STEREOTACTIC RADIOSURGERY OF THE POSTOPERATIVE RESECTION CAVITY FOR BRAIN METASTASES

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Purpose: The purpose of this study was to analyze results of adjuvant stereotactic radiosurgery (SRS) targeted at resection cavities of brain metastases without whole-brain irradiation (WBI).

Methods and Materials: Patients who underwent SRS to the tumor bed, deferring WBI after resection of a brain metastasis, were retrospectively identified.

Results: Seventy-two patients with 76 cavities treated from 1998 to 2006 met inclusion criteria. The SRS was delivered to a median marginal dose of 18.6 Gy (range, 15–30 Gy) targeting an average tumor volume of 9.8 cm³ (range, 0.1–66.8 cm³). With a median follow-up of 8.1 months (range, 0.1–80.5 months), 65 patients had follow-up imaging assessable for control analyses. Actuarial local control rates at 6 and 12 months were 88% and 79%, respectively. On univariate analysis, increasing values of conformality indices were the only treatment variables that correlated significantly with improved local control; local control was 100% for the least conformal quartile compared with 63% for the remaining quartiles. Target volume, dose, and number of sessions were not statistically significant.

Conclusions: In this retrospective series, SRS administered to the resection cavity of brain metastases resulted in a 79% local control rate at 12 months. This value compares favorably with historic results with observation alone (54%) and postoperative WBI (80–90%). Given the improved local control seen with less conformal plans, we recommend inclusion of a 2-mm margin around the resection cavity when using this technique.

INTRODUCTION

Brain metastases are the most common form of brain tumor. Approximately 25% of patients with cancer develop intracranial metastases (1). The incidence appears to have increased during the past decade, perhaps because of increasing survival in patients with better systemic treatment (2). Improved survival of patients with intracranial metastatic disease may lead to a greater incidence of neurocognitive deficits for long-term survivors.

Treatment options for patients with brain metastases include medical management, surgical resection, whole-brain irradiation (WBI), and stereotactic radiosurgery (SRS) (3). After resection of a brain metastasis, adjuvant radiotherapy in the form of WBI decreased the rate of local recurrence from 46% to 10% and elsewhere in the brain from 37% to 14% (4). Should immediate WBI be deferred, the option is retained to manage distant intracranial relapses with such repeated local modalities as SRS and surgery or with salvage WBI.

To minimize the potential late effects of WBI (5–7), investigators explored the use of SRS alone, deferring the use of WBI for salvage treatment if needed. Both retrospective analyses (8–11) and prospective trials (12, 13) reported no apparent survival benefit in patients with brain metastases when WBI was combined with SRS as opposed to using SRS alone.

Given the lack of a survival benefit for using immediate WBI after resection or radiosurgery and the potential late effects of WBI, we generally deferred WBI in patients locally treated with limited number of brain metastases. However, recognizing the high local failure rate of surgical removal alone, we used adjuvant SRS to the resection cavity. The purpose of this retrospective review was to analyze the outcome in this patient population.

METHODS AND MATERIALS

Patient characteristics

Patient characteristics were obtained from a review of a prospectively maintained institutional review board–approved database of radiosurgical system; and Dr. Gibbs is a nonpaid member of the Clinical Advisory Board of the same company.

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patients treated using CyberKnife (Accuray, Sunnyvale, CA) radiosurgery at Stanford University Medical Center. All patients with resected metastases were advised to receive adjuvant radiotherapy or radiosurgery. In general, after consultation regarding benefits and risks of WBI, patients with Karnofsky performance status (KPS) of 70 or greater and one to four total metastases were offered SRS alone, deferring the immediate use of WBI. Patients were included for analysis in this study if a brain metastasis was surgically removed and the resection cavity subsequently was treated with radiosurgery. Patients were excluded if they received immediate WBI after surgery and postsurgical SRS without indication of cranial progression because of referring physician preference or small-cell lung carcinoma histologic state on final pathologic examination. Patients were deemed ineligible for this study if they underwent previous WBI or any other form of cranial external beam irradiation.

Radiosurgical technique

The CyberKnife Robotic Radiosurgical System (Accuray) was used to deliver radiosurgical treatments. In this frameless method, patients were immobilized supine on the CyberKnife treatment table with an Aquaplast mask (WFR/Aquaplast Corp., Wyckoff, NJ). A high-resolution thin-slice (1.25-mm) computed tomogram was obtained by using a GE Light Speed 8i or 16i Scanner (Milwaukee, WI) after administration of 125 ml of Omnipaque intravenous contrast (iohexol, 350 mg I/ml. Nycomed, Inc., Princeton, NJ). In selected patients, when resection cavity borders or other intact metastases could not be well visualized on computed tomographic (CT) imaging, a postcontrast stereotactic magnetic resonance imaging (MRI) scan also was obtained and fused to the stereotactic CT scan to improve target identification. The acquired scans were transferred by network to the CyberKnife treatment planning workstation.

The neurosurgeon, radiation oncologist, and radiation physicist performed tumor delineation, dose selection, and planning. Given the limitations of a retrospective analysis with multiple treating physicians, final target definition and dose selection were variable. Target volume was delineated as the edge of the resection cavity, including any residual tumor in cases of subtotal resection (Fig. 1). In these cases, the surrounding intact brain parenchyma received a fall-off dose outside the prescription isodose line. As we gained additional experience, in a minority of cases (n = 10), the resection cavity volume was expanded with a 2-mm margin to define the final target volume. Prescribed dose was physician dependent, but based roughly on guidelines from Radiation Therapy Oncology Group 90-05 (14), with multisession treatments primarily used for treatment volumes larger than 3-cm diameter targets.

Nonisocentric iterative inverse planning was performed to generate a radiosurgical treatment plan (15) encompassing the surgical resection cavity. Quality of treatment plans was assessed by evaluating target coverage, dose heterogeneity, and conformality. The conformity index (prescribed isodose volume [PIV]/tumor volume encompassed by the prescription isodose line [TIV]) and the modified conformity index ([PIV * TIV]/tumor volume^3) was calculated (16–18). No attempt was made to include the operative corridor, which is often seen with deep resection cavities. Digitally reconstructed radiograms were computationally synthesized to allow real-time patient tracking throughout radiosurgery. Informed consent for treatment was obtained for all patients. Patients received 4 mg of dexamethasone immediately after each treatment.

Statistical analysis

Overall survival time, local control rate, and distant control rate were calculated using the Kaplan-Meier product-limit method (19). Local control was defined as the absence of new nodular contrast enhancement adjacent to the resection cavity on magnetic resonance imaging (MRI). Distant control was defined by the lack of new brain metastases or leptomeningeal disease outside the radiosurgical treatment volume. Time of local and distant control was calculated from the date of radiosurgery to the last MRI that showed no local or regional tumor recurrence. After salvage WBI, no additional local or distant control events were recorded, with control rates censored at the time of WBI. Patients continued to be followed up for survival and toxicity analysis. As proposed by Patchell et al. (4), death was considered to be from neurologic causes if the patient died with evidence of progressive neurologic symptoms from tumor progression or treatment-related neurotoxicity, independent of the presence or absence of systemic disease control.

Using StatView, version 5.0.1 (SAS Institute Inc., Cary, NC), survival and failure curves were generated by using the Kaplan-Meier product-limit method. Univariate analysis with log-rank p values of factors associated with survival and control was performed. These factors included age, sex, KPS, recursive partitioning analysis (RPA) class, extent of surgical resection, presence of extracranial metastases, control of primary tumor site, histologic characteristics, presence of metastases other than the resection cavity, tumor volume, marginal dose, single fraction equivalent dose, number of treatment sessions, conformity index, and modified conformity index.

Fig. 1. Axial (left), coronal (middle), and sagittal (right) views of a representative CyberKnife radiosurgical treatment plan. The resection cavity (red volume) was covered by the 70% prescription isodose line (green contour). The 50% isodose line (blue contour) is shown. The fusion of computed tomographic (top left) and magnetic resonance (bottom right) images for planning is shown in each panel.
index. Significant factors were then tested in a multivariate Cox proportional hazard model (20).

RESULTS

Patients analyzed

From 1998 to 2006, a total of 72 patients with one to four brain metastases were managed with a combination of surgical removal and radiosurgical boost to the resection cavity; WBI was deferred in every case. Four patients underwent resection of two metastases, yielding 76 total cavities. Seven of 72 patients, each with a single resection cavity, died before their first scheduled follow-up MRI at 3 months, thereby yielding 65 patients with 69 cavities assessable for control analyses. All deaths were attributed to progression of extracranial disease. All 72 patients were analyzed for survival.

Table 1 lists patient and treatment characteristics for this series. For each, RPA class (21) was determined. Forty-seven patients had only resected metastases, whereas 25 patients had other lesions in addition to resected metastases. The additional metastases, which tended to be smaller (median volume of resection cavity, 7.7 cm³; range, 0.1–66.8 cm³ vs. median volume of intact metastases, 0.34 cm³; range, 0.04–13.6 cm³), were managed with SRS as the primary treatment.

Follow-up

Patients were followed up from the time of radiosurgery until death. Median follow-up was 8.1 months (range, 0.1–80.5 months). During the first year after SRS, MRI was repeated at 3-month intervals and every 4–6 months thereafter. Additional treatment for tumor recurrence was recorded.

Treatment characteristics

The SRS was prescribed to a median marginal dose of 18.0 Gy (range, 15.0–30.0 Gy) to the median 79% isodose line (range, 60–90%). Median maximum dose was 22.8 Gy (range, 17.8–40.5 Gy). The SRS was delivered in a single session in 78% of treatments, with multisession SRS performed in the remainder (two sessions, 9%; three sessions, 12%; four sessions, 1%). The choice to perform single- or multisession SRS was based primarily on the size of the resection cavity and preference of the treating physicians (median target volume for multisession SRS, 13.8 cm³ compared with 6.8 cm³ for single-session SRS). Multiple sessions of radiosurgery were separated by a minimum of 12 hours on separate days; typically, 24 hours was used between each session. Given the range of marginal prescribed doses and number of sessions, the biologically effective dose and equivalent single-session dose, derived from the linear quadratic formula, were calculated (22, 23). An α/β ratio of 10 was used: biologically effective dose (Gy₁₀) = nd [1 + d/(α/β)], where n is number of fractions of dose, d. Using this formulation, the median single-session equivalent dose was 16.0 Gy (range, 12.4–24.0 Gy).

Local and distant control

Overall, local failure was observed in 10 of 69 cavities. Of note, all failures were adjacent to the resection cavity and none occurred along the unirradiated surgical corridor leading to the resection cavity. Crude overall local tumor control rate was 86%. Kaplan-Meier local control rates at 6 and 12
months were 88% and 79%, respectively (Fig. 2). Of 10 patients who experienced local failure, median time to progression was 5.7 months (range, 3.2–14.2 months). Two patients experienced local failure at an intact metastasis treated using primary SRS.

Using univariate analysis, conformality index and modified conformality index (by quartile) were the only significant predictors of local failure. Increases in absolute values of both conformality and modified conformality indices, which correspond to less conformal plans, resulted in improved local control (Fig. 3). The rate of local control in the least conformal quartile was 100%, significantly different than the 64% rate of control observed with the 75% most conformal plans ($p < 0.05$). Although smaller tumor volume generally was associated with larger conformality indices, target volume was not associated with local control ($p = 0.29$).

Through analysis of the conformality index (prescription isodose volume/target isodose volume [PIV/TIV]), one can roughly estimate the additional volume of brain irradiated compared with the outlined target volume. If one assumes that the TIV and PIV correspond to idealized spheres (volume = \(4/3 \pi r^3\)), the additional margin provided by the PIV covering the TIV can be calculated. Patients with a 2.4-mm margin of brain tissue included in the prescribed volume (the least conformal quartile) had 100% local control compared with 1.7-mm (78% local control), 1.5-mm (52% local control), and 0.8-mm (43% local control) margins in the remaining quartiles (Table 2).

The addition of a planned 2-mm margin on the resection cavity ($n = 10$) yielded local control of 100% compared with 70% ($n = 59$) for those treated without the planned addition of a margin. However, this difference was not significant ($p = 0.15$). No other factors, including tumor volume, dose, single-session equivalent dose, number of sessions, fusion of MRI for planning, histologic characteristics, extent of tumor resection, and number of metastases, proved significant on univariate analysis.

Distant failure occurred in 32 of 65 patients (49%). Kaplan-Meier 6- and 12-month distant control rates were 70% and 47%, respectively. Median time to distant failure was 10.2 months.

Salvage therapy

For local tumor recurrence in 10 patients, SRS ($n = 2$), WBI ($n = 1$), repeated resection plus WBI ($n = 3$), repeated resection plus SRS to cavity ($n = 3$), and hospice care ($n = 1$) were performed.

The 32 patients with distant intracranial recurrence were treated with primary SRS ($n = 18$), SRS plus WBI ($n = 3$), WBI ($n = 6$), resection then WBI ($n = 1$), and hospice care ($n = 4$).

Overall, 19% of patients received WBI, with median time to delivery of 6.1 months after initial SRS (range, 3–16 months).

Survival

Overall, 34 of 72 patients (47%) had died at last follow-up. Median overall survival time was 15.1 months (range, 0.8–80.5 months). Six- and 12-month Kaplan-Meier overall survival rates were 77% and 57%, respectively. Median survival times for RPA Classes 1, 2, and 3 were not reached, 12.5, and 7.1 months, respectively (Fig. 4).

Only RPA Class 1 vs. 2 or 3 ($p = 0.03$) and the presence of extracranial metastases ($p = 0.005$; Fig. 5) were significant factors on univariate analysis. No factor proved significant on multivariate analysis; however, the presence of extracranial metastases approached significance ($p = 0.06$).

Cause of death could be determined in 28 of 34 patients. Death was attributed to neurologic causes in 7 patients (25%). Time to neurologic death was 16.9 months.

Toxicity

Seven patients required a course of steroid treatment because of symptomatic posttreatment edema. Because of persistent mass effect, 3 of these patients also underwent surgical resection of a region of necrosis. No treatment factor on logistic regression, including radiosurgery dose, target volume, or number of targets, correlated with the development of edema.
DISCUSSION

In patients with limited brain metastases, WBI is associated with an acute detriment in quality-of-life measures (24, 25), potential delayed neurocognitive deficits (6, 7), and lack of overall survival benefit (4, 10, 13). Consequently, an alternative to conventional cranial irradiation for patients who have undergone surgical resection of brain metastases remains desirable. Based on this rationale, with patients in whom surgical resection is preferred to obtain histologic confirmation or alleviate mass effect, we generally deferred immediate WBI for those with a limited number of brain metastases and a favorable KPS. In place of WBI, we used SRS as the primary treatment for unresected metastases or as adjuvant therapy to the postoperative resection cavity. To the best of our knowledge, this retrospective analysis is the first published report describing the use of postoperative radiosurgery to the surgical resection bed of brain metastases, thereby reserving WBI.

To justify the use of SRS alone to the resection cavity, local control rates should be similar to those reported for postoperative WBI. In this regard, Patchell et al. (4) reported outcomes in 95 patients with a gross totally resected isolated metastasis who were randomly assigned to either no additional therapy or postoperative WBI. The WBI decreased the rate of local failure at the original tumor site from 46% to 10%. Of note, no difference in overall survival or functionally independent survival was seen with the addition of WBI; observed median survival was approximately 11 months. Moreover, an additional study by Patchell et al. (26), in which patients with single metastases were randomly assigned to either WBI or surgery and WBI, reported a 20% rate of local failure in the postoperative WBI arm.

A similar retrospective series of postoperative radiosurgical boost to the resection cavity, reported in only abstract form (27), analyzed 61 patients treated to a median marginal dose of 16 Gy to a median target volume of 8.7 cm³. Local failure occurred in 30% of patients, with 1-year probability of 39%. Median survival time was 14.9 months.

Results of a Phase II trial investigating the use of GliSite RTS (Cytyc Surgical Products II, Mountain View, CA) intracavitary low-dose rate brachytherapy for treatment of the postsurgical cavity for single metastases, deferring immediate WBI, recently were reported (28). Sixty-two patients underwent brachytherapy balloon catheter system placement at the time of surgical resection. During a median dwell time of 114 hours, 60 Gy was delivered at a 1-cm depth. Assessed by using MRI, the crude local control rate was 83%, with a predicted 1-year rate of 79%.

Table 2. Analysis of the additional margin of the PIV on the TIV per CI quartile if volumes are converted to an idealized spherical volume (4/3 \( \pi \) radius³)

<table>
<thead>
<tr>
<th>CI quartile</th>
<th>Median CI per quartile</th>
<th>Median volumes per quartile (cm³)</th>
<th>Corresponding radius of idealized spherical volume (mm)</th>
<th>Additional margin of PIV on TIV (mm)</th>
<th>Local control per quartile (%)</th>
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</thead>
<tbody>
<tr>
<td>Most conformal</td>
<td>1.22</td>
<td>TIV = 8.50, PIV = 10.37</td>
<td>12.7, 0.8</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.37</td>
<td>TIV = 10.80, PIV = 14.80</td>
<td>13.7, 1.5</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.50</td>
<td>TIV = 7.20, PIV = 10.80</td>
<td>12.0, 1.7</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Least conformal</td>
<td>1.76</td>
<td>TIV = 5.80, PIV = 10.21</td>
<td>11.1, 2.4</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TIV = target isodose volume; PIV = prescription isodose volume; CI = conformality index.

Fig. 4. Kaplan-Meier overall survival by recursive partitioning analysis (RPA) class. Median survival for RPA Class 1 (filled circle), not reached; RPA Class 2 (filled diamond), 12.5 months; and RPA Class 3 (+), 7.1 months (\( p = 0.03 \) for 1 vs. 2 and 3).

Fig. 5. Kaplan-Meier overall survival by presence (bottom curve [filled diamond]; median survival, 10 months) or absence (top curve [filled circle]; median survival, 28 months) of known extracranial metastases.
The local control rate in our series was 86% overall, with actuarial rates of 88% and 79% at 6 and 12 months, respectively. The 14% rate of local failure we observed when using SRS to treat the resection cavity compares favorably with the 46% recurrence rate described after surgical resection alone (4) and 10% (4) to 20% (26) in patients who underwent surgical resection and subsequent WBI. Moreover, the local relapse rate we observed is similar to that reported for resected brain metastases treated with GliaSite brachytherapy (17%) (28).

When the present series was analyzed by means of univariate analysis, conformity indices were the only factors associated with local failure; a higher conformity index (i.e., a less conformal isodose volume) was associated with a decreased likelihood of local relapse. Although smaller target volumes tend to be associated with higher conformity indices, in the present series, no significant correlation could be discerned between the size of the resection cavity treated and rate of local control. Two possible explanations for this phenomenon are: (1) the difficulties encountered in accurately delineating the margins of a recent resection cavity on MRI and CT scans, or (2) in some cases, the possibility of an infiltrating radiographically invisible tumor margin. The end result is that an overly conformal margin in such cases appears to be counterproductive. In lieu of using less conformal plans, we recommend the addition of a margin that encompasses the cavity. Given the approximately 2 mm suggested through calculation of the idealized spherical margin of the PIV on the TIV based on conformity index, as well as a trend toward improved local control seen with the planned addition of a 2-mm margin, we suggest and now routinely add a 2-mm margin with this technique. Similar recommendations for the addition of a 1-mm margin for SRS treatment of intact metastases were made (29, 30). Although inclusion of a margin may improve local control rates, it is notable that failure rates of 17% were seen with brachytherapy (28), even when the median balloon surface dose was 314 Gy, a dose expected to be adequate for treating malignant disease.

The actuarial distant intracranial failure rate in this series was 53% at 1 year, similar to other series: 50% for brachytherapy alone (28), 43–63% for SRS alone (9, 13, 31), and 50% for surgery alone (estimated from survival curve) (4). A concern with the omission of immediate WBI in the treatment of patients with brain metastases is that a greater distant brain failure rate may lead to more deaths from neurologic progression of disease; Patchell et al. (4) reported that the addition of WBI decreased the rate of death from neurologic causes from 44% to 14%. However, a recent randomized trial involving patients with unresected brain metastases showed no differences in neurologic function when combined WBI and SRS treatment was compared with SRS alone (13). At 1 year, neurologic death rates were 19% and 23%, respectively; these are similar to the 25% seen in our series. Meanwhile, other series reported lower neurologic death rates, with 13% (1-year actuarial) for SRS alone (31) and 11% (crude) for brachytherapy (28). Given the limitations inherent to retrospective studies, it was not possible with the current series to formally measure the impact of tumor recurrence on quality of life.

As with any approach in which WBI is omitted, frequent surveillance imaging is required to detect distant occurrence of new metastases at a time when they are small and amenable to treatment. Studies reported that of 21% of patients with breast cancer who required repeated SRS, 12% and 50% experienced failure within 2 and 6 months, respectively (32). Therefore, in patients for whom such surveillance imaging is not possible, postoperative WBI is recommended.

Historically, the use of WBI after surgical resection of a brain metastasis was considered the standard of care. Although interpretation of available data regarding the omission of WBI is controversial (33), we routinely defer the use of immediate postsurgical WBI in patients with limited number of metastases and favorable KPS to minimize the acute toxicities and potential long-term neurocognitive dysfunction in these patients. In our series, SRS treatment of the postoperative resection cavity yields local control rates similar to previous reports investigating postoperative WBI. Less conformal treatment plans appear to produce greater rates of local control. As a surrogate, we recommend the addition of a 2-mm margin around the resection cavity when using the current technique.

REFERENCES


