 3 in the S + SRS group ($P < .001$).

Leptomeningeal disease rates

The posttreatment leptomeningeal disease (LMD) rates are shown in Figure 2. The Kaplan-Meier estimate of 6-month and 12-month leptomeningeal disease rates was 25% and 45% in the S + SRS group compared with 12% and 19% in the FSRT alone group ($P = .048$). A multivariable analysis evaluating known predictors of LMD was performed, suggesting that increasing total number of brain metastases and undergoing surgical resection seem to be associated with increased risk of LMD (Table 2). Among patients in the S + SRS group, LMD developed in 38% ($n = 15$ out of 40) treated with

Table 1   Baseline patient and tumor characteristics

Characteristics	S + SRS	FSRT Alone	P value
Total no. of patients	82	43	
Total no. of brain metastases ≥3 cm	82	43	
Sex (male:female)	41:41	24:19	.538
Median age in years (IQR)	59 (53-67)	63 (53-70)	.164
Histology			.454
NSCLC (%)	34 (41%)	25 (58%)	
Breast (%)	13 (16%)	4 (9%)	
Melanoma (%)	17 (21%)	3 (7%)	
GI (%)	5 (6%)	2 (5%)	
Renal (%)	5 (6%)	0 (0%)	
Other (%)	8 (10%)	9 (21%)	
Resection extent			
Gross total	60 (73%)	N/A	
Subtotal	22 (27%)	N/A	
Location			.064
Supratentorial	56 (68%)	36 (84%)	
Infratentorial	26 (32%)	7 (16%)	
Total number of brain metastases			<.001
1	62 (76%)	18 (42%)	
>1	20 (24%)	25 (58%)	
Median KPS (IQR)	90 (80-90)	80 (70-80)	<.001
Median GPA (IQR)	2.5 (2.0-3.0)	1.5 (1.0-2.5)	<.001
Median DS-GPA (IQR)	3.0 (2.5-3.5)	2.0 (1.5-2.5)	<.001
Median tumor diameter (IQR)	4.0 cm (3.4-4.9)	3.5 cm (3.2-4.0)	.004

Abbreviations: DS-GPA = diagnosis specific graded prognostic assessment; FSRT = fractionated stereotactic radiation therapy; NSCLC = Non-Small Cell Lung Cancer; GI = gastrointestinal; KPS = Karnofsky Performance Status; GPA = graded prognostic assessment; IQR = interquartile range; S + SRS = surgical resection followed by radiosurgery.

Gamma Knife and 38% (n = 16 out of 42) treated with LINAC-based radiosurgery. Additionally, LMD developed in 38% (n = 23 out of 60) of patients undergoing a GTR, whereas 36% (n = 8 out of 22) developed LMD after a subtotal resection. Of the patients who experienced LMD, the median time to development was 5.4 months in the FSRT group and 5.5 months in the S + SRS group.

Local control, survival, toxicity

There was no statistically significant difference in local tumor control when comparing the 2 groups (Fig 3). The Kaplan-Meier estimate of 6-month and 12-month local control was 91% and 70% in the S + SRS group compared with 84% and 69% in the FSRT alone group (P = .753). The Kaplan-Meier estimate of 6-month overall survival was 86% in the S + SRS group compared with 63% in the FSRT alone group (P = .008). However, this difference was no longer significant in a multivariable model that also included the significantly better GPA in the S + SRS group (P = .257). Among patients who experienced LMD failure, the median survival from time of LMD failure was 5 months overall, and the median survival from date of LMD failure was 5 and 6 months in the S + SRS and FSRT groups, respectively.

No patient experienced irreversible grade 3 toxicity, and no patient died as a result of treatment. Four patients (2 in each group) experienced a grade 4 CNS toxicity, requiring surgical resection of a single treated tumor. Across all patients, the Kaplan-Meier estimate of 6-month freedom from grade ≥3 CNS toxicity rate was 97%. The 12-month estimate of grade ≥3 toxicity was 1.4% in S + SRS group versus 6.3% in the FSRT alone group (P = .248). Tumor diameter was not significantly associated with increased risk of CNS toxicity in this patient cohort (hazard ratio 0.760; 0.245-2.361; P = .636).

Discussion

In our series of 125 patients with 125 treated brain metastases that were ≥3 cm in diameter, FSRT alone was associated with a lower risk of LMD and a similar rate of LC compared with surgical resection and postoperative radiosurgery. CNS toxicity rates were low in both groups with a slightly numerically higher rate of grade ≥3 CNS toxicity in the FSRT alone group, but this difference was not statistically significantly different. Overall survival initially seemed to be longer in the S + SRS group, but this difference resolved after adjusting for GPA. We observed no statistically significant difference between
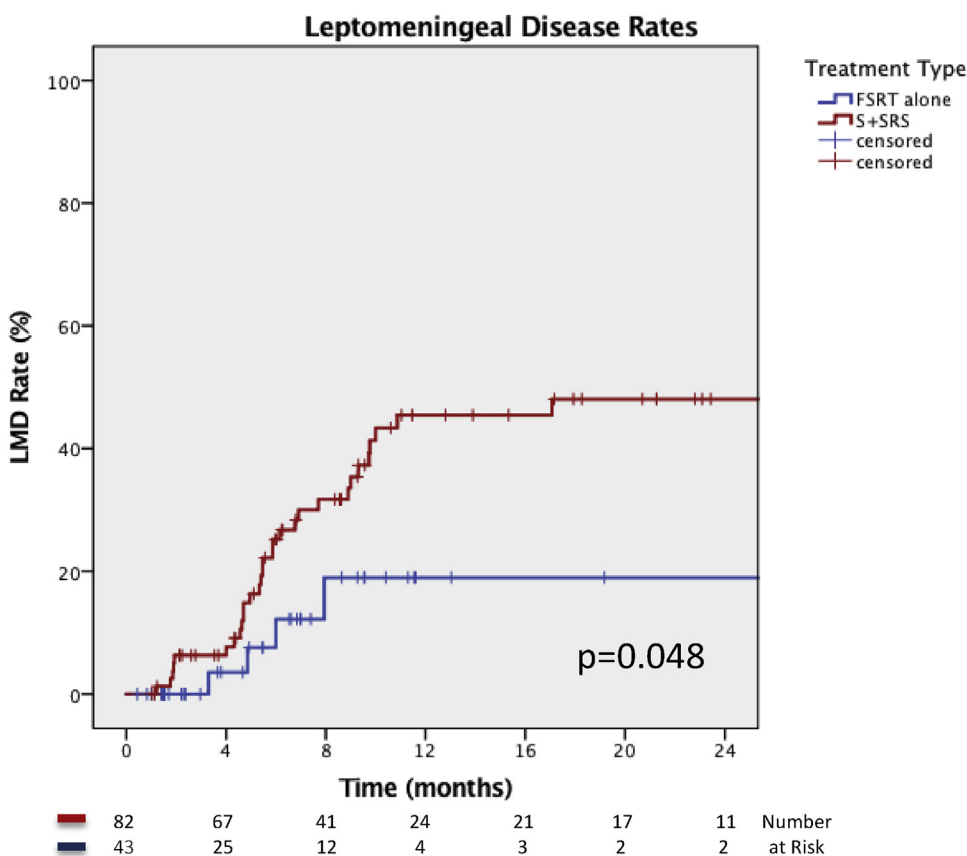
Figure 2   Rate of leptomeningeal disease in patients treated with surgery and postoperative radiosurgery compared with fractionated stereotactic radiation therapy alone.

Table 2   Multivariable analysis of known predictors of LMD

	Hazard ratio	P value
Surgery vs no surgery	3.697 (1.232-11.095)	.020
Breast histology vs other	2.021 (0.872-4.686)	.101
Infratentorial vs supratentorial	1.057 (0.481-2.320)	.891
Total number of brain metastases	1.290 (1.087-1.530)	.003

Abbreviation: LMD = leptomeningeal disease.

the 2 treatment strategies with regard to time to development of LMD or survival after LMD diagnosis.

Surgery is often appropriate for large or symptomatic brain metastases, but it is associated with a risk of developing leptomeningeal dissemination.[14] Emerging data suggests that FSRT is a viable management strategy in large brain metastases.[12,13] Although many tumors require upfront surgical resection due to mass effect, FSRT may in fact be a reasonable alternative in carefully selected patients and tumors. Surgery is necessarily associated with disruption of anatomic barriers, which theoretically exposes meningeal surfaces to malignant

cells. Because FSRT uses ablative radiation doses spread out over multiple treatments, a tumoricidal dose of radiation is able to be delivered while minimizing the effects on normal tissue. In large brain metastases, FSRT may serve as an alternative to both single-fraction SRS and surgery, in which the side effects of single-fraction SRS in large volume disease and the risks of LMD associated with surgery are able to be minimized. In this series, the local tumor control of FSRT alone seems very similar to surgical resection followed by radiosurgery; however, the relatively short median follow-up time in this study is a limitation and may underestimate late failures. Also, the median tumor diameter in the S + SRS group was statistically larger (4.0 cm vs 3.5 cm), which is a known risk factor for local tumor recurrence, but tumor size has not been clearly associated with increased risk of LMD and the absolute difference in median diameter (5 mm) is small. Additionally, the rate of local tumor control in the S + SRS group is lower than has been reported in multiple series. This may be due to a bias to operate on larger tumors or our institutional practice to target the resection cavity only with postoperative radiosurgery for a large portion of treated patients because inclusion of the surgical corridor is a more recent treatment planning consideration. It may be that additional margin on the
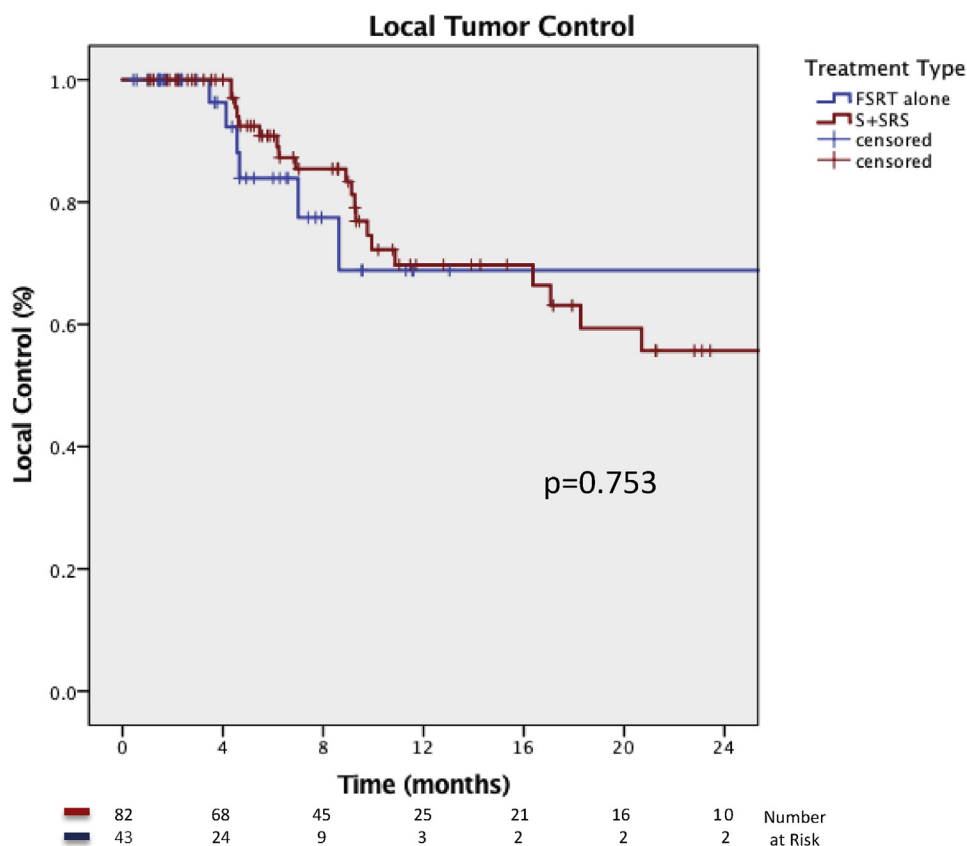
Local Tumor Control

Figure 3 Local tumor control in patients treated with surgery and postoperative radiosurgery compared with fractionated stereotactic radiation therapy alone.

surgical cavity and inclusion of the surgical corridor in the radiosurgery target volume, as described in recent contouring guidelines, will translate to superior tumor control and potentially lower rates of LMD.[17] Despite these factors, our 12-month LC estimate of 70% is similar to recent prospective randomized data, suggesting that our local control data may very well be externally valid.[18,19]

We recognize that prior published reports have used varying definitions of LMD; furthermore, the rates of leptomeningeal disease observed in this study are notably higher than often reported in the literature,[14,20,21] which we attribute to the conservative LMD definition we used, the retrospective study design, and the fact that this is a single-institution experience. Our definition included focal or diffuse leptomeningeal enhancement of the brain, spinal cord, cauda equina, cranial nerves, or dura that was >5 mm from the index metastasis, which likely captures many patients who do not have leptomeningeal carcinomatosis. LMD can have a variable clinical, cytologic and radiographic presentation, making direct comparisons across data sets challenging.[22] To ensure high quality, consistent reporting of LMD, each case was reviewed by a radiation oncologist, neurosurgeon, and neuroradiologist. We constructed a multivariable model of previously reported predictors of leptomeningeal disease development (Table 2),

and it suggests that surgery and a patient's total number of brain metastases may be the drivers of LMD occurrence. A limitation of this data are relatively short median follow-up and paucity of patients in the FSRT arm at later time points, but there is a clear separation of the LMD rates that was evident by 6 months (Fig 2).

Leptomeningeal metastasis is often associated with poor overall survival, typically measured in weeks to months, which makes reducing the rate of LMD a potentially important goal.[22] Although patients developing LMD are generally considered to have poor survival, we found that patients receiving surgery and postoperative radiosurgery did not have a shortened median survival despite higher LMD rates compared with patients receiving FSRT alone. We attribute this in part to the superior GPA and DS-GPA of the patients in the surgery group. Another important consideration is our definition of LMD that includes both focal LMD and diffuse LMD; it is possible that focal LMD has a more favorable prognosis and disease course than diffuse LMD, which is supported by a recent multi-institutional experience.[23] Our findings are consistent with previous reports that higher LMD rates are not necessarily associated with worse survival.[14,20] This raises the question of the clinical relevance of leptomeningeal failure as presently defined

and also highlights the fact that iatrogenically introduced LMD may in fact be biologically distinct from LMD that occurs as a result of natural disease progression.[24] Although LMD formation is traditionally considered to be a CSF seeding phenomenon, emerging data suggest that hematogenous spread of disease may in fact lead to LMD formation[25]; it is currently unclear if the route of disease spread affects the natural history and prognosis of LMD. Despite the lack of clear association with survival, LMD in the currently studied setting is often associated with the need for additional treatments and interventions.[22] In light of this, it seems important to use a treatment strategy that effectively controls intracranial disease while minimizing the risk of LMD. One such treatment strategy is the utilization of preoperative radiosurgery, which has been reported to reduce the risk of LMD in patients requiring surgical resection of a brain metastasis.[20]

The management of brain metastases is evolving as we discover improved treatment options for metastatic cancer that translate into improved oncologic outcomes. Treatment decisions should be made in a multidisciplinary setting to accurately account for the nuances of each patient and their respective brain metastases. We recognize that many patients need surgical resection of a brain metastasis owing to mass effect or need for tissue diagnosis; however, our study suggests that surgery and postoperative radiosurgery may increase the risk of leptomeningeal disease compared with FSRT alone. Additionally, the local tumor control of FSRT alone seems to be comparable to S + SRS in our study. Recognizing the known limitation that retrospective studies may have unexpected differences between groups that are only adequately addressed in a prospective randomized trial, our study suggests that FSRT alone appears to be associated with a reduced risk of developing LMD while maintaining tumor control rates comparable to S + SRS, making FSRT alone a viable alternative to S + SRS in select patients with large brain metastases.

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