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Clinical Outcomes of Patients with Limited Brain Metastases Treated with Hypofractionated (5 × 6 Gy) Conformal Radiotherapy

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Abstract

Background and Purpose—Hypofractionated conformal radiotherapy (hfCRT) is used for larger brain metastases or metastases near critical structures. We investigated hfCRT outcomes for newly diagnosed brain metastases.

Materials and Methods—We identified 195 patients with 1–3 brain metastases who underwent 5 × 6Gy hfCRT for 231 lesions from 2007–2013. Associations among clinical factors, local control (LC), distant brain control (DC) and overall survival (OS) were tested using univariate and multivariate (MVA) Cox regression analysis and Kaplan-Meier method.

Results—Median follow-up was 12.8 months. One hundred forty-three (62%) lesions were treated with hfCRT post-operatively, and 88 (38%) with definitive hfCRT. LC for all lesions was 83% at 1 year. For lesions treated with post-operative hfCRT, tumor size (HR=4.7, p=0.04) and subtotal resection (HR=2.7, p=0.02) were predictive of local failure on MVA. For lesions ≥ 2.8cm in size, LC was 61% at 12 months for lesions status-post subtotal resection, compared to 84% status-post gross total resection (p=0.004). Extracranial disease presence was associated with worse DC (HR=1.8, p=0.008) and OS (HR=3.1, p<0.001).

Conclusions—We showed 5 × 6Gy hfCRT provides acceptable LC at 1 year for limited brain metastases. For large lesions not grossly resected, more aggressive strategies can be considered to improve LC.

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Conflict of Interest Statement

YY discloses Varian Medical Systems and BrainLab speakers bureaus. The remaining authors report no conflicts of interest.

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Keywords

hypofractionated conformal radiation; brain metastases; local control

Introduction

The incidence of brain metastases in cancer patients is approximately 25% [1], and the incidence is increasing with improvements in systemic therapy resulting in prolonged patient survival as well as earlier diagnosis [2]. The mainstay of treatment of brain metastases has largely included surgery and radiation due to poor penetrance of many chemotherapeutic agents across the blood brain barrier [3]. Patients who undergo surgery for brain metastases often receive post-operative whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) for improved local disease control [4, 5]. Alternatively, patients who do not require surgery or are not surgical candidates may be treated with radiation alone. Lesions amenable to single fraction SRS typically measure less than 3 cm in maximum dimension, and SRS combined with WBRT has been shown to improve survival and local control compared to WBRT alone for patients with 1 to 4 brain metastases [6]. However, SRS alone without WBRT has surfaced as a preferred modality to WBRT in patients with limited brain metastases due to high rates of locoregional control and similar survival rates with minimal toxicity and shorter interruption of systemic therapy [7–10].

Tumors treated with lower doses (<18Gy) have been shown to have inferior local control rates after single-fraction SRS due to inferior doses required to meet normal structure constraints [11, 12]. For patients with limited number of brain metastases measuring greater than 3 cm in size or located within eloquent cortex or brainstem, hypofractionated conformal radiation therapy (hfCRT) has emerged as an alternative to single-fraction SRS in both the post-operative and definitive settings [13–15]. One retrospective study reported superior local control for brain metastases >2cm treated with $3 \times 9\text{Gy}$ compared to single fraction SRS [16]. However, the optimal hypofractionated regimen is still unclear. In this study, we investigated the efficacy and predictors of outcomes in patients who received hfCRT using $5 \times 6\text{Gy}$ for newly diagnosed brain metastases at a single center.

Materials and Methods

Study population

Patients with the presence of 1–3 newly diagnosed brain metastases treated with hypofractionated conformal radiotherapy (hfCRT) to a dose of 30Gy in 5 fractions at our institution from 2007 to 2013 were eligible. At our institution, patients with lesions >3cm in size or near critical structures generally receive hfCRT either definitively or postoperatively, while lesions <3cm in size generally receive single fraction stereotactic radiosurgery (SRS). Patients with prior cranial radiotherapy were excluded. Institutional Review Board approval was obtained. Medical records were reviewed and clinical information including patient age, primary tumor histology, Karnofsky performance status (KPS), extracranial disease (ECD), present versus absent within 60 days of hfCRT), concurrent systemic therapy (systemic treatment within 30 days of hfCRT), number of brain metastases (1 versus 2–3), brain

metastasis size, tumor location (supratentorial versus infratentorial) and clinical outcomes including pathological diagnosis of radiation necrosis following radiotherapy were collected. Brain metastasis size was defined as the largest dimension of the lesion prior to surgical resection for patients who received hfCRT following craniotomy, or at the time of definitive hfCRT for patients who did not undergo surgical resection. We chose presurgical size for analysis as it was shown to be predictive of local control in a prospective trial at our institution [4].

Radiotherapy technique

A T1-weighted magnetic resonance imaging (MRI) scan with gadolinium contrast (dosing 0.1 mg of gadolinium per kg of body weight) at 3 mm slice thickness was obtained prior to radiotherapy and reviewed by a board-certified neuroradiologist at the time of simulation. Patients were immobilized with a three-point face mask and a computed tomography (CT) scan was obtained with intravenous contrast at the time of simulation. The CT images were transferred to in-house treatment planning system (Top Module) and fused to the post-gadolinium T1-weighted MRI for target delineation. The gross target volume (GTV), defined as the contrast-enhancing lesion, was delineated on T1-weighted MRI and on the planning CT (contrast enhancement on MRI and CT). Surrounding areas of edema were not considered part of the target volume. For patients who had undergone resection, the postoperative cavity was defined as clinical target volume (CTV). The planning target volume (PTV) was defined as a 3-dimensional 2mm to 5mm margin around the GTV or CTV. The prescribed dose was 30Gy given over 5 daily fractions with either 3D-conformal radiation or intensity modulated radiation therapy (IMRT) (Figure 1). All patients received the same dose. The treatment plan typically consisted of 5–7 coplanar and non-coplanar IMRT fields. The plans were normalized so that 100% of the prescription dose is delivered to 95% of the PTV and with a PTV Dmax <110%. The plans were designed to meet our departmental dose criteria for normal tissues with maximum point dose constraints of 31.2Gy, 30Gy, and 23Gy to the brainstem, spinal cord, and optic structures, respectively. Dose-volume histograms were used to document coverage for target volume and normal structures. Treatment was delivered either on a Trilogy, C-2100EX or C-600EX LINAC (Varian Medical Systems, Palo Alto, CA).

Statistical analysis

Patients were followed up with MRI following radiation according to standard clinical practice: 6 to 8 weeks after radiotherapy then 3 to 4 months thereafter. Clinical outcomes examined included local control (LC), distant brain control (intracranial control outside of treatment target, DC) and overall survival (OS). Outcomes were measured from the initiation of radiation until last follow up or death. LC was defined as absence of recurrence within the treatment target, determined both clinically by the treating physicians' consensus and radiographically, including the use of advanced imaging modalities such as brain positron emission tomography and MRI perfusion imaging. DC was defined as absence of new brain lesions outside of the treatment target. Association between clinical factors and outcomes were tested using univariate and multivariate Cox regression analysis. The Kaplan-Meier

method was used to assess actuarial LC, DC and OS. Analyses were performed with IBM SPSS Statistics (IBM, Armonk, New York).

Results

A total of 195 consecutive patients with 231 newly diagnosed limited brain metastases treated with hfCRT between 2007 and 2013 were identified for the study. Patient and lesion characteristics are summarized in Table 1. The median follow-up time was 12.8 months (range 0.6–71.4 months). The median age of patients was 61.3 years (range 22–87.5 years), and the majority of patients (94%) had KPS 70. The most common primary tumor histology was non-small cell lung cancer in 70 patients (36%) and 80 lesions (35%), followed by breast cancer and melanoma. The median lesion size for all 231 brain metastases was 2.8cm (range, 0.4 – 6.3cm). The majority of brain metastases were treated with surgery followed by hfCRT (n=143, 62%), and 88 (38%) were treated with definitive hfCRT. Of 143 resected brain lesions, a gross total resection was achieved in 120 lesions (84%), and a subtotal resection was obtained in 23 lesions (16%). Lesion characteristics grouped by surgical status are shown in Table 2. Lesions treated with postoperative hfCRT had a median pre-operative size of 3.2cm (range 0.7–6.3cm) and were significantly larger than definitive hfCRT lesions which had a median size of 2.0cm (range 0.4 – 4.6cm, $p=0.001$).

Of the 231 brain metastases, local failure occurred in 37 lesions (16%). Local control was 83% at 12 months and 76% at 24 months. Brain metastasis size was independently associated with LC. Larger lesions at diagnosis had a significantly higher risk for local failure (HR=2.1, 95% CI: 1.0–4.2, $p=0.045$) on univariate analysis. The 12-month LC rate for lesions ≥ 2.8 cm (median lesion dimension) was 79% versus 87% for lesions <2.8 cm ($p=0.04$, Figure 2A). Histology (lung versus other), surgical status (definitive versus postoperative hfCRT), tumor location, ECD status, and concurrent systemic therapy were not associated with LC on univariate analysis.

Subgroup analysis was carried out based on resection status. In the subgroup of 88 lesions treated with definitive hfCRT, LC was 81% at 12 months. Tumor histology, tumor size, tumor location, ECD status and concurrent systemic therapy were not significantly associated with LC on univariate analysis. In the subgroup of 143 lesions treated with post-operative hfCRT, LC was 84% at 12 months. Larger lesions based on pre-operative size had a significantly higher risk of local failure on univariate analysis (HR=5.4, 95% CI: 1.3–22.8, $p=0.02$) in this subgroup. Subtotal resection (STR), determined by postoperative MRI and surgical reports, compared to gross total resection (GTR) prior to hfCRT also had a higher risk of LF on univariate analysis (HR=3.2, 95% CI: 1.4–7.4, $p=0.007$). On multivariate analysis, both tumor size ≥ 2.8 cm (HR=4.7, 95% CI: 1.1–20.4, $p=0.04$) and subtotal resection (HR=2.7, 95% CI: 1.2–6.3, $p=0.02$) remained predictive of increased risk for local recurrence in this subgroup. The 12-month LC rate for lesions ≥ 2.8 cm was 80% versus 97% for lesions <2.8 cm ($p=0.01$, Figure 2B), and the 12-month LC was 59% for lesions with subtotal resection versus 88% for lesions with gross total resection ($p=0.004$, Figure 2C). The majority of brain metastases in the postoperative hfCRT subgroup were ≥ 2.8 cm in size and status-post gross total resection, and the LC rate in these lesions was 84% at 12 months

(16 local recurrences among 81 treated lesions at time of assessment, Figure 2D). For lesions that were ≥ 2.8 cm and had a subtotal resection, the LC was 61% at 12 months with 7 local recurrences observed in 20 treated lesions. The LC rate was the highest (97% at 12 months) for lesions that were <2.8 cm and had a gross total resection with 1 local failure observed in 39 treated lesions. While a 50% 12-month LC rate was found for lesions that were <2.8 cm and were subtotally resected, this group only had 3 lesions with 1 local recurrence at time of assessment.

A total of 17 patients underwent surgery following hfCRT, and 11 surgical specimens confirmed radiation necrosis pathologically. Of 11 specimens showing radiation necrosis, 3 showed radiation necrosis and absence of tumor, while 8 showed a combination of radiation necrosis and tumor cells. Six surgical specimens showed tumor alone without radiation necrosis. The cumulative incidence of development of pathologically-proven radiation necrosis at following hfCRT was 4.2% at 12 months and 5.4% at 24 months. Histology (lung vs other), surgical status (definitive versus postoperative hfCRT), tumor size (as continuous variable and categorical ≥ 2.8 cm vs <2.8 cm), tumor location (supratentorial vs infratentorial), and concurrent systemic therapy were not significantly associated with development of pathologically-proven radiation necrosis following hfCRT on univariate analysis.

The median overall survival was 13.9 months (range 0.6 – 71.4 months) with 53% of patient surviving at 12 months. On univariate analysis, age >60 years, KPS <80 , and the presence of extracranial disease (ECD) were associated with worse OS, while tumor histology, number of brain lesions, and concurrent systemic therapy were not. On multivariate analysis, presence of ECD (HR=3.1, 95% CI: 2.0–4.6, $p<0.001$), age >60 (median, HR=1.7, 95% CI: 1.2–2.3, $p=0.006$) and KPS <80 (HR=2.2, 95% CI: 1.4–3.5, $p<0.001$) were associated with worse OS. Median OS for patients without ECD was 38 months versus 8 months in patients with ECD ($p<0.001$, Figure 2E).

Of the 195 patients, 89 (46%) demonstrated a distant intracranial failure outside of hfCRT targets at the time of assessment. The median DC was 17 months, and DC was 55% at 12 months and 44% at 24 months. Of the clinical factors examine using UVA (age, KPS, histology, presence of ECD, number of brain lesions, brain metastasis size, brain metastasis location, and concurrent systemic therapy), the only factor associated with worse DC was presence of ECD (HR=1.8, 95% CI: 1.2–2.9, $p=0.009$). The 12-month DC in patients without ECD was 65% versus 48% in patients with ECD ($p=0.008$, Figure 2F).

Discussion

In this study, we investigated the efficacy and predictors of outcomes of 195 patients with 231 newly diagnosed limited brain metastases treated with hypofractionated conformal radiation therapy (hfCRT) to dose 30Gy over 5 fractions at a single center. The local control rate at 12 months in our patient cohort was 83% similar to other reports in the literature for hfCRT. Ernst-Stecken *et al.* reported 76% local control rate at 12 months in a phase II trial of hfCRT for 72 unresectable brain metastases not amenable to radiosurgery treated to doses of 7Gy $\times$ 5 fractions in the setting of no prior whole brain radiation and 6Gy $\times$ 5 fractions in the setting of prior whole brain radiation [15]. Aoyama *et al.* reported an actuarial 12 month

local control of 81% in 87 patients with 159 metastases treated with hfCRT to a median dose of 35 Gy in 4 fractions [14], and Aoki *et al.* reported an actuarial 12-month local control of 72% in 44 patients with 65 metastases treated to median dose of 24 Gy in 3–5 fractions [7]. Most recently, Minniti *et al.* reported a 12-month cumulative local control rate of 90% in 138 patients treated with hfCRT to dose 27Gy in 3 fractions for brain metastases >2.0cm [16]. And for brain lesions ≤ 3.0cm, Minniti *et al.* reported 12-month local control of 73% with hfCRT [16]. For brain metastases ≤ 3.0cm that were resected, Minniti *et al.* demonstrated a local control of 93% at 12 months by delivering 27Gy in 3 fractions to the postoperative cavity in an earlier report [17]. Given the differences in inclusion criteria, it is difficult to compare our study directly with the cited series. Nevertheless, it is reasonable to conclude that the 5 × 6Gy used in our study resulted in local brain metastasis control that is comparable to other institutional experiences with hfCRT in both the definitive setting as well as the postoperative setting.

Compared to outcomes reported in the literature for single fraction stereotactic radiosurgery for similar tumor sizes to our series, our results from hfCRT also appear comparable. For lesions ≤ 2.8cm, we reported local control of 79% at 1 year which is comparable to a local control at 1 year of 77% reported by Minniti *et al.* for lesions >2cm in size treated with single fraction stereotactic radiosurgery [16]. In our series, we reported local control of 80% at 1 year for lesions measuring ≤ 2.8cm treated with hfCRT in the post-operative setting, which seems perhaps superior when compared to a phase 2 trial by Brennan *et al.* which reported local control of 61% at 1 year for lesions >3cm treated with post-operative single-fraction stereotactic radiosurgery [4]. However, direct comparisons are limited in the retrospective setting. Our current study did include a large proportion of tumors <3cm in diameter and for these tumors a hypofractionated approach was chosen versus single fraction SRS due to proximity to critical tissues such as optic structures or brainstem.

In our study, larger lesion size was significantly associated with local failure, and the 12-month local control rate for lesions ≤ 2.8cm was 79% versus 87% for lesions <2.8cm ($p=0.04$). This finding is also consistent with prior studies for hfCRT. Aoyama *et al.* likewise reported tumors >3cc were associated with poorer local control at 12 months (59% for lesions >3cc and 96% for lesions ≤ 3cc) [14]. Kwon *et al.* reported outcomes of 52 brain metastases treated with either a combination of WBRT and hfCRT or hfCRT alone with a median dose of 25Gy in 5 fractions with 68% local control rate at 12 months, and similarly reported tumor dimension was associated with local tumor control [18]. Eaton *et al.* also reported local control was negatively associated with tumor volume in a cohort of 42 patients treated with hfCRT in 3–5 fractions for intact or resected brain metastases with a 12-month local control rate of 61% [19]. Interestingly, when analyzed separately based on surgical status, we did not find size to be a predictor of local control for lesions that were treated definitively without upfront surgical resection. This likely is due to that the great majority of lesions treated definitively were smaller than 3cm (88%), indicating hfCRT is an effective approach in managing smaller intact lesions located in eloquent cortex in the brain.

In the subgroup of lesions treated with post-operative hfCRT, larger lesions based on pre-operative size (≤ 2.8cm) had a significantly higher risk of local failure. In addition, we found that lesions that were subtotally resected also resulted in suboptimal local control. When

analyzed by both tumor size and resection status, we found that for ≥ 2.8 cm lesions that were subtotally resected the local failure rate was 39% at 12 months, significantly higher than lesions that were ≥ 2.8 cm and completely resected (16%) and lesions that were <2.8 cm and completely resected (3%). This indicated that adjuvant hfCRT using 30Gy in 5 fractions may not be adequate for larger lesions for which gross total resection is not achieved. Likewise, larger margins may be warranted for these patients. Advancing understanding of tumor biology in these lesions through molecular platforms will help generate clinical strategies to improve disease control. While lesions that were <2.8 cm and subtotally resected demonstrated a 50% local failure rate at 1 year, we were not able to draw meaningful conclusion with this result as only 3 lesions were included in this category.

We found that the predictors for worse OS included age >60 , KPS <80 , and presence of ECD. Presence ECD was also associated with increased distant brain failure. The median OS in our patient cohort was 13.9 months and comparable to the survival of the other cohorts treated with hfCRT reported in the literature [13–16, 18, 20–22]. Aoki *et al.* investigated clinical outcomes of 44 patients with 1 to 3 brain metastases treated with hypofractionated conventional conformation radiotherapy treated with a median dose of 24Gy in 3–5 fractions [13]. Similar to our findings, the authors reported active extracranial disease and poor performance status were also associated with poorer prognosis [13]. Patient performance status and active extracranial disease have been shown to be associated with OS in patients treated with hfCRT in several other reports in the literature as well [14, 16, 20]. As ECD continues to improve over time with the advent of better systemic therapy options, local intracranial control will become even more important for patient morbidity and mortality.

We reported distant intracranial failure at 1 year of 45% following hfCRT, which is comparable to the literature and is to be noted in the absence of whole brain radiotherapy. In a randomized trial of single fraction SRS alone versus whole brain radiation plus single fraction SRS, Aoyama *et al.* reported distant intracranial failure of 42% following whole brain radiation plus SRS compared to 64% in the SRS alone group [7]. Kocher *et al.* reported results of the EORTC phase III trial demonstrating that overall intracranial progression (at initial or distant sites) was reduced in patients treated with adjuvant whole brain radiotherapy following surgery or SRS for brain metastases [8]. Recently, Kepka *et al.* published results of a randomized trial examining neurological and cognitive function outcomes for patients with single brain metastases treated with surgery followed by single (1×15 – 18 Gy) or hypofractionated stereotactic (5×5 Gy) radiosurgery versus whole brain radiotherapy [23]. The study was underpowered but did not demonstrate non-inferiority of focal radiation compared to whole brain radiotherapy. In regards to intracranial failure, there were no differences in the two arms.

Finally, it is worth noting that in our series a majority of lesions were treated with IMRT. However, we are now changing at our institution to stereotactic radiosurgery planning technique with more rapid dose fall off outside of the target, accepting a hotspot up to 140%. This may improve the therapeutic ratio for these patients, particularly with large tumors and is a topic for further investigation in future studies. In addition, future directions include

developing a prospective study comparing $5 \times 6\text{Gy}$ versus $3 \times 9\text{Gy}$ to determine the most ideal hypofractionation scheme.

In conclusion, we provide the largest single institution series reporting outcomes hfCRT for brain metastases and show that hfCRT with $5 \times 6\text{Gy}$ regimen provides comparable local control at 1 year compared to other regimens reported in literature. Most importantly, we also identified that for brain metastases that were $\geq 2.8\text{cm}$ and underwent a subtotal resection, the local control was significantly lower compared to completely resected lesions or smaller lesions. More aggressive clinical strategies, such as dose escalation or combination therapy with radiosensitizers, can be considered in order to maximize intracranial control, especially in younger patients with good KPS and without active extracranial disease.

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References

1. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. *J Neurooncol.* 2005; 75:5–14. [PubMed: 16215811]
2. Soffietti R, Ruda R, Trevisan E. Brain metastases: current management and new developments. *Curr Opin Oncol.* 2008; 20:676–84. [PubMed: 18841050]
3. Mehta MP, Paleologos NA, Mikkelsen T, Robinson PD, Ammirati M, Andrews DW, et al. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol.* 2010; 96:71–83. [PubMed: 19960229]
4. Brennan C, Yang TJ, Hilden P, Zhang Z, Chan K, Yamada Y, et al. A phase 2 trial of stereotactic radiosurgery boost after surgical resection for brain metastases. *Int J Radiat Oncol Biol Phys.* 2014; 88:130–6. [PubMed: 24331659]
5. Kalkanis SN, Kondziolka D, Gaspar LE, Burri SH, Asher AL, Cobbs CS, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol.* 2010; 96:33–43. [PubMed: 19960230]
6. Linskey ME, Andrews DW, Asher AL, Burri SH, Kondziolka D, Robinson PD, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol.* 2010; 96:45–68. [PubMed: 19960227]
7. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA.* 2006; 295:2483–91. [PubMed: 16757720]
8. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, 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; 29:134–41. [PubMed: 21041710]
9. Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD. Radiosurgery with or without whole-brain radiotherapy for brain metastases: the patients' perspective regarding complications. *Am J Clin Oncol.* 2005; 28:173–9. [PubMed: 15803013]
10. Sneed PK, Suh JH, Goetsch SJ, Sanghavi SN, Chappell R, Buatti JM, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys.* 2002; 53:519–26. [PubMed: 12062592]

11. Mori Y, Kondziolka D, Flickinger JC, Kirkwood JM, Agarwala S, Lunsford LD. Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. *Int J Radiat Oncol Biol Phys.* 1998; 42:581–9. [PubMed: 9806518]
12. Shiau CY, Sneed PK, Shu HK, Lamborn KR, McDermott MW, Chang S, et al. Radiosurgery for brain metastases: relationship of dose and pattern of enhancement to local control. *Int J Radiat Oncol Biol Phys.* 1997; 37:375–83. [PubMed: 9069310]
13. Aoki M, Abe Y, Hatayama Y, Kondo H, Basaki K. Clinical outcome of hypofractionated conventional conformation radiotherapy for patients with single and no more than three metastatic brain tumors, with noninvasive fixation of the skull without whole brain irradiation. *Int J Radiat Oncol Biol Phys.* 2006; 64:414–8. [PubMed: 16271441]
14. Aoyama H, Shirato H, Onimaru R, Kagei K, Ikeda J, Ishii N, 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. [PubMed: 12788187]
15. Ernst-Stecken A, Ganslandt O, Lambrecht U, Sauer R, Grabenbauer G. Phase II trial of hypofractionated stereotactic radiotherapy for brain metastases: results and toxicity. *Radiother Oncol.* 2006; 81:18–24. [PubMed: 16978720]
16. Minniti G, Scaringi C, Paolini S, Lanzetta G, Romano A, Ciccone F, et al. 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. *Int J Radiat Oncol Biol Phys.* 2016; 95:1142–8. [PubMed: 27209508]
17. Minniti G, Esposito V, Clarke E, Scaringi C, Lanzetta G, Salvati M, et al. Multidose stereotactic radiosurgery ($9 \text{ Gy} \times 3$) of the postoperative resection cavity for treatment of large brain metastases. *Int J Radiat Oncol Biol Phys.* 2013; 86:623–9. [PubMed: 23683828]
18. Kwon AK, Dibiasi SJ, Wang B, Hughes SL, Milcarek B, Zhu Y. Hypofractionated stereotactic radiotherapy for the treatment of brain metastases. *Cancer.* 2009; 115:890–8. [PubMed: 19132728]
19. Eaton BR, Gebhardt B, Prabhu R, Shu HK, Curran WJ Jr, Crocker I. Hypofractionated radiosurgery for intact or resected brain metastases: defining the optimal dose and fractionation. *Radiat Oncol.* 2013; 8:135. [PubMed: 23759065]
20. Manning MA, Cardinale RM, Benedict SH, Kavanagh BD, Zwicker RD, Amir C, et al. Hypofractionated stereotactic radiotherapy as an alternative to radiosurgery for the treatment of patients with brain metastases. *Int J Radiat Oncol Biol Phys.* 2000; 47:603–8. [PubMed: 10837942]
21. Narayana A, Chang J, Yenice K, Chan K, Lymberis S, Brennan C, et al. Hypofractionated stereotactic radiotherapy using intensity-modulated radiotherapy in patients with one or two brain metastases. *Stereotact Funct Neurosurg.* 2007; 85:82–7. [PubMed: 17167236]
22. Wang CC, Floyd SR, Chang CH, Warnke PC, Chio CC, Kasper EM, et al. Cyberknife hypofractionated stereotactic radiosurgery (HSRS) of resection cavity after excision of large cerebral metastasis: efficacy and safety of an $800 \text{ cGy} \times 3$ daily fractions regimen. *J Neurooncol.* 2012; 106:601–10. [PubMed: 21879395]
23. Kepka L, Tyc-Szczepaniak D, Bujko K, Olszyna-Serementa M, Michalski W, Sprawka A, et al. Stereotactic radiotherapy of the tumor bed compared to whole brain radiotherapy after surgery of single brain metastasis: Results from a randomized trial. *Radiother Oncol.* 2016; 121:217–24. [PubMed: 27793446]

Figure 1.

Representative intensity modulated treatment (IMRT) plan of hypofractionated conformal radiotherapy. A 58 year-old man with squamous cell carcinoma of the lung presented with 3.5×3.4 cm right parietal lobe metastasis status-post gross total resection for post-operative radiation to dose 5×6 Gy. (A) Pre-operative axial T1-weighted MRI with gadolinium contrast. (B) IMRT treatment plan with axial post-operative planning CT scan. Planning target volume (PTV) and isodose lines (%) showing rapid dose fall off are labelled.

Figure 2.

Kaplan Meier curve for local control for all brain metastases (BM) following hypofractionated conformal radiotherapy (hfCRT) by lesion size (A), for BM that were treated with surgery followed by hfCRT by lesion size (B), for BM that were treated with surgery followed by hfCRT by resection status (C), for BM that were treated with surgery followed by hfCRT by both lesion size and resection status (D). Kaplan Meier curve for overall survival (E) and distant intracranial control (F) following hypofractionated conformal radiotherapy for patients with absent or present extracranial disease.

Table 1

Patient and lesion characteristics and treatment data

Characteristic	No. of patients; n=195 (%)	No. of lesions; n=231 (%)	Median (range)
Age (years)			61.3 (22.0 – 87.5)
KPS			
90	90 (46.2)		
70–80	94 (48.2)		
< 70	11 (5.6)		
No. of lesions			
1	144 (73.8)		
2–3	51 (26.2)		
Extracranial disease			
Absent	62 (31.8)		
Present	132 (67.7)		
Primary disease site			
Non-small cell lung	70 (35.9)	80 (34.6)	
Breast	35 (17.9)	42 (18.2)	
Melanoma	24 (12.3)	30 (13.0)	
Renal	13 (6.7)	16 (6.9)	
Gastrointestinal	21 (10.8)	25 (10.8)	
Other	32 (16.4)	38 (16.5)	
Location of lesion			
Supratentorial		182 (78.8)	
Infratentorial		49 (21.2)	
Tumor maximal dimension (cm)			2.8 (0.4 – 6.3)
Operative status			
Definitive		88 (38.1)	
Post-operative		143 (61.9)	
Gross total resection		120 (83.9)	
Subtotal resection		23 (16.1)	
Concurrent or recent systemic therapy			
Yes	92 (47.2)	113 (48.9)	
No	103 (52.8)	118 (51.1)	

Abbreviations: KPS=Karnofsky performance status

Table 2

Lesion characteristics by surgical status

Characteristic	Post-operative hfCRT	Definitive hfCRT	p-value
	No. of patients n=143 (%)	No. of patients n=88 (%)	
Primary histology			0.05 ^a
Non-small cell lung	51 (35.7)	29 (33.0)	
Breast	24 (16.8)	18 (20.5)	
Melanoma	24 (16.8)	6 (6.8)	
Renal	6 (4.2)	10 (11.4)	
Gastrointestinal	18 (12.6)	7 (8.0)	
Other	20 (14.0)	18 (20.5)	
Location of lesion			0.32 ^b
Supratentorial	116 (81.1)	66 (75.0)	
Infratentorial	27 (18.9)	22 (22.0)	
Concurrent systemic therapy			0.01 ^b
Yes	60 (42.0)	53 (60.2)	
No	83 (58.0)	35 (39.8)	
Tumor maximal dimension, (cm, [median (range)])	3.2 (0.7 – 6.3)	2.0 (0.4 – 4.6)	<0.001 ^c
2cm	17 (11.9)	47 (53.4)	
>2cm - 4cm	95 (66.4)	39 (44.3)	
>4cm - 6cm	29 (20.3)	2 (2.3)	
>6cm	2 (1.4)	0 (0.0)	

Abbreviations: hfCRT = hypofractionated conformation radiation therapy; KPS = Karnofsky performance status

^a Pearson Chi square test^b Fisher's exact test^c ANOVA test