Radiosurgery

Combined surgical resection and stereotactic radiosurgery for treatment of cerebral metastases

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Abstract Background: Patients with limited intracranial metastatic disease traditionally have been treated with surgery followed by WBRT. However, there is growing concern for the debilitating cognitive effects after WBRT in long-term survivors. We present a series of patients treated with surgery followed by SRS, while reserving WBRT as a salvage therapy for disease progression.

Methods: Medical records from 15 patients with 1 to 2 cerebral metastases who underwent both resection and SRS were reviewed. Outcome measures included overall survival, survival by RPA class, EOR, local tumor control, progression of intracranial disease, need for WBRT salvage therapy, and COD.

Results: Fifteen patients with cerebral metastases were treated with the combined surgery-SRS paradigm. Eight of the 15 patients (53.3%) were designated RPA class 1, with 6 of 15 (40.0%) in class 2 and 1 of 15 (6.7%) in class 3. Gross total resection was achieved in 12 cases (80.0%). Overall median survival was 20.0 months, with values of 22.0 and 13.0 months for RPA classes 1 and 2, respectively. Local recurrence occurred in 16.7% of those patients with GTR. Six patients (40.0%) went on to receive WBRT at a median of 8.0 months from initial presentation. Twelve patients (80.0%) had died at the completion of the study, and the COD was CNS progression in 33.3%.

Conclusions: Surgical resection combined with SRS is an effective treatment for selected patients with limited cerebral metastatic disease. Survival using this combined treatment was equivalent to or greater than that reported by other studies using surgery + WBRT or SRS + WBRT.

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Keywords: Cerebral metastasis; Gamma knife; Stereotactic radiosurgery; Surgery; Whole-brain radiotherapy

1. Introduction

Cerebral metastases affect 20% to 40% of all cancer patients and are the most common type of intracranial neoplasm [23,27]. Patients with widespread cerebral metastatic disease routinely are treated with WBRT [25]; however, the treatment of those patients with limited intracranial disease remains controversial. Based largely on 2 randomized controlled studies conducted in the 1990s, patients with a single brain metastasis traditionally have been treated with surgical resection followed by WBRT [34,35]. Since the time of those trials, newer treatment strategies, particularly those involving SRS, have become increasingly popular. Indeed, SRS is now considered by
many groups to represent an alternative to surgery for focal control of cerebral metastases in certain situations [7,16,17,19,28,46].

Although cranial RT has been used in the treatment of intracranial malignancy for many years, the neurologic effects of the radiation treatment itself have not been clearly delineated. The poor survival of these patients and the confounding factors such as chemotherapy and tumor recurrence make it difficult to accurately gauge the long-term neurocognitive effects of cranial RT [4,8]. Although clinically administered dosages of RT have been chosen to maximize therapeutic effect and minimize toxicity, it is estimated that as many as 20% to 50% of those patients surviving >1 year after cranial RT develop debilitating cognitive effects [12,22]. With this in mind and as more patients are surviving longer because of earlier recognition of disease and improved medical therapies, it is reasonable to explore alternative treatment strategies that defer WBRT in patients with limited metastatic disease.

This report presents a series of 15 patients with limited intracranial metastatic disease who were treated with an aggressive paradigm of surgical resection combined with SRS. In this group, WBRT was reserved for only those patients who developed progressive or multifocal disease. The results presented herein indicate that survival after this combined treatment paradigm may be equivalent to the conventional treatment regimen of surgery and WBRT, while also sparing these patients the potential toxicities and risk to quality of life effected by WBRT.

2. Clinical materials and methods

2.1. Patient data

Retrospective analysis was performed by reviewing medical records from all patients with cerebral metastases treated with both surgical resection and SRS at Barnes-Jewish Hospital/Siteman Cancer Center/Washington University Medical Center between June 1998 and September 2003. Patients were then followed in a serial fashion in both Neurosurgery and Radiation Oncology clinics until the date of their death (12 patients) or until the closure of the study in May 2007 (3 patients). Patients receiving WBRT before surgery or SRS were excluded from the study. Patients were assessed for KPS and classified into RTOG RPA class 1 (KPS ≥70, age ≤65 years, no extracranial disease), class 2 (KPS ≥70 but age ≥65 and/or extracranial disease), or class 3 (KPS ≤70). Please refer to Table 1 for patient characteristics as well as information regarding size, number, and location of metastases; EOR; and status of systemic and CNS disease. All aspects of the current study were approved by the Human Studies Committee and Institutional Review Board of the Siteman Cancer Center and Washington University in St Louis.

Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at cranial surgery (yr)</th>
<th>RPA class</th>
<th>Primary Location of metastasis</th>
<th>Location of metastasis</th>
<th>Tumor diameter (cm)</th>
<th>Time b/t primary and metastasis (mo)</th>
<th>EOR</th>
<th>SRS dose (Gy)/isodose line</th>
<th>CNS disease and treatments after surgery and SRS</th>
<th>Survival (mo)</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>66</td>
<td>2</td>
<td>Lung</td>
<td>Left F</td>
<td>3.6</td>
<td>0</td>
<td>GTR</td>
<td>20/50%</td>
<td>Local recurrence (repeated SRS)</td>
<td>10</td>
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<tr>
<td>2</td>
<td>F</td>
<td>44</td>
<td>1</td>
<td>Breast</td>
<td>Cerebellum</td>
<td>2.5</td>
<td>27</td>
<td>GTR</td>
<td>22/50%</td>
<td>None</td>
<td>53 (censor)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>47</td>
<td>1</td>
<td>Lung</td>
<td>Intraventricular/thalamic</td>
<td>4.0</td>
<td>0</td>
<td>STR</td>
<td>20/50%</td>
<td>Local recurrence (repeated SRS)</td>
<td>46 (censor)</td>
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<tr>
<td>4</td>
<td>M</td>
<td>56</td>
<td>2</td>
<td>Esoph</td>
<td>1. Cerebellum</td>
<td>1.40</td>
<td>7.5</td>
<td>1. GTR</td>
<td>18/50%</td>
<td>Drop metastases (spinal RT)</td>
<td>13</td>
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<tr>
<td>5</td>
<td>F</td>
<td>69</td>
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<td>Lung</td>
<td>Left F</td>
<td>3.5</td>
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<td>GTR</td>
<td>18/45%</td>
<td>Remote progression (WBRT)</td>
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<tr>
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<td>F</td>
<td>50</td>
<td>2</td>
<td>Breast</td>
<td>Left F</td>
<td>3.5</td>
<td>81</td>
<td>GTR</td>
<td>20/50%</td>
<td>No local recurrence</td>
<td>51</td>
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<tr>
<td>7</td>
<td>M</td>
<td>50</td>
<td>1</td>
<td>Lung</td>
<td>Left F</td>
<td>2.8</td>
<td>10</td>
<td>STR</td>
<td>16/50%</td>
<td>Remote progression (WBRT)</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>84</td>
<td>3</td>
<td>RCC</td>
<td>Cerebellum</td>
<td>2.7</td>
<td>130</td>
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<td>18/50%</td>
<td>Remote progression (surgery)</td>
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<td>9</td>
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<td>Lung</td>
<td>1. Right F-P</td>
<td>1.20</td>
<td>11</td>
<td>1. GTR</td>
<td>18/50%</td>
<td>Remote progression (WBRT)</td>
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<tr>
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<td>1</td>
<td>Lung</td>
<td>Left P</td>
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<td>0</td>
<td>GTR</td>
<td>24/50%</td>
<td>Local recurrence (surgery)</td>
<td>20</td>
</tr>
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<td>60</td>
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<td>Breast</td>
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<td>1.9</td>
<td>26</td>
<td>GTR</td>
<td>20/50%</td>
<td>Remote progression (WBRT)</td>
<td>166 (censor)</td>
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<tr>
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<td>M</td>
<td>54</td>
<td>1</td>
<td>RCC</td>
<td>Left P</td>
<td>2.0</td>
<td>0</td>
<td>GTR</td>
<td>15/45%</td>
<td>Remote progression (WBRT)</td>
<td>22</td>
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<tr>
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<td>Breast</td>
<td>Right occ</td>
<td>3.2</td>
<td>18</td>
<td>GTR</td>
<td>20/50%</td>
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<td>1</td>
<td>Ovarian</td>
<td>Cerebellum</td>
<td>3.5</td>
<td>30.5</td>
<td>STR</td>
<td>18/45%</td>
<td>Remote progression (WBRT)</td>
<td>6</td>
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<tr>
<td>15</td>
<td>F</td>
<td>41</td>
<td>2</td>
<td>RCC</td>
<td>1. Right F</td>
<td>1.10</td>
<td>0</td>
<td>1. GTR</td>
<td>20/50%</td>
<td>No local recurrence</td>
<td>35</td>
</tr>
</tbody>
</table>

B/t indicates between; F, frontal; T, temporal; P, parietal; occ, occipital; Lt, left; Rt, right. Please note that tumor diameter is that measured before initial resection.
2.2. Surgical resection

Surgical resection of cerebral metastases was performed by 5 different staff neurosurgeons using standard neurosurgical techniques for tumor resection. All patients included in the study underwent routine preoperative evaluation and were considered to be medically stable at the time of surgery and to have life expectancies >6 months. Extent of resection was classified as GTR or STR based on surgeon’s operative reports. Patients with evidence of tumor on postoperative MRI were considered to have residual tumor (STR) and not recurrent disease.

2.3. Stereotactic radiosurgery

Stereotactic radiosurgery was performed in the Leksell Gamma Knife facility (Elekta Instruments, Inc, Atlanta, GA) of the Siteman Cancer Center, Barnes-Jewish Hospital, Washington University in St Louis. Extensive description of the Gamma Knife may be found elsewhere [45]. After application of the Leksell stereotactic frame under local anesthesia, all patients underwent stereotactic CT and MRI imaging. GammaPlan software (Elekta Instruments, Inc) was used to construct a single or multiple isocenter plan to treat the conformal tumor volume. Tumor volumes (postresection) ranged from 0.18 to 16.0 cm³ and comprised the entirety of the resection cavity, including enhancing and nonenhancing areas. Radiosurgery doses were prescribed at the 45% to 50% isodose contour and ranged from 16 to 24 Gy (Table 1), depending on the tumor volume and location. All lesions treated with SRS were ≤3 cm in greatest diameter. Indications for SRS included radiosurgical boost to the postsurgical tumor bed (in cases of GTR), treatment of residual tumor (for STR), or local postoperative recurrence. In some cases, the primary target was treated in conjunction with a second, distant metastasis (Table 1). Each SRS session was conducted by a team including a neurosurgeon, radiation oncologist, and medical physicist.

2.4. Patient follow-up and data evaluation

All 15 patients were followed routinely in both neurosurgery and radiation oncology clinics. Clinical assessment included obtaining interval history with an emphasis on functional capacity (for calculation of KPS) and physical examination. Tumor recurrence and intracranial disease progression were assessed using serial MRI scans. Primary outcome measures included patient survival (calculated from the date of surgery) and progression of local or distant intracranial metastatic disease. Secondary outcome measures included systemic vs CNS COD and use of salvage WBRT. Outcome measures were expressed as the median value (in months) except in cases of categorical data. In patients who had died, the date of death was confirmed using the online Social Security Death Index (http://ssdi.genealogy.rootsweb.com). Actuarial survival was calculated using the Kaplan-Meier method with 95% Greenwood CIs (95% CI). The Mantel-Cox log-rank test was performed to assess for statistical differences in survival between patient groupings. Linear regression analysis and the paired t test were used to compare groups of data where patient survival was not being evaluated. All statistical calculations were performed using SPSS 13.0 for Windows (SPSS, Inc, Chicago, IL). Graphing was performed with SigmaPlot 2004 for Windows Version 9.0 (Systat Software, Inc, Point Richmond, CA).

3. Results

3.1. Patient characteristics

Fifteen patients with cerebral metastases were treated with craniotomy and resection followed by SRS at Barnes-Jewish Hospital/Siteman Cancer Center/Washington University Medical Center between June 1998 and September 2003. Please see Table 1 for patient characteristics and tumor and treatment parameters. Patient age ranged from 41 to 85 years, with a median of 56.8 years. Ten (66.7%) patients were female, and 5 (33.3%) were male. Karnofsky Performance Scores for all patients were >70 except for the oldest patient (85 years) whose KPS was 60. Eight of 15 patients (53.3%) were designated RPA class 1, with 6 of 15 (40.0%) in class 2 and 1 of 15 (6.7%) in class 3. In the study population of 15 patients, primary tumors were as follows: lung (6 cases, 40.0%), breast (4 cases, 26.7%), RCC (3 cases, 20.0%), ovarian (1 case, 6.7%), and esophageal (1 case, 6.7%) (Table 1). In 9 cases, cerebral metastases were found after the diagnosis of systemic disease, with intervals ranging from 7.5 to 130.0 months (median, 26 months). Initial presentation with CNS-related symptoms and the discovery of a cerebral mass prompted a “metastatic workup” and the identification of a systemic primary tumor in 6 patients. In 14 cases, the histopathology of the cerebral metastasis was in agreement with identified systemic cancer. Two patients (cases 1 and 6) harbored 2 different systemic malignancies. A definite primary was not identified in one patient, although the specimen histopathology was felt to represent lung adenocarcinoma. Eleven (73.3%) of the initially identified cerebral metastases were supratentorial in location, whereas 4 (36.4%) were infratentorial.

3.2. Combined surgery and SRS treatment paradigm

A diagram depicting the treatment patterns of the 15 patients included in the study is presented in Fig. 1. All patients underwent craniotomy and resection of their metastasis as their primary intervention. Gross total resection was achieved in 12 cases (80.0%), whereas STR was performed in 3 cases (20.0%). In these 3 cases, GTR was not possible because of tumor adherence to the thalamus, brainstem, and anterior cerebral artery, respectively. Three patients had 2 known metastases at the time of surgery, and the second lesion was not removed in 2 of these cases. In the third case, both tumors were removed through separate craniotomies on the same day (surgery performed at another institution).
All patients received SRS as outlined in Fig. 1. Indications for initial SRS included radiosurgical boost to the resection cavity in 10 cases of GTR (3 of these cases were performed simultaneously with SRS of a second, remote metastasis), treatment of residual tumor in the 3 cases of STR, or treatment of local postoperative recurrence in the 2 cases of documented GTR (Table 1). After SRS, all patients were followed closely with routine office visits and serial MRI scans to monitor for local or remote CNS progression. Treatment after the combined treatment paradigm was individualized to each patient (Fig. 1, Table 1). Of the 15 patients in the study, 6 developed remote, multifocal disease and received WBRT. Three patients exhibited local recurrence and had second craniotomies with resection of the metastasis. In all 3 cases, pathological examination demonstrated metastatic tumor consistent with recurrence. Four patients received additional SRS treatments, either for remote lesions (1 patient; this patient ultimately had a second craniotomy and a total of 3 subsequent SRS treatments for new metastases) or for local recurrence (2 patients, one of whom went on to have spinal radiation for “drop metastases”). Six patients received no further definitive treatment beyond routine examination and serial MRI scans (Table 1).

3.3. Patient survival and modifying factors

At the time of analysis, 12 of the 15 patients (80.0%) in the study had died. Using the Kaplan-Meier method, median survival for all 15 patients was calculated as 20.0 months (range, 5.0-68.0 months; Fig. 2). When patients were classified using RTOG RPA, RPA class 1 patients had a median survival of 22.0 months (8 patients; 3 censored; range, 6.0-68.0 months), whereas class 2 patients exhibited a median survival of 13.0 months (6 patients; 0 censored; range, 5-51 months) (Fig. 3). Only one class 3 patient underwent treatment with the combined surgery and SRS paradigm, and this patient survived for 15 months after surgery. Although a trend toward significance is apparent, statistical evaluation of the relationship between RPA class and survival did not show statistical difference ($P = .20$).

Median survival in the 12 patients in whom GTR was achieved was 20.0 months, with a range of 5.0 to 68.0 months. However, 2 of these patients had second, remote metastases at the time of surgery (Table 1). Therefore, for the purposes of evaluating the effect of EOR on survival, patients were subdivided into 3 groups: those with no known additional intracranial disease at the time of SRS (10 cases; 2 censored; median survival, 22.0 months); those with a single, remote metastasis (2 cases; 0 censored; survival, 13.0 and 18.0 months, respectively); and those who underwent STR (3 cases, 1 censored). Survival times for those in the STR group were 6 months (died), 16 months (died), and 46 months (censored). Statistical comparison of the relationship between EOR and survival revealed no significant difference between the 3 categories ($P = .44$).

To evaluate the relationship between patient survival and the time interval from the diagnosis of the primary tumor to the discovery of a cerebral metastasis, a linear regression analysis was performed. The results are shown in Fig. 4. The Kaplan-Meier survival curve for patients grouped by RPA class is also presented in Fig. 5. The median survival times for RPA class 1 and RPA class 2 patients are 22.0 months and 13.0 months, respectively (Fig. 5).

Fig. 1. Algorithm and treatment course for 15 patients with cerebral metastases that underwent surgical resection followed by SRS. After initial resection and SRS, treatment was individualized to each patient.

Fig. 2. Survival after treatment of cerebral metastases with surgical resection + SRS. Kaplan-Meier survival curve for 15 patients treated with the combined paradigm. Censored patients are represented by vertical hash marks.

Fig. 3. Survival by RPA class after treatment with the combined surgery-SRS paradigm. Kaplan-Meier survival curves for patients grouped by RPA class 1 (8 patients) and RPA class 2 (6 patients). One patient was graded as RPA class 3 and was not included in this representation. Censored patients are represented by vertical hash marks.
analysis was performed. The $r^2$ value for these parameters was 0.01, indicating that no correlation exists between these 2 parameters. It should be noted, however, that in 5 of the 15 patients in the study, the primary tumor and metastasis were diagnosed concurrently. When these patients were removed from the analysis, the $r^2 = 0.11$. Thus, in this small series of patients, it can be concluded that no correlation existed between patient survival and time between diagnosis of the primary tumor and discovery of the cerebral metastasis.

Ten patients (66.6%, 1 censored) experienced progressive systemic disease resulting from their primary tumor, whereas systemic disease remained stable in the remaining 5 patients (33.3%, 2 censored). Median survival for patients with progressive or stable systemic disease was 20.0 and 18.0 months, respectively. Statistical evaluation of the status of systemic disease on overall patient survival did not reveal a significant relationship ($P = .44$).

### 3.4. Control of intracranial metastatic disease

For evaluating the effect of the combined treatment with surgery and SRS, patients were initially divided into those who had undergone GTR and those who had undergone STR. Subsequently, both groups were combined to evaluate overall local control. For the GTR group (12 patients), local recurrence rate was noted in 2 patients, yielding a local recurrence rate of 16.7%; and time to recurrence was 10 and 11 months for the 2 cases. Of note, 2 patients included in the GTR group underwent GTR as documented in the surgeon’s operative report, but had enhancement noted on the postoperative MRI (preceding the SRS treatment). Neither of these 2 patients showed evidence of local progression after SRS. Of those patients with STR (3 patients), one patient showed no local progression, whereas the other 2 demonstrated local progression at 11 and 19 months, respectively. When considering all cases in the study (GTR and STR), local progression occurred in 26.7% at a median of 11 months after treatment.

Distant CNS progression, evidenced by the appearance of new brain metastases on MRI, occurred in 9 patients (60.0% of patients), with a median time to failure of 8 months. Of note, 3 of these patients had 2 metastases at the time of surgery; and further distant intracranial progression was noted at 3, 10, and 10 months, respectively. The median time to any CNS failure, local or distant, was 8 months, although it is noteworthy that 5 of 15 (33.3%) patients showed no CNS progression whatsoever.

### 3.5. Remote CNS progression and treatment with WBRT

In the treatment paradigm of combined surgical resection and postoperative SRS, WBRT is reserved as a salvage therapy for patients who exhibit multifocal disease or for palliative treatment. In this study, 6 of 15 patients (40.0%) received WBRT, including one for palliation and 5 for multifocal disease. The median time from SRS to WBRT in these 6 patients was 8 months, and median patient survival after WBRT was 9.0 months. Overall, median patient survival (from the time of surgery) for those patients who underwent WBRT was 16.0 months, whereas those who did not undergo WBRT had a median survival of 22.0 months (9 patients total, 3 patients censored). Comparison of these 2 groups revealed no statistical significance ($P = .23$).

### 3.6. Cause of death

Of the 15 patients in the study, 3 patients were still surviving at the time of data analysis and 12 had died. In the surviving patients, there has been no progression of CNS disease (survival times of 46, 53, and 68 months, respectively). Five patients in the study died from CNS progression, yielding an overall neurologic death rate of 33.3%. The remaining patients died of progression of systemic disease (5 patients, 66.7%), or of unknown (1 patient) or an unrelated cause (1 patient) (Fig. 4).

### 4. Discussion

Although efforts have been made to generate guidelines regarding the treatment of cerebral metastases [15,24], the appropriate management of this disease with WBRT, surgery, SRS, or some combination thereof remains a highly controversial topic in the neurooncology community. It is clear, however, that aggressive treatment regimens do positively impact patient outcome and survival [6]. Currently, many centers base their treatment of these lesions on the findings of Patchell et al with surgical resection in combination with WBRT [34]. In this study, we present an alternative to the conventional regimen whereby selected patients with 1 to 2 cerebral metastases are treated with both surgical resection and postoperative SRS. Using this combined treatment paradigm, WBRT is deferred and used as a salvage therapy for progressive disease. Median survival in this small series was 20 months, which is among the highest reported survival.
for similar series (Table 2) and compares favorably with the 11 months reported by Patchell et al for patients receiving surgery + WBRT [34].

The rationale behind this combined surgery-SRS paradigm is focal treatment of limited intracranial metastatic disease while reserving WBRT as a salvage therapy for disease...
progression. With this strategy, local disease progression occurred in only 26.7% of all patients in the study and in only 16.7% of the patients in whom GTR had been achieved. Patchell et al reported a local recurrence rate of 10% when complete surgical resection was followed by WBRT. Notably, all patients in the Patchell et al study had GTR of a solitary metastasis; and, importantly, the median follow-up in that study was only 48 weeks [34]. Thus, the data presented in the current study, with a median follow-up of 20 months, demonstrate that the combined surgery-SRS paradigm offers durable, effective control of local metastatic disease and is equivalent to that observed with surgery followed by WBRT.

Sixty percent of patients in the current study had progressive intracranial metastatic disease remote from the original lesion(s) at a median of 8 months postoperation. When only those patients with a completely resected single lesion were considered, the rate of progression of distant disease decreased to 44.4%. This value is clearly higher than the 14% reported by Patchell et al for those patients treated with postoperative WBRT; however, the patients in the current study who did show progression of distant disease then went on to receive further surgery, SRS, or WBRT (Fig. 1) and survived a median of 18.0 months from the time of diagnosis of the initial cerebral metastasis.

It can be reasonably argued that the 15 patients included in this series represent a highly selected group and that the increased median survival is therefore biased and not typical for patients with cerebral metastatic disease. It is exactly this argument that underlies the basis of the combined surgery-SRS treatment; selected patients with stable systemic disease and limited intracranial disease, because of the potential for long-term survival, may benefit from aggressive local treatment and deferral of WBRT. By delaying WBRT and its possible deleterious effects on cognition, such a paradigm would theoretically maximize functional capacity without jeopardizing survival.

Appropriate selection of candidates for the combined surgery-SRS will require additional studies with larger numbers of patients. In the current study, attempts to predict outcome based on RPA class failed to reach statistical significance; however, there was a clear trend toward increased survival with RPA class 1. Thus, we believe that individuals with 1 to 2 surgically accessible cerebral metastases, KPS \( \geq 70 \), and RPA 1 classification are good candidates for the combined treatment paradigm.

It should be noted that one other group reported a limited experience with the combination of surgery and linear accelerator SRS. This article showed a median survival of 15.3 months after the combined treatment [42]. These numbers are in good agreement with the data presented in the current study and provide further evidence that the combined treatment paradigm deserves careful consideration in selected patients.

In recent years, owing to longer patient survival with evolving and improving therapies, there has been increased recognition of the adverse effects of cranial irradiation. These effects are commonly classified into acute, early-delayed, and late-delayed reactions [8]. Whereas acute (fatigue, hair loss, encephalopathy) and early-delayed (somnolence, memory deficit) reactions may cause transient disability, the late-delayed effects, including dementia, ataxia, and memory deficits, may be permanently disabling [8,31]. Although the exact biological mechanisms of radiation-related neurocognitive deficits remain unclear, oxidative stress and inflammation consistently have been implicated; and damage may occur to neurons directly or indirectly through effects on cerebral microvasculature, glial cells, myelination, or neural stem cells [8]. Long-lasting effects are also seen at the molecular level, with specific alterations in the expression of such key proteins as NMDA receptor subunits NR1 and NR2A, directly impairing learning and memory [1,38].

Radiation fractionation schemes are designed to reduce these toxicities, but the exact incidence of these effects and the WBRT safety profile in long-term survivors remain unknown [25]. Some reports estimate that debilitating cognitive decline occurs in 20% to 50% of patients who survive for 1 year [12,22,31]. Certainly, if the incidence even approaches 20%, it is worthwhile to investigate alternatives to WBRT in those patients expected to have a prolonged survival. Other groups have studied the use of focal treatment (SRS) without WBRT; they have found an increase rate of tumor recurrence but no difference in patient survival without up-front use of WBRT [3,18,43]. One small series suggested that long-term survivors may experience improved neurocognitive function with SRS alone (no WBRT) [10]. Another recent report investigated the efficacy of surgical resection coupled with placement of I-125 seeds and found excellent local control with a median survival of 17.8 months [13]. In the current study, we present another strategy wherein, by combining 2 powerful local treatments (surgical resection and SRS), WBRT and its potential toxicities may be deferred without jeopardizing survival (median survival, 20 months).

5. Conclusions

The results from this study indicate that, among all patients with cerebral metastatic disease, there is a select subset of patients that would likely benefit from aggressive management of local disease with the combined treatment paradigm of surgery and postoperative SRS. The relatively small size of the study precludes any definitive identification of patients in this subset, and attempts to do so failed to show statistical significance (though trends were observed). However, we believe that individuals with 1 to 2 surgically accessible cerebral metastases, KPS \( \geq 70 \), and RPA 1 classification are good candidates for the combined treatment paradigm. With well-controlled systemic disease, these patients would be expected to have a prolonged functional survival; and their quality of life potentially would be negatively impacted by the
toxicities of early WBRT. If and when patients do develop further multifocal disease, they can be treated with additional SRS or WBRT, which can then be given with little risk to the patient’s functional status.

Currently, when patients in this limited subset are referred to our center, we present them with treatment options, including the standard treatment with surgery followed by postoperative WBRT, or the combined treatment paradigm of surgery plus SRS with deferral of WBRT. The literature is reviewed, with an emphasis on the data supporting surgery followed by WBRT as well as the potential for radiation-related toxicities associated with up-front WBRT. Informed patients often choose up-front treatment with surgery and SRS and elect to defer WBRT until disease progression. In the current study, we provide preliminary evidence that, with vigilant follow-up, this approach is reasonable and can be used safely and effectively to increase patient survival without jeopardizing quality of life. Thus, we will continue to offer this combined treatment paradigm to appropriate patients as more information regarding this protocol is generated by our group and others and as the field continues to evolve.

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[29] Mehta MP, Rosenzweig JM, Levin AB, Mackie TR, Kubsad SS, Gehring MA, Kinsella TJ. Defining the role of radiosurgery in the


Commentary

This is a small but excellent study making the case of avoiding the use of WBRT in patients with 1 to 2 metastatic lesions. The authors recommend the use of resection followed by SRS of the tumor bed and additionally the treatment of a distant lesion if present also with SRS. They achieved a remarkable survival in this much selected group of patients (RPA 1 and RPA 2, one grade 3). The survival of 20 months from surgery (intracranial diagnosis) is one of the longest in the literature. Whole-brain radiation therapy was deemed necessary in 40% of the patients during the follow-up period. Judicious use of WBRT has gained popularity with the advent SRS. There have not been clean data supporting the use of SRS alone, without WBRT, on the treatment of limited number of brain metastases. There are randomized studies showing the usefulness of surgery and SRS associated with WBRT, but not the avoidance of this approach. A recent review article confirms the lack of data supporting the use of radiosurgery alone in the treatment of limited intracranial disease [2].

Our group has shown that WBRT can be avoided in 70% of the patients with up to 4 lesions at the time of brain metastatic involvement [1]. Close surveillance with 3-month–interval MRI is necessary for one to delay or avoid WBRT, as shown in this study and others. The incidence of distal recurrence of the disease in patients receiving WBRT is lower than in those who had WBRT withheld; however, this patients can be rescued with SRS of the new lesions. Larger studies carrying the concept presented in this study with randomized arms are necessary before WBRT can be withheld for most patients with brain metastases. This is difficult to accomplish because all designed studies of WBRT vs focal radiation have experienced difficulty with accrual because of the formidable adverse effects of WBRT vs SRS now that patients with metastatic disease are having longer survival than in the past.

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