J Radiat Oncol
DOI 10.1007/s13566-013-0136-1

ORIGINAL RESEARCH

A retrospective review of SBRT for larger brain metastases or post-resection cavities: preliminary evidence from the Knight Cancer Institute

Kristina H. Young · Faisal Siddiqui · James A. Tanyi · Carol Marquez · Charlotte Dai Kubicky · Martin Fuss

Received: 3 June 2013 / Accepted: 5 December 2013

Abstract
Objective Radiation for brain metastases is typically delivered by whole brain radiation (WBRT), stereotactic radiosurgery (SRS), or a combination thereof. There are patients with lesions that are not candidates for SRS owing to a maximum target diameter >3 cm, for which avoiding WBRT may provide a quality of life benefit. Here, we report our early experience with stereotactic hypofractionated radiation therapy for brain metastases or resection cavities (SBRT brain) as an alternative to WBRT.
Methods We performed a single-institution retrospective review of 44 patients treated with SBRT brain between July 2007 and February 2012. Median lesion diameter was 3.65 cm. The most common fractionation was 30 Gy in five fractions. Treatments were delivered via BrainLAB/Varian NovalisTx linear accelerator with daily stereotactic x-rays for 6D setup correction, and cone-beam CT for validation.
Results Mean follow-up was 5.4 months. Seventy-seven percent of patients underwent post-resection radiation. Median overall survival was 10 months. There was a trend for survival advantage in patients who underwent resection compared to the group with intact tumors, 10.8 versus 5.7 months (p=0.18), between systemic burden of disease and overall survival (p=0.06), and number of brain metastases (p=0.08). Twenty-seven percent had tumor recur locally, with median local recurrence-free survival of 21 months. Local control did not stratify by BED_{10} (p=0.02), but did correlate with tumor size (p<0.001). Forty-three percent of patients failed elsewhere in the brain, with median recurrence-free survival of 9 months. Acute side effects were mild. Radionecrosis occurred in 14 %, with median onset of 41 months; a single patient was symptomatic requiring bevacuzimab.
Conclusions SBRT brain for larger brain metastases and post-resection cavities can be administered with a favorable side effect profile. Outcomes compare favorably to the historical data for WBRT. While longer-term survival was observed, in-brain failure and/or systemic disease progression are limiting overall survival.

Keywords Stereotactic radiation therapy · Stereotactic radiosurgery · Whole brain radiation

Introduction

Approximately 10 % of all cancer patients will develop symptomatic brain metastases [1]. As systemic therapeutics improves overall survival, an increase in the incidence of brain metastases is expected. Treatment of brain metastases has been shown to prolong life and improve quality of life [2]. Originally, therapy for brain metastases involved surgical resection or whole brain radiation. Patchell et al. demonstrated that surgical resection followed by whole brain radiation (WBRT) was superior to surgical resection alone for in-brain tumor recurrence and neurologic death [3]. However, WBRT is associated with significant quality of life decrements related to radiation-induced cognitive impairment. Radiation-related cognitive impairment, characterized by decrements in verbal and spatial memory, attention, and problem solving ability [4], has been estimated to occur in up to 90 % of patients receiving WBRT with increasing incidence and severity over time, and correlated with increasing doses [5]. Initial symptoms appear as early as 6 months, and can

K. H. Young (✉) · F. Siddiqui · J. A. Tanyi · C. Marquez · C. D. Kubicky · M. Fuss
Department of Radiation Medicine, Knight Cancer Institute, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, USA
e-mail: youngkri@ohsu.edu

Published online: 20 December 2013

progress to dementia in up to 5 % of long-term survivors [6–8]. Reduced quality of life related to neurocognitive decline is included in many prospective trials, recognized as an increasingly important parameter [9].

More advanced treatment techniques lead to the development of stereotactic radiosurgery (SRS) resulting in high-dose single fraction treatment. SRS has been utilized alone or in conjunction with WBRT and has demonstrated excellent local control and survival outcomes comparable to surgical resection [10]. Tumor size greater than 3 cm limits the safety of SRS; however, patients with these larger lesions may wish to avoid the toxicity of WBRT. For these patients, we support using a hypofractionated technique of up to five fractions of radiation which we call stereotactic radiation therapy for brain metastases (SBRT brain). In this retrospective study, we evaluated our early institutional experience using SBRT brain as an alternative to WBRT for the treatment of metastases or post-resection cavities.

Methods

Patients

After Institutional Review Board approval, we reviewed the medical records of patients with brain metastases treated with a hypofractionated stereotactic radiation therapy utilizing between two and five fractions between July 2007 and February 2012 for outcome characteristics including local recurrence, intracranial disease progression outside of the treatment field considered non-local in-brain recurrence, overall survival, and side effects including radionecrosis. A total of 42 patients with 44 tumors were included for analysis. This article does not contain any studies with human or animal subjects performed by any of the authors.

Radiotherapy and response evaluation

Treatments were delivered using a BrainLAB/Varian Novalis Tx linear accelerator over consecutive days in 28 patients, and every other day in 16 patients. Image-guidance employed daily stereotactic x-rays for 6D setup correction (ExacTrac, BrainLAB), and subsequent cone-beam CT (OBI, Varian) for volumetric validation. Clinical and dosimetric data was obtained from the chart. The most common fractionation was 30 Gy in five fractions (n=20), followed by 35 Gy in five fractions (n=16), and 25 Gy in five fractions (n=3). Tumor size was determined by the largest diameter measurements on MRI performed independently by two physicians. Tumor volume was extracted from the dosimetric planning system as contoured by the treating physician. Recurrence was determined by chart review of radiologic data, with the date of recurrence or progression coinciding with the date of the MRI.

Statistics

Survival analysis was performed using Kaplan-Meier survival curves and utilizing a log-rank analysis or Gehan-Breslow-Wilcoxon test for significance. Correlative data was analyzed using two-way ANOVA or chi-squared test. For all analyses, $p<0.05$ was considered as significant. Statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Software, Inc, La Jolla, CA).

Results

Baseline characteristics

Between July 2007 and February 2012, 42 patients with 44 tumors were treated with SBRT brain in our department. Patient characteristics are provided in Table 1. Mean follow-up was 5.4 months (range 0 to 48.6 months). Forty three percent of treated metastases were non-small cell lung cancer, 15 % were melanoma, and 7 % were renal cell carcinoma. Seventy seven percent of patients underwent resection prior to radiation, while 23 % of tumors were intact. Four patients had their metastases previously radiated, including one patient receiving prior WBRT, and three patients receiving prior SRS or SBRT brain. There was a high level of systemic disease burden in our patient population, with 31 patients having wide metastatic disease, 3 patients with uncontrolled primary along with brain metastases, and only 10 patients with brain metastases exclusively. The majority of patients had more than one brain metastasis, with 52 % receiving treatment to >1 lesion concurrently; one patient underwent concurrent WBRT with SBRT as a boost, five underwent SBRT brain to multiple lesions concurrently, and 17 underwent concurrent SRS to other lesions while receiving SBRT brain.

Treatment outcomes

Median overall survival was 10 months, 1-year overall survival was 41 % (Fig. 1a). There was a non-significant trend for survival advantage in patients who underwent resection compared to the group with intact tumors, 10.8 versus 5.7 months (p=0.18) (Fig. 1b). There was a trend towards significance between the systemic burden of disease and overall survival (p=0.06) (Fig. 1c) and number of brain metastases (p=0.08) (Fig. 1d). Patients with a single brain metastasis had a median survival of 12 versus 6 months in those with multiple brain metastases. There was a positive correlation between whether or not a patient died and systemic burden of disease ($p<0.0001$) or number of brain metastases ($p<0.0001$). If a patient suffered a local recurrence, there was a significant correlation with worse overall survival ($p<0.0001$).

Table 1 Patient characteristics

Male, *n* (%)	32 (73 %)
Age, years: median (range)	59 (25–80)
Follow up, months: median (range)	5.4 (0–48.6)
Primary tumor histology	
NSCLC	19 (43)
Melanoma	7 (15)
Renal cell	3 (7)
Adrenocortical carcinoma	2 (4)
Breast	2 (4)
Esophageal	2 (4)
Hepatocellular carcinoma	2 (4)
Ovarian	2 (4)
Unknown primary	2 (4)
Colon	1 (2)
Sarcoma	1 (2)
Lymphoma	1 (2)
Tumor volume, cc: median (range)	12.6 (2.5–56.3)
Largest tumor diameter, cm: median (range)	3.65 (1.9–5.7)
Tumor previously radiated, *n* (%)	4 (9)
Number of brain metastases, median (range)	2 (1–7)
Widely metastastic extracranially, *n* (%)	30 (68)
Resected, *n* (%)	36 (77)
BED_{10}, Gy: median (range)	48 (28–65.6)

Twelve patients (27 %) had tumor recur locally within the treatment field (Fig. 2a), with a median local recurrence-free survival of 21 months. No difference was observed between resected and intact tumors. The 1-year local recurrence rate was 47 %. Patients treated with a BED_{10} of <40 did not recur, and patients with a BED_{10} of 51–60 had a trend towards improved local control compared to those treated to BED_{10} 41–50, though this was not significant (p=0.2) (Fig. 2b). Rate of local recurrence did not correlate with dose or histology, but did correlate with tumor size (p<0.001) (data not shown). There was no advantage in time to local recurrence based on systemic disease burden (Fig. 2c) or number of brain metastases (Fig. 2d), but there was a positive correlation between whether or not someone recurred locally and systemic burden of disease (p<0.001) and total number of brain metastases (p<0.001). Forty-two percent of patients with local failure also failed elsewhere in the brain.

Nineteen patients (43 %) developed non-local in-brain failure characterized as in-brain failure outside of the treatment field (Fig. 3a), with a median non-local in-brain recurrence free survival of 9 months. Thirteen of these patients underwent additional radiation therapy including seven receiving WBRT alone, six with SRS or SBRT brain, and one with both WBRT and SRS, with a median time to re-irradiation of 30 months. No difference was observed in non-local in-brain recurrence between resected and unresected groups. There was no difference on timing of in-brain recurrence based on systemic burden of disease (Fig. 3b). However, there was a positive correlation between whether or not a patient had non-local in-brain recurrence and systemic burden of disease (p=0.002) or number of metastases (p=0.001). There was a non-significant trend towards earlier in-brain failure and the number of metastases at the time of SBRT brain (1 vs ≥2, p=0.3) (Fig. 3c and d).

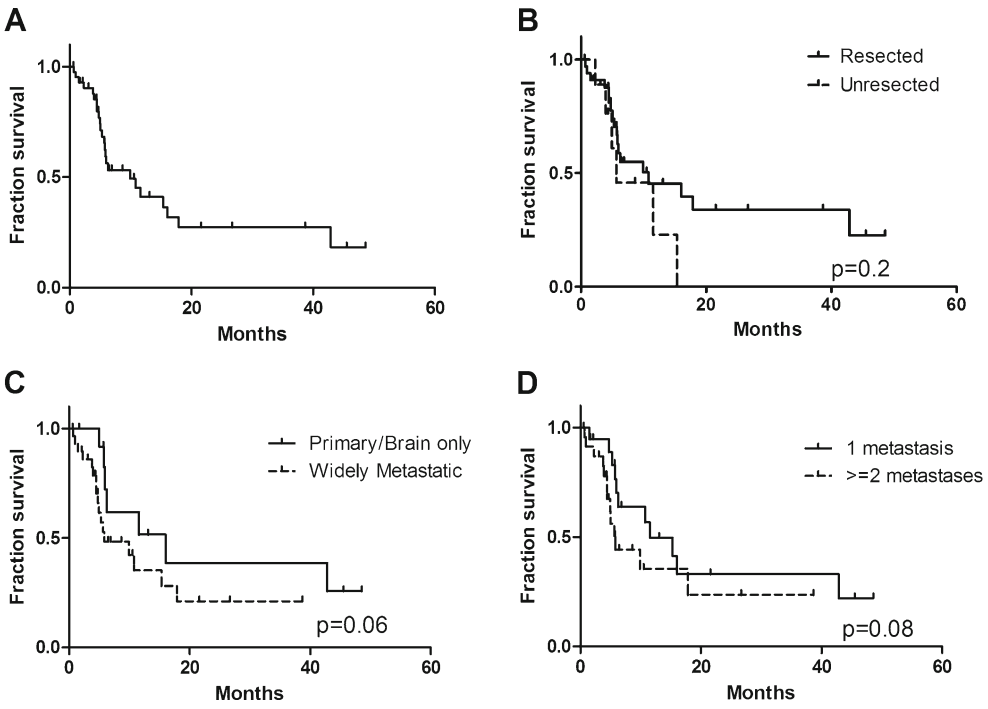

Fig. 1 Overall survival. **a** Median overall survival was 10 months. **b** Overall survival was non-significantly improved in the patients with resected tumors. Median overall survival 5.7 months in the unresected group versus 10.8 months in the resected group (p=0.2). **c** Trend to overall survival benefit in patients without systemically metastatic disease (p=0.06) with median survival of 6 months (metastatic) versus 16 months (brain +/− primary tumor). **d** Trend towards improved survival in patients with a single versus multiple brain metastases (p=0.08). Median survival 12 months (single) versus 6 months (multiple)

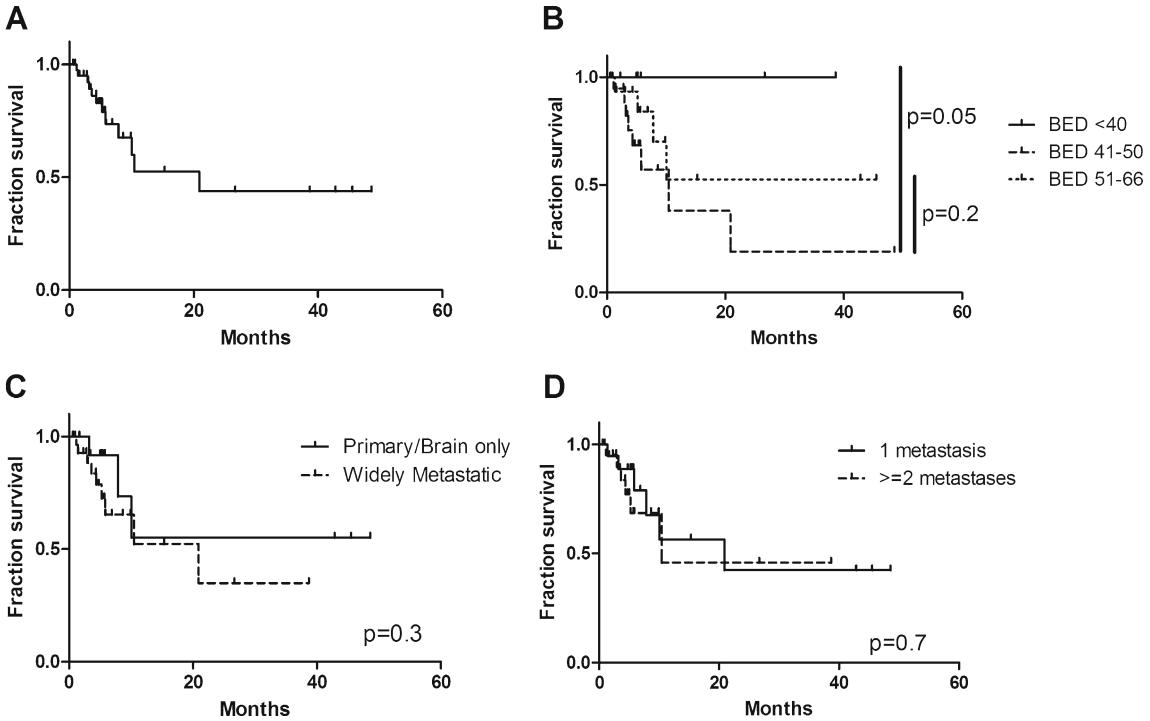

Fig. 2 Local recurrence-free survival. **a** Median local recurrence-free survival for all patients of 21 months. **b** No difference in local control for tumors based on BED_{10} (p=0.2). **c** Trend towards worse local control based on disseminated systemic metastases (p=0.3). **d** No difference was observed in local control based on a single versus multiple brain metastases

Side effects

Acute side effects were mild and included fatigue and focal hair loss. The incidence of radiologically evident radionecrosis was 13.6 %, with median onset of 41 months. One patient suffered headaches as a result of radionecrosis, and underwent a 3-month course of bevacuzimab, with resolution of symptoms. There was no grade 3 or higher toxicity. The incidence and timing of radionecrosis was equivalent in resected and unresected population (11 vs 14 %, chi-squared= 1.0, 27 vs 41 months, log-rank=0.7). There was a correlation between the size of tumor and development of radionecrosis (p<0.0001). Of the 12 tumors >22 cm^3, one third developed radionecrosis.

Discussion

This study demonstrates that SBRT brain may be an alternative to whole brain radiotherapy for patients who wish to avoid the quality of life deficits associated with WBRT. Local control rates using SBRT brain are similar to those seen historically with WBRT, but reduced compared to SRS [2, 3, 11, 12]. Given that our patient population underwent SBRT brain due primarily to large lesion size (>3 cm in largest diameter), but in some cases due to highly irregular shape, highly eloquent location such as the internal capsule, or for re-irradiation, and included a large proportion of patients with disseminated metastatic disease, the local control and overall survival rates are within what would be expected within this population [13]. The majority of our patients had undergone resection prior to SBRT brain and had multiple brain metastases concurrently treated with other radiation modalities, effectively utilizing SBRT as an alternative to WBRT. Our analysis did not identify a clear break point for which treating focally instead of WBRT may lose its benefit. However, we did see with increasing systemic disease burden and more than one intracranial metastasis, there was a trend to reduced efficacy with high rates of non-local in-brain recurrence, local recurrence, and reduced overall survival. These data indicate a strong set of selection criteria and should be utilized when offering a patient SBRT brain over conventional WBRT given the probability of re-treatment, and caution should be used when offering SBRT brain to patients with extensive extracranial disease and multiple brain metastases.

We did not see a clear benefit to dose escalation within our patient cohort. Recently, a dose-effect relationship was evaluated for SRS and SBRT brain which established a higher rate of local control achieved with doses greater than BED_{12} 40 Gy, which our 6 Gy × five fractions meets at 45 Gy [14]. No BED range provided a statistically significant local control benefit, though our sample size was low and limited our ability to detect a difference in groups despite separation of the survival curves. Patients treated at our lowest dose range appeared to have the best local control, but likely represented a biased cohort given that some of their disease was more radiosensitive (DLBCL),

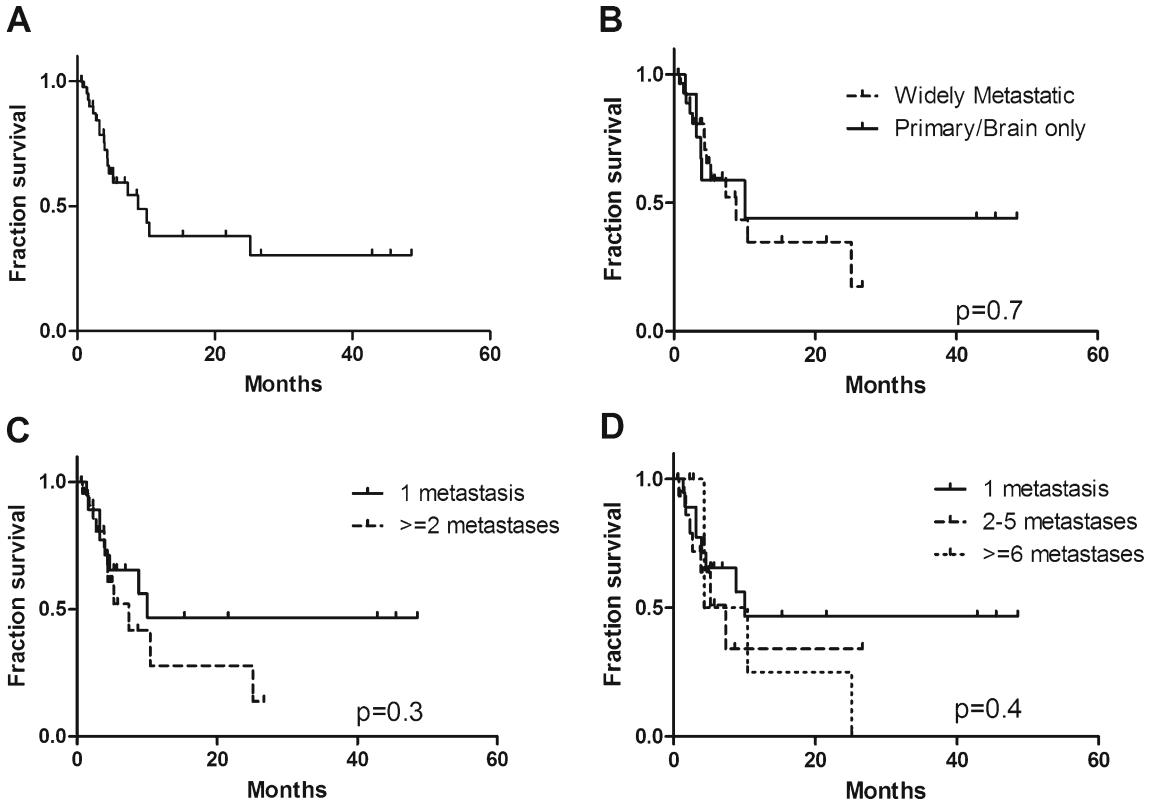

Fig. 3 Non-local in-brain recurrence-free survival. **a** In all patients, median time to non-local in-brain recurrence was 9 months. **b** No difference was observed in non-local in-brain recurrence for patients with systemic metastatic disease compared to those with in-brain metastasis only or primary plus in brain metastasis only. **c** Trend towards worse non-local in-brain recurrence with multiple versus single brain metastases (p=0.3). **d** A non-significant relationship was observed between in-brain recurrence with the increasing number of metastases

and the median tumor volume was smaller (<13 cm^3). The intermediate dose range did fare worse than the high-dose range, though this was not statistically significant. The intermediate dose range tumors were larger, with an average volume of 19.8 vs 14.1 cm^3 (p=0.1). A recent study found that adjusting the dose-fractionation based on achieving a BED_{10} 80 Gy provided similar control outcomes to our cohort, with a 2 % incidence of symptomatic radionecrosis requiring hypobaric oxygen [15]. We did not treat to as high a dose in our cohort; however, our treatment was well tolerated with low rates of radiologically evident radionecrosis, and a single case of symptomatic necrosis requiring a short course of bevacuzimab. Our safety profile was similar to that seen at other institutions that employ more prolonged treatment courses, such as 4 Gy × ten fractions [11]. In addition, approximately two thirds of our patients received consecutive daily treatments while one third received treatment every other day. This was based on physician discretion, but our analysis did not identify the differences between these two cohorts in local control or toxicity. We did observe a correlation between size of the treated tumor and incidence of radionecrosis, with one third of patients with treatment volumes >22 cm^3 developing radionecrosis suggesting caution should be exercised in treating very large lesions with SBRT brain. This re-emphasizes the difficulty of treated larger brain metastases both safely and effectively. A recent publication of SBRT brain for larger post-resection cavities demonstrated better local control with a higher dose regimen (9 Gy × 3), but also with a 5 % rate of grades 3–4 neurologic toxicity [16] suggesting perhaps a higher dose is needed for better local control though it may come with higher toxicity. Our results, together with the discussed studies above, indicate a discussion with the patient regarding the pros and cons of dose escalation with regards to local control and toxicity may be warranted for those patients with larger brain metastases.

Forty-two percent of patients failed outside the treatment field within the brain and 13 of these 19 patients went on to receive additional radiation. We were able to delay re-irradiation with either WBRT or SRS by approximately 2.5 years, potentially prolonging an improved quality of life. Two thirds of the patients with local recurrence also failed elsewhere in the brain. Several studies have attempted to correlate in brain control and survival with systemic disease control, performance status, age, etc. and appear to vary by primary tumor type. The majority of our patients had NSCLC, where survival has correlated with number of brain metastases, performance status, and control of the primary tumor [13]. Given that this was a retrospective study, we were unable to control for these factors, but the majority of patients had a multiple brain metastasis and a high burden of

disease, while maintaining a favorable KPS. The local and in-brain control and overall survival rates are comparable to those reported for a similarly burdened group undergoing WBRT followed by salvage SRS [13].

Conclusion

Our single institution retrospective study demonstrated hypofractionated stereotactic radiotherapy for brain metastases is a safe treatment option for patients who wish to avoid WBRT, particularly for patients with tumors <22 cm^3, controlled systemic disease, and solitary resected brain metastases. Local control compared favorably with historical rates of control with whole brain radiation, but we were unable to achieve levels consistent with SRS. Treatment of larger brain metastases or resection cavities remains challenging. Combined, our data supports the safety of our dose and fractionation scheme, and provides rationale for discussing SBRT brain with patients an alternative to WBRT based on patient preferences regarding potential quality of life side effects of each treatment, risk of recurrence, and probability of re-irradiation in the future necessitating reliable follow-up.

Acknowledgments Data included in this study were presented at the ASTRO Annual Meeting in 2012 and the Radiosurgery Society Annual Meeting in 2013. The authors would like to thank the hard working radiation therapists who treated these patients: Linette Chapman, Dorothy Hargrove, Erica Oh, and Joanne Reasoner; as well as the nursing team who cares for our patients: Nicole Moxon, Shelley Plott, Wanda Roberts, LaDonna Robey, and Amanda Wissel. A special thank you to Dr. Charles R. Thomas Jr, who gave valuable advice regarding this manuscript.

Conflict of interest Kristina H. Young, Faisal Siddiqui, James A. Tanyi, Carol Marquez, and Charlotte Dai Kubicky declare that they have no conflict of interest. Martin Fuss is a consultant and speaker for Varian, BrainLab, and Philips.

Ethical standards This article does not contain any studies with human or animal subjects performed by any of the authors.

Statement of informed consent Statement of informed consent was not applicable since the manuscript does not contain any patient data.

References

1. Barnholtz-Sloan JS, Sloan AE, Davis FG et al (2004) Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol Off J Am Soc Clin Oncol 22(14):2865–2872. doi:10.1200/JCO.2004.12.149
2. Patchell RA, Tibbs PA, Walsh JW et al (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322(8):494–500. doi:10.1056/NEJM199002223220802
3. Patchell RA, Tibbs PA, Regine WF et al (1998) Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA J Am Med Assoc 280(17):1485–1489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9809728. Accessed 12 Mar 2013.
4. Roman DD, Sperduto PW (1995) Neuropsychological effects of cranial radiation: current knowledge and future directions. Int J Radiat Oncol Biol Phys 31(4):983–998. doi:10.1016/0360-3016(94)00550-8
5. Nieder C, Leicht A, Motaref B et al (1999) Late radiation toxicity after whole brain radiotherapy: the influence of antiepileptic drugs. Am J Clin Oncol 22(6):573–579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10597741. Accessed 1 May 2013.
6. Crossen JR, Garwood D, Glatstein E et al (1994) Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. J Clin Oncol Off J Am Soc Clin Oncol 12(3):627–42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8120563. Accessed 1 May 2013.
7. Meyers CA, Brown PD (2006) Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. J Clin Oncol Off J Am Soc Clin Oncol 24(8):1305–1309. doi:10.1200/JCO.2005.04.6086
8. Vigliani MC, Duyckaerts C, Hauw JJ et al (1999) Dementia following treatment of brain tumors with radiotherapy administered alone or in combination with nitrosourea-based chemotherapy: a clinical and pathological study. J Neuro-Oncol 41(2):137–49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10222434. Accessed 1 May, 2013.
9. Liu R, Page M, Solheim K et al (2009) Quality of life in adults with brain tumors: current knowledge and future directions. Neuro-Oncol 11(3):330–339. doi:10.1215/15228517-2008-093
10. Muacevic A, Wowra B, Siefert A et al (2008) Microsurgery plus whole brain irradiation versus gamma knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. J Neuro-Oncol 87(3):299–307. doi:10.1007/s11060-007-9510-4
11. Fokas E, Henzel M, Surber G et al (2012) Stereotactic radiosurgery and fractionated stereotactic radiotherapy: comparison of efficacy and toxicity in 260 patients with brain metastases. J Neuro-Oncol 109(1):91–98. doi:10.1007/s11060-012-0868-6
12. Prabhu RS, Dhabaan A, Hall WA et al (2013) Clinical outcomes for a novel 6 degrees of freedom image guided localization method for frameless radiosurgery for intracranial brain metastases. J Neuro-Oncol. doi:10.1007/s11060-013-1093-7
13. Caballero JA, Sneed PK, Lamborn KR et al (2012) Prognostic factors for survival in patients treated with stereotactic radiosurgery for recurrent brain metastases after prior whole brain radiotherapy. Int J Radiat Oncol Biol phys 83(1):303–309. doi:10.1016/j.ijrobp.2011.06.1987
14. Wiggenraad R, Verbeek-de Kanter A, Kal HB et al (2011) Dose-effect relation in stereotactic radiotherapy for brain metastases. A systematic review. Radiother Oncol J Eur Soc Ther Radiol Oncol 98(3):292–297. doi:10.1016/j.radonc.2011.01.011
15. Matsuyama T, Kogo K, Oya N (2013) Clinical outcomes of biological effective dose-based fractionated stereotactic radiation therapy for metastatic brain tumors from non-small cell lung cancer. Int J Radiat Oncol Biol Phys 85(4):984–990. doi:10.1016/j.ijrobp.2012.09.008
16. Minniti G, Esposito V, Clarke E et al (2013) Multidose Stereotactic Radiosurgery (9 Gy × 3) of the postoperative resection cavity for treatment of large brain metastases. Int J Radiat Oncol Biol Phys 86(4):623–629. doi:10.1016/j.ijrobp.2013.03.037