A Prospective Phase II Trial of Fractionated Stereotactic Intensity Modulated Radiotherapy With or Without Surgery in the Treatment of Patients With 1 to 3 Newly Diagnosed Symptomatic Brain Metastases

**BACKGROUND:** Several studies have demonstrated that omitting the routine use of adjuvant whole-brain radiation therapy for patients with newly diagnosed brain metastases may be a reasonable first-line strategy. Retrospective evidence suggests that fractionated stereotactic radiotherapy (fSRT) may have a lower level of toxicity with equivalent efficacy in comparison with radiosurgery.

**OBJECTIVE:** To study the phase II efficacy of using a focally directed treatment strategy for symptomatic brain metastases by the use of fSRT with or without surgery and omitting the routine use of adjuvant whole-brain radiation therapy.

**METHODS:** We used a Fleming single-stage design of 40 patients. Patients were eligible if they presented with 1 to 3 newly diagnosed symptomatic brain metastases, Karnofsky performance scale (KPS) greater than 60, and histological confirmation of primary disease. Patients underwent fSRT with the use of a dose of 30 Gy in 5 intensity-modulated fractions as primary or adjuvant treatment after surgical resection. The primary end point was the proportion of patients who experienced neurological death. Secondary end points were overall survival, time to KPS 70, and progression-free survival.

**RESULTS:** Of 40 patients accrued, 39 were eligible for analysis. The proportion of patients dying of neurological causes was 13% (5 patients), which includes 3 patients with an unknown cause of death. Median overall survival, time to KPS 70, and progression-free survival were 16 (95% confidence interval, 9-23), 14 (95% confidence interval, 7-20), and 11 (95% confidence interval, 4-21) months, respectively.

**CONCLUSION:** A focally directed treatment strategy using fSRT with or without surgery appears to be an effective initial strategy. Based on the results of this phase II clinical trial, further study is warranted.

**KEY WORDS:** Brain metastasis, Clinical outcome, Fractionated stereotactic radiotherapy, Neurosurgery, Phase II clinical trial, Radiosurgery

Although whole-brain radiation therapy (WBRT) has long been used in the treatment of brain metastases, the role of routine adjuvant WBRT at diagnosis has been called into question recently. The reason for attempting to avoid WBRT is that it has some key disadvantages and toxicities. First, WBRT takes more time to deliver (typically 2-3 weeks), thereby delaying systemic therapy because systemic and radiation therapy are typically not delivered...
concurrently. Second, WBRT results in loss of hair, which can impact quality of life. Third, routine adjuvant WBRT may negatively impact the ability to optimally treat new local disease should WBRT fail. Finally, and most significantly, several studies have suggested an increased risk of neurocognitive decline.4-6

As a result of the concerns associated with WBRT, several centers have employed initial or adjuvant stereotactic radiosurgery (SRS) instead of WBRT.7-14 The advantage of WBRT over focal radiotherapy is that it can treat distant microscopic disease. Class I evidence comparing SRS alone with SRS with routine adjuvant WBRT demonstrates a decreased rate of progression of distant metastases when WBRT is used.5,15-19 However, these trials repeatedly fail to show any improvement in overall survival or functional preservation.5,15-17,19,20

Although the use of SRS as a primary modality or in a consolidation mode after surgical resection is increasing, there are some targets (metastasis or resection cavity) that are too big to be treated effectively with single-fraction SRS.21,22 Fractionated stereotactic radiotherapy (fSRT) may be of value in such clinical situations.23-26 In addition, there may be a radiobiological advantage to fractionation.27-29 Previous studies using fSRT for brain metastases have all been retrospective.23,24,30-37 with the exception of one prospective study that included patients undergoing WBRT and had a target size limit of 3 cm.38 In a prospective phase II clinical trial, we evaluated the efficacy of fSRT alone or in combination with surgery in the treatment of patients with 1 to 3 newly diagnosed symptomatic brain metastases.

METHODS

Trial Design

We chose a Fleming single-stage design39 of 40 patients with an α of 0.10 and β of 0.10. Statistical assumptions included the following: the treatment is ineffective if more than 25% of patients die of neurological causes (nonneurological death 0.75 (p0) or less) and the treatment would be worthy of further study if the proportion of neurological death drops to 0.10 or less (nonneurological death 0.90 (p1) or greater). In this study design, p0 represents the maximum response rate of a poor treatment and p1 is the minimum response of a good treatment. The cutoff (R) that would justify a phase III study is calculated by solving the following equations:

\[ N = \left( \left[ Z_1 - \beta \left( p_1 (1 - p_1) \right) \right] + Z_1 - \alpha \left( p_0 (1 - p_0) \right)^{1/2} \right) / \left( p_1 - p_0 \right) \]^2 \]

and

\[ R \geq N \times p_0 + Z_1 - \alpha \left( N \times p_0 (1 - p_0) \right)^{1/2} \ast + 1, \]

where Z denotes the a quantile of the normal distribution and * denotes the nearest integer.39 Calculating R, if 6 or fewer of the 40 patients die of neurological causes, it would justify further study.

Participants

Patients were eligible for the study if they were 18 years or older and presented with 1 to 3 newly diagnosed symptomatic brain metastases. Brain metastases were diagnosed by magnetic resonance imaging (MRI) or computed tomography (CT) (if contraindication to MRI) within 28 days before entry into the trial. At least one of the lesions had to be clinically symptomatic (neurological signs and/or symptoms related to the metastasis) or radiographically symptomatic (mass effect present with or without brain shift). Patients with more than 3 metastases were eligible if 1 to 3 of the metastases were considered symptomatic and all others asymptomatic. Histological confirmation of primary cancer was required. Eligible patients had to have a Karnofsky performance status (KPS) of at least 60. Patients were excluded if they had previously undergone radiation for brain metastases, if they had leptomeningeal disease, or if they had a brainstem metastasis. If surgery was performed for the symptomatic brain metastases, they were eligible for the study if they could start adjuvant radiotherapy within 28 days of surgery. Patients with known metastases from lymphoma, small-cell carcinoma, germ cell tumors, and multiple myeloma were also excluded. KPS and Radiation Therapy Oncology Group Recursive Partition Analysis (RPA) classification for brain metastases40 were obtained at presentation. This study was approved by the Ohio State Institutional Review Board (2007C0013) and registered with www.clinicaltrials.gov (NCT00983359). Written informed consent was obtained from each patient before entry into the trial.

Intervention

All patients were evaluated by a multidisciplinary team including neuro-oncology, radiation oncology, and neurosurgery. The decision for surgical intervention before radiotherapy was at the discretion of the treatment team and patient. In general, surgery was offered for metastases that were larger (>3 cm), had extensive edema, or for patients with worsening neurological deficit. Surgery was performed with the extensive use of neuronavigation and an operating microscope. PEACOCK (NOMOS Corporation, Sewickley, Pennsylvania) Intensity Modulated fSRT was used according to a regimen of 30 Gy divided in 5 fractions over 5 days (generally Monday through Friday). A dose regimen of 30 Gy in 5 treatments was chosen for fSRT regimen because the calculated acute-effect dose was equivalent to 40 Gy (at 2 Gy fractions) and the calculated late-effect dose was 60 Gy (at 2 Gy fractions), assuming an α/β ratio of 2 for acute effects and 10 for late effects. Thus, the proposed regimen did not exceed the normal brain tolerance of 60 Gy, and the peripheral dose of 40 Gy was felt to be adequate for control of microscopic disease. For this treatment, the surgical placement of talon anchors was required for immobilization and localization. Port-ports were taken and approved by the radiation oncologist before each fraction. After the 5-day treatment, these anchors were removed in the clinic setting. If surgical resection was performed, the tumor bed was irradiated postoperatively after the wound had healed. For planning target volume (PTV), a 3-mm margin was placed around the metastasis (enhancing-margin, gross tumor volume [GTV]) or surgical cavity (clinical target volume [CTV]). There was no prespecified dexamethasone regimen, and dosing varied according to clinical situation and the judgment of the treatment team. If additional symptomatic brain metastases (distant to the treated site) arose during follow-up, patients were eligible to undergo additional treatment not dictated by the study.

Outcomes

Follow-up clinical assessment, neurological examination, and contrasted MRI or CT (only if MRI contraindicated) were performed at 1 and

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2 months, and then every 3 months thereafter. If follow-up imaging revealed no progression for 3 years, interval scans were obtained at 6- to 12-month intervals at the discretion of the treating physician. Repeat imaging was also performed if a patient developed new neurological symptoms suggestive of neurological disease progression. Functional status was determined by measuring KPS at each follow-up. Investigators were not blinded to the patient’s treatment. Follow-up assessments were made by the physicians that treated the patient.

The primary outcome was the proportion of patients dying of neurological death. Neurological death was defined as death as a result of brain hemorrhage or brain disease progression with increasing mass effect or hydrocephalus resulting in herniation. Patients with progressive neurological symptoms who died of any cause were also considered to have died a neurological death. Patients with medication effects, cachexia, and failure to thrive from progressive systemic disease without clear neurological disease were considered nonneurological deaths. Any patient with an unknown cause of death was counted as a neurological death.

Secondary outcomes measured were overall survival (OS), time to KPS <70, and progression-free survival (PFS). All time-dependent outcomes were measured from the date of treatment. Patients who were still alive or lost to follow-up were censored at the date last known alive. If a patient had a confirmed neurological death, they were considered to have progression of brain disease. Patients who were still alive without any progression, died of nonneurological causes, or were lost to follow-up were censored. Local progression was defined as an increase by 25% or more in the bidimensional product compared with the pretreatment scan. If a lesion decreased in size during follow-up scans, this new bidimensional product was used as the new baseline by which to compare subsequent scans. Suspected progression in which biopsy revealed radiation effect was not counted as disease progression. Distant progression of brain disease was defined as new remote metastatic lesion, leptomeningeal disease, or increase in size of asymptomatic untreated lesions by more than 25% of bidimensional product as compared with the pretreatment scan. Local or distant progression of brain disease was treated if symptomatic and observed for another 1 to 3 months if asymptomatic at the discretion of the treatment team.

Statistical Methods

Descriptive statistics were used to summarize demographic data and adverse events. Kaplan-Meier survival analysis was used to determine time-dependent end points. Survival curves were compared by the log-rank test. Estimated median with 95% confidence intervals are reported. Associations between preoperative categorical characteristics and the occurrence of secondary end points were evaluated using Fisher exact test. Data were analyzed using SAS Version 9.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Recruitment and Participant Flow

During the recruitment period of June 2007 to March 2010, we accrued 40 eligible patients. Final end points were obtained in August 2012, which resulted in a minimum follow-up of 29 months for the last patient entered in the trial. One patient left the protocol immediately after enrolling and opted for WBRT, leaving 39 (97.5%) patients that were eligible for analysis (Figure 1). A power analysis based on 39 patients resulted in at least 85% power (β = 0.15), which is well accepted for a phase II trial. With 39 patients, if 6 or fewer patients died of neurological causes, it would warrant further study.

Baseline Patient Characteristics

Baseline patient characteristics are listed in Table 1. There were more men (56%) than women (44%). The mean age was 60.4 years. Before treatment, 10 (26%) patients were in RPA class I and 29 (74%) patients were in RPA class II. Because we had no patients presenting with KPS <70, there were no patients in RPA class III. Of the 39 patients, the most common 3 primary tumor sites were lung (54%), melanoma (13%), and breast (10%). Extracranial metastases were present in 51% of patients on initial presentation.

The majority (64%) of patients presented with a single metastasis. Two patients had ≥4 metastases. One of them had diffuse asymptomatic miliary disease (31 small lesions, 2-5 mm in major diameter) and 1 symptomatic metastasis, while the other patient had 4 metastases, of which only one was symptomatic. Treatment characteristics are listed in Table 2. The majority of patients (79%) had a single symptomatic metastasis treated. For treatment, most (77%) patients received surgery with adjuvant fSRT. Of the 62 metastatic lesions evaluated, 37 (60%) were treated with surgery and adjuvant fSRT, 12 (19%) were treated with fSRT alone, and 13 (21%) asymptomatic lesions were observed (excluding the 31 asymptomatic metastases in 1 patient with miliary disease). Two patients (5%) were diagnosed and

FIGURE 1. Flow diagram of study participants. fSRT, fractionated stereotactic radiotherapy; WBRT, whole-brain radiation therapy.
followed with contrasted CT instead of MRI owing to the presence of a pacemaker.

CTVs in the 36 postsurgical targets (surgical cavities) ranged from 1.04 to 67.52 cm³ (mean 16.06, median 10.25). GTVs in the 11 unresected lesions ranged from 0.1 to 24 cm³ (mean 4.89, median 0.41). Target volume (CTV and GTV aggregate) in the 48 targets ranged from 0.1 to 67.52 cm³ (mean 14.25; median 8.95). One patient had 2 metastases treated as a single target because of the proximity of treatment volumes. CTV and GTV calculations exclude the 2 metastases treated as a single target, while the CTV and GTV aggregate calculation includes this combined target. PTVs ranged from 1.1 to 109.21 mL (mean 27.59, median 20.14 mL) (Table 2).

Follow-up and Primary End Point

Follow-up ranged from 1 to 62 months, with a median of 16 months. Of the 39 patients, 6 were still alive (15%) between 37 and 62 months after treatment. Given that they survived substantially past the expected survival for brain metastases, they were counted as successful outcomes and censored. Of the 33 known deaths, 2 were confirmed due to neurological causes, 3 were from unknown causes, and 28 were secondary to nonneurological causes (Table 3). Per protocol, the overall neurological death rate was 5 (13%) of 39 patients in the final analysis, thus meeting the criteria for further study. There were no preoperative characteristics predictive of neurological death.

Secondary End Points

The estimated median OS was 16 months (95% confidence interval [CI], 9-23) (Figure 2). Comparing preoperative characteristics with OS, the only significant predictor of increased OS was RPA (Table 4). Patients in RPA class I had a median OS of 33.5 months compared with 10 months for RPA class II (P = .006). The estimated median time to KPS <70 was 14 months (95% CI, 7-20) (Figure 3). RPA was the only predictor of Karnofsky decay. Patients in RPA class I had a median time to KPS <70 of 30 months in comparison with 8 months for those in RPA class II (P = .01). Median PFS was 11 months (95% CI, 4-21) (Figure 4). The 23 (59%) patients that were confirmed to have progression of disease were treated with surgery or fractionated stereotactic radiotherapy.
patients with multiple brain metastases on presentation ($P < .001$). These secondary end point subgroup analyses were exploratory and meant to be used as hypothesis generating for future trials.

**Evolution of Metastases Untreated at Presentation**

At presentation, there were 8 patients who harbored metastases that were deemed not symptomatic according to the protocol. Seven of these patients had a total of 13 asymptomatic metastases and 1 patient with non-small-cell lung cancer had miliary disease with 31 asymptomatic metastases. Of the 13 asymptomatic metastases, 5 required treatment (2 lesions in different patients treated with SRS, 1 with gamma knife SRS, and 2 in the same patient with WBRT); treatment was delivered 1, 2, 12, and 13 months, respectively, after initial diagnosis and the patients lived for 7, 6, 38, and 1 month, respectively, after this secondary treatment. The patient with miliary disease had WBRT 13 months after the initial diagnosis and died 28 months after WBRT. Five of these 8 patients also had chemotherapy. All 8 patients died of nonneurological causes.

**Toxicities**

One patient could only tolerate 3/5 fractions because of intolerable back pain when lying supine. Three (7.7%) patients developed symptomatic radiographic local progression that was diagnosed as radiation effect on histopathology after surgical excision. There were no other radiation-related toxicities or adverse events related to talon placement and removal.

**DISCUSSION**

**Interpretation**

Why select neurological death as the primary end point? The goal of a brain metastases localized treatment such as surgery and
radiation therapy is that of controlling the brain disease. Hence, neurological death is an important metric of successful brain metastases treatment, especially when robust longitudinal follow-up is available, as in our report. A similar concept was put forward by Patchell in 1990.

The 13% proportion of neurological death represents a conservative estimate, because 3 of the 5 deaths counted as neurological were of unknown cause. In Patchell’s 1998 study, surgery without adjuvant radiation had a higher rate of neurological death (44%) compared with surgery with adjuvant WBRT (14%), likely because of increased local and distant recurrence rates. In Aoyama’s 2006 study, which did not use surgery, neurological death was seen in 23% and 19% in SRS + WBRT and SRS-alone cohorts, respectively. There have been several retrospective studies using fSRT (3 studies, 291 patients) and they report overall neurological death between 13% and 42% (mean 31.3%). However, direct comparison is difficult, because 90% of these patients did not undergo surgical resection and 27% underwent WBRT. Additional nonsurgical studies report death due to neurological causes between 19.3% and 44% for SRS alone, and between 22.8% and 36% for SRS with the routine use of adjuvant WBRT. Four studies report a neurological death rate in resected metastases with adjuvant radiation: 14% and 29% for surgery + WBRT, 318 25% and 42% for surgery + SRS or fSRT. Unlike our study, most of these studies did not tabulate patients with unknown cause of death as neurological deaths. All in all, our 13% conservative neurological death rate appears reasonable.

The largest randomized trial comparing the routine use of adjuvant WBRT with observation after focal therapy (surgery or SRS) enrolled 359 patients. They found no difference in the primary end point (World Health Organization performance status deterioration to ≥2 [median time 10.0 after observation vs 9.5 months after WBRT]). They did find a significant difference in neurological death defined more loosely as “intracranial metastasis as a component of death” (44% observation vs 28% routine adjuvant WBRT, P < .002). One of the limitations of this recent trial is that it may not be capturing relevant treatment alternatives in its randomization. Few providers today would choose between observation or WBRT after surgical resection, because the benefit of postoperative WBRT in terms of neurological death and local and distant progression, albeit not OS, has already been well documented in patients with resected single-brain metastases.

A more relevant comparison would be between adjuvant SRS and adjuvant WBRT. Unfortunately, there are no published data comparing the rate of neurological death between these 2 treatment alternatives. Currently, there is a phase III clinical trial (NCCTG N107C) randomly assigning patients with resected metastatic brain disease to WBRT (37.4 Gy in 15 treatments or 30 Gy in 10 treatments) vs SRS (12-20 Gy, dose dependent on cavity volume).

Our median OS of 16 months compares favorably to previous studies using adjuvant SRS or adjuvant WBRT after surgery. Class I studies report a median OS of 10.9 to 11.1 months for patients with surgery + WBRT. Class II and III studies utilizing fSRT report median OS times between 5 and 20.2 months. Our higher OS may in part be skewed from the fact that we had no enrolled patients in RPA class III. However, looking at our OS by RPA, patients in RPA class I and II had median survivals of 33.5 and 10 months, respectively. This compares favorably to previous studies as well. The distribution of primary tumor histology and extracranial disease at presentation in our group was similar to previous studies. This
difference may be treatment related or due to progress in treatment of systemic disease. In addition to survival, this study demonstrates functional preservation similar to previously reported rates in SRS, surgery + WBRT, and SRS + WBRT groups.\textsuperscript{16,18,19} Median PFS was 11 months (95\% CI 4-21). We had numerous distant failures, which is consistent with other studies omitting the routine use of adjuvant WBRT.\textsuperscript{9,11,14,16,19} However, many distant failures are small and asymptomatic and therefore may not impact neurological function and OS. As a result, a high rate of distant failures may be tolerable. Using neurological death as the primary end point, as opposed to local control or OS, this study can demonstrate that good neurological outcome may be obtained with substantial distant failures as long as these are closely followed and further treatment is used as necessary.

Our definition of local progression was more inclusive to include all cases of MRI size progression without biopsy-proven diagnosis of radiation effect. Other studies that diagnose radiation effects based solely on imaging findings may report lower relative local recurrence rates. In our study, 4 patients considered to have local recurrence by study definition were observed without intervention and had MRI lesion size that stabilized, suggesting the possibility that these cases may have been radiation effect rather than true tumor progression. In addition, 3 patients with MRI features highly suggestive of local failure had biopsy-proven radiation effect. Clearly, in patients heavily treated with a combination of surgery and focal radiation therapy, it may be very challenging to unequivocally differentiate tumor progression vs treatment-related effect if one relies exclusively on neuroradiological criteria.

Our study was set up to enroll only patients with symptomatic brain metastases; hence, the median size of our targets tended to be significantly larger than that of other studies.\textsuperscript{8,9,11,12,14,47-50} The overwhelming majority of our targets were unsuitable for single fraction radiosurgery owing to their large volume (median target volume 8.95 mL). It has been reported that, for example, gamma knife radiosurgery is associated with a higher rate of local failure (25\% vs 3\%) in metastases $\geq$2 cm$^3$ when Radiation Therapy Oncology Group dosing guidelines are used.\textsuperscript{51} Previous studies have also reported diminished local control with increasing tumor size.\textsuperscript{52,53}

We accrued a small number of metastases that were not treated with fSRT or surgery at enrollment because they were not deemed to be symptomatic according to the protocol criteria. Less than 50\% of these metastases ended up needing treatment during the study period. The fact that these metastases did not receive focal treatment (surgery and/or radiation) does not necessarily mean that they did not receive any treatment, because 5 of the 8 patients having asymptomatic metastases at presentation received systemic chemotherapy and it is known that systemic therapy may have a role, albeit still undefined, in the treatment of brain metastases.\textsuperscript{34,55} Indeed, with the widespread use of MRI, the number of small brain lesions found in patients with cancer is increasing,\textsuperscript{56} and the question of how to best treat these asymptomatic small lesions is a relevant one to be addressed.

Finally, our trial utilized fSRT as opposed to single-session SRS. The relative efficacy of fSRT in terms of local control and survival appears comparable to SRS based on previous studies.\textsuperscript{23,24,30-38} In particular, retrospective evidence suggests that fSRT may have a lower level of toxicity compared with radiosurgery.\textsuperscript{23,24} However, data have been retrospective for all but one of these fSRT studies.\textsuperscript{38} The only prospective study included patients that already had, or were scheduled to have, WBRT.\textsuperscript{38} Also, data from the University of Pittsburgh arteriovenous malformation radiosurgery series demonstrates that the volume receiving 12 Gy or more directly correlates with the percentage of patients developing symptomatic radiation necrosis.\textsuperscript{57} With 29\% (14 of 48) of our PTVs greater than 40 cm$^3$, a symptomatic radiation necrosis rate of 7.7\% is acceptable.

In a randomized trial, Aoyama et al\textsuperscript{16} found that there was a lower local recurrence rate in the WBRT + SRS group than in the SRS group alone, even though the SRS dose was 30\% lower in the former group. The authors hypothesized that this result might indicate a radiobiological advantage of hypofractionation. Some authors have described a theoretical advantage in hypofractionated radiotherapy in malignancy owing to the reoxygenation of hypoxic tumor cells in between fractions.\textsuperscript{27-29} In addition, fractionation may reduce damage to late-responding normal tissues.\textsuperscript{28} The relative safety and efficacy of fSRT regimens compared with single-session SRS needs further study in prospective studies.

**Generalizability**

The baseline patient characteristics demonstrate a range of age, sex, and primary tumor histologies that suggest these results are applicable to a wide range of patients presenting with newly diagnosed symptomatic brain metastases. In addition, the large size of our targets is representative of what is seen in an unselected clinical series. Different devices exist that can deliver fractionated intensity-modulated radiotherapy, and therefore, small differences in treatment effect are possible.

**Limitations**

We chose neurological death as the primary end point in this study to reflect the hypothesis that this may be the more relevant outcome in the current management of intracranial metastases.\textsuperscript{3} One of the potential limitations of neurological death as an end point is that it requires obtaining a detailed history from providers and family members regarding the circumstances surrounding each death. We used criteria similar to those used in Patchell’s 1998 study.\textsuperscript{58} In particular, there is difficulty in distinguishing decline in functional status due to a neurological cause vs pain mediation, cachexia, failure to thrive, or chemotherapy effect. Therefore, this end point may be more susceptible to increased interobserver variation.

**CONCLUSION**

A focally directed treatment strategy utilizing fSRT with or without surgery appears to be an effective strategy for patients with 1 to 3 newly diagnosed symptomatic brain metastases. This study demonstrates favorable rates of death from neurological causes,
OS, time to KPS <70, and PFS. Avoiding WBRT even in patients with large metastases or large resection cavities, both of which are not ideal candidates for single-fraction radiosurgery, can potentially avoid deleterious neurocognitive effects. The results from this trial justify a randomized controlled trial.

Disclosure
The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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**COMMENT**

This article highlights the growing practice of fractionated stereotactic radiosurgery (fSRS). In this article, the authors use the term fractionated stereotactic radiotherapy (fSRT) in patients with postsurgical cavities and intact brain metastases. Radiobiologically, fSRS can overcome the dosing limitation inherent to single-fraction SRS, i.e., the total dose prescribed is reduced to respect the risk of radiation necrosis as the tumor dimensions increase, and therefore more relevant for large targets. Thirty grays in 5 fractions is fairly common practice, and the idea is that fractionation may reduce the risk of radiation necrosis within the surrounding normal brain tissue while allowing still a high total dose within the tumor. It is well known that the normal brain tissue is sensitive to the dose per fraction.

The use of fSRS has been primarily for targets larger than 3 to 4 cm, and my practice has shifted for these tumors from single-fraction SRS to fSRS.