Incidence, timing, and treatment of new brain metastases after Gamma Knife surgery for limited brain disease: the case for reducing the use of whole-brain radiation therapy

Clinical article

Stephen Rush, M.D.,1,2 Robert E. Elliott, M.D.,7 Amr Morsi, M.D.,2 Nisha Mehta, B.A.,2 Jeri Spriet, B.S.,2 Ashwatha Narayana, M.D.,1 Bernadine Donahue, M.D.,3 Erik C. Parker, M.D.,2 and John G. Golfinos, M.D.2

Departments of 1Radiation Oncology and 2Neurosurgery, New York University Langone Medical Center, New York; and 3Department of Radiation Oncology, Maimonides Medical Center, Brooklyn, New York

Object. In this paper, the authors’ goal was to analyze the incidence, timing, and treatment of new metastases following initial treatment with 20-Gy Gamma Knife surgery (GKS) alone in patients with limited brain metastases without whole-brain radiation therapy (WBRT).

Methods. A retrospective analysis of 114 consecutive adults (75 women and 34 men; median age 61 years) with KPS scores of 60 or higher who received GKS for 1–3 brain metastases ≤ 2 cm was performed (median lesion volume 0.35 cm³). Five patients lacking follow-up data were excluded from analysis. After treatment, patients underwent MR imaging at 6 weeks and every 3 months thereafter. New metastases were preferentially treated with additional GKS. Indications for WBRT included development of numerous metastases, leptomeningeal disease, or diffuse surgical-site recurrence.

Results. The median overall survival from GKS was 13.8 months. Excluding the 3 patients who died before follow-up imaging, 12 patients (11.3%) experienced local failure at a median of 7.4 months. Fifty-three patients (50%) developed new metastases at a median of 5 months. Six (7%) of 86 instances of new lesions were symptomatic. Most patients (67%) with distant failures were successfully treated using salvage GKS alone. Whole-brain radiotherapy was indicated in 20 patients (18.3%). Thirteen patients (11.9%) died of neurological disease.

Conclusions. For patients with limited brain metastases and functional independence, 20-Gy GKS provides excellent disease control and high-functioning survival with minimal morbidity. New metastases developed in almost 50% of patients, but additional GKS was extremely effective in controlling disease. Using our algorithm, fewer than 20% of patients required WBRT, and only 12% died of progressive intracranial disease. (DOI: 10.3171/2011.2.JNS101724)

KEY WORDS • radiosurgery • brain metastasis • whole-brain radiation therapy • stereotactic radiosurgery

Metastases to the brain are a cause of significant morbidity and mortality in patients with cancer.7 Fractionated WBRT has been the mainstay of treatment of cerebral metastases but extends median survival by only 3–6 months.9,10,21,43,53 Although prospective, randomized studies have demonstrated improved LC and OS when WBRT is combined with resection or SRS,3,4,40,50,54,55 its routine use with SRS remains controversial.

Decisions to administer WBRT are dependent on multiple factors including systemic disease status, the number of lesions, and patient, physician, or institutional preference.56 Many centers, however, routinely use SRS alone to treat patients with single or multiple cerebral metastases, avoiding adjuvant WBRT and its potential adverse effects, reported in over 50% of long-term survivors.32 For high-functioning patients with few brain metastases, our preference is to use SRS alone with close follow-up.

Herein, we report our experience in consecutively treated patients with 1–3 brain metastases whose sole treatment was 20-Gy GKS. Patients were followed closely, and new lesions were preferentially treated with GKS. We examined the incidence, symptoms, size, timing, and treatment of new metastases as well as ultimate neurological outcome and the need for WBRT.

Methods

Study Design and Eligibility Criteria

In 2001, we standardized our GKS-alone protocol as

Abbreviations used in this paper: GKS = Gamma Knife surgery; HR = hazard ratio; KPS = Karnofsky Performance Scale; LC = local control; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RPA = recursive partitioning analysis; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.
20 Gy for 1–3 metastases 2 cm or smaller. The records of all patients with metastatic brain tumors who underwent GKS at our center between 2001 and 2009 were retrospectively reviewed. All patients underwent 6 months or more of follow-up following initial GKS treatment unless death occurred before that time. Similar to the modified Pittsburgh protocol, eligibility criteria included the following: 1) adults with 1–3 cerebral metastases; 2) a maximum tumor diameter of 2 cm; 3) KPS score of 60 or greater (functionally independent); 4) estimated life expectancy of 4 months or more; and; 5) no prior WBRT. We identified 114 consecutive adults who fulfilled these criteria. Five patients were lost to follow-up, and the remaining 109 patients constitute the study group.

Following approval by the New York University institutional review board, data were retrospectively collected by reviewing office and inpatient records, pretreatment and serial post-GKS imaging studies, operative reports, and pathological findings. Patient characteristics, KPS score, RPA score, prior treatments, time to progression, symptoms at progression, treatment at recurrence, and other oncological treatments were recorded. Long-term follow-up information was obtained in 2009 by contacting patients, families, and referring physicians and from records of the last follow-up office visit. Dates of death were obtained from a Social Security Death Index when otherwise unavailable.

Radiosurgery Technique

On the day of GKS, a nonrelocatable Leksell stereotactic headframe was applied under local anesthesia. Our MR imaging protocol was performed after injection of triple-dose Gd and acquisition of contiguous 1-mm T1-weighted axial images.

Radiosurgery was performed using a Leksell GKS unit (Elekta Instruments). At initial GKS treatment, all patients were uniformly treated with a dose of 20 Gy at the 50% isodose line at the margin of the tumor. Subsequently, 14–18 Gy was administered for retreatment after local failure, after interval WBRT, proximity to a previously treated site, or new tumor size larger than 2 cm. Otherwise, new tumors 2 cm or smaller received 20 Gy.

Follow-Up and Treatment at Progression

Patients were observed clinically and radiographically at 6 weeks and every 12 weeks thereafter. Neurotoxicity was graded as per the RTOG (Radiation Therapy Oncology Group) toxicity scale. Local control was defined as stabilization or a decrease in lesion enhancement and T2 signal change. Local failure was defined as a persistent increase in the size of the contrast-enhancing lesion (≥ 20% in volume) and T2 signal change. Radiation necrosis, often radiographically similar to failure, was suspected when restricted diffusion was present and clinical and radiographic improvement was observed with corticosteroid treatment. Local treatments, including resection or additional GKS, were attempted in all cases of local failure in patients with high-functional status or in patients who refused recommended WBRT. There were no limitations on the maximal number of metastases that were treated during subsequent GKS sessions or the number of secondary GKS sessions. Whole-brain radiotherapy was reserved for patients with numerous metastases, leptomeningeal dissemination, and diffuse recurrences at surgical margins not amenable to GKS. The cause of death was classified using the criteria proposed by Patchell et al. All patients who died directly of progression of brain disease or those who had active brain disease at the time of death due to systemic progression or intercurrent illness were classified as deaths from brain disease. The cause of death was determined from inpatient charts, outpatient records, or discussions with family members. In patients for whom the cause of death was unclear, we considered such cases neurological deaths.

End Points and Statistical Analysis

Primary end points included local failure of metastases treated using GKS, development of new cerebral lesions, need for WBRT, and death. All times were measured from the date of GKS at New York University. Patients who died before 6-week follow-up imaging were excluded from analysis of local and distant PFS. Distant failures were divided into early (≤ 3 months) and late (> 3 months) to estimate which patients may have had microscopic disease (“micrometastases”) present but untreated at initial GKS.

Univariate and multivariate analyses were performed using the Cox proportional hazards model to determine the influence of the presenting clinical characteristics on OS and distant PFS. Averages are expressed as median values in addition to means ± SDs. The Fisher exact test was used to compare proportions between groups. Student t-tests and Mann-Whitney U-tests were used to analyze parametric and nonparametric variables, respectively. All statistics were calculated using SSPS (version 17.0 for Mac; SSPS, Inc.) software. A 2-tailed p value < 0.05 was considered statistically significant for all analyses.

Results

Presenting Characteristics

Table 1 summarizes the demographic and clinical data for 109 patients with complete follow-up. There were 34 males and 75 females with a median age of 61 years and median KPS score of 90 at the time of GKS. Prior to GKS, 24 patients underwent resection of brain metastases and 2 underwent prior SRS at outside centers. At the initial GKS session, 109 patients underwent treatment of 164 brain metastases with a median tumor volume of 0.35 cm³.

Eighty-three patients (76.1%) were neurologically intact, and 26 (23.9%) patients had deficits at the time of GKS. Nine patients had fixed neurological deficits due to prior resection (hemiparesis in 3 and hemianopia in 5) or multiple sclerosis (hemiparesis). All patients with hemiparesis were ambulatory. The remaining 17 patients had deficits due to new metastases.
Local Failure

Three patients with 3 metastases died of systemic disease prior to 6-week follow-up MR imaging and were excluded from LC analysis. Twelve (11.3%) of 106 patients experienced local failure at a median of 7.4 months (mean 11 ± 8.5 months, range 3–29 months). Fourteen (8.7%) of 161 treated lesions experienced local failure, yielding a crude LC rate of 91.3% with initial GKS.

Table 2 summarizes the characteristics and treatments of the 17 lesions that failed GKS, including 14 lesions that failed initial and 3 lesions that failed secondary GKS. Progression of 13 lesions (76.5%) was discovered radiographically on surveillance imaging, and 4 patients (23.5%) had symptoms referable to progression. Three patients with local failure of 5 metastases were treated again using GKS (14 Gy in 4 patients and 18 Gy in 1). Three lesions in 1 patient treated with an additional 14 Gy continued to progress and required resection.

Distant Failure

New metastases developed in 53 (50%) of 106 patients at a median of 5 months (mean 6.4 ± 6.4 months, range 0.5–9.5 months). The 3-, 6-, 12- and 24-month actuarial rates of distant PFS were 80%, 54%, 44%, and 29%, respectively.

These 53 patients exhibited 86 instances of new lesions on follow-up imaging studies. Figure 1 illustrates the incidence and timing of distant failures from the time of initial GKS. After occurrence and treatment of the first distant failure, the median time to further instances of distant failures was 6.5 months (mean 9.0 ± 6.3 months, range 2.5–26.5 months). Five of 31 instances of repeat distant failure occurred 3 months or less from the time of initial distant failure. Only 6 instances (7%) of distant progression were associated with symptoms (headache in 4 patients) or neurological deficits (ataxia and hemiparesis in 1 patient each). The remaining instances of new metastases (93%) were discovered radiographically.
Fifty-three patients (48.6%) underwent 97 total salvage treatments for local failure, surgical site recurrence, or new metastases. Salvage therapy consisted of one or more of the following modalities: additional GKS (35 patients), WBRT (16 patients), and resection (11 patients). Figure 2 is a flow diagram summarizing the management of all patients after initial GKS.

Thirty-five patients underwent 63 subsequent GKS treatments for 110 new lesions. Figure 3 shows the total number of GKS treatments administered. The most common locations for new lesions at retreatment were frontal (42.6%), cerebellar (16%), temporal (11.7%), parietal (16%), and occipital (8.5%). The median lesion volume was 0.30 cm$^3$ (mean 0.53 ± 1.3 cm$^3$, range 0.005–10.9 cm$^3$), and the median number of lesions treated during each salvage GKS session was 2 (range 1–5). Nineteen of these lesions received a mean of less than 20 Gy (range 14–18 Gy) due to large size (8 lesions), overlap with prior partial field radiotherapy region (4 lesions), retreatment of lesion treated by initial GKS (5 lesions), or interval treatment with WBRT (2 lesions). Of the 35 patients who had GKS for distant failure, 28 (80%) were managed with 1 or more GKS sessions without surgery or WBRT.

One patient died before posttreatment imaging following secondary GKS and was excluded from LC analysis. Two patients with a total of 3 lesions experienced local failure after secondary GKS, yielding a crude local failure rate of 5.7% per patient and 3.2% per metastasis. One patient had resection of 2 failed lesions (pathology confirmed tumor), and the other patient had WBRT for concomitant distant failure.

Indications for WBRT included development of numerous brain metastases (in 13 patients), numerous metastases plus local failure (in 2), leptomeningeal disease (in 2), and diffuse recurrence at the surgical margin (in 3). Both patients with leptomeningeal disease underwent Ommaya reservoir placement and received intrathecal chemotherapy (OS from WBRT was 7.5 and 10.5 months, respectively). Two patients refused WBRT. Overall, 16 patients (14.7%) received WBRT, and 2 additional patients died of systemic disease progression prior to commencing WBRT, yielding a rate of 18.3% for intended or received WBRT for the entire cohort. Two patients who received

---

**TABLE 2: Salvage therapy of 17 metastases after local failure following 20-Gy GKS**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Tumor Pathology</th>
<th>Location</th>
<th>Tumor Vol (cm$^3$)</th>
<th>Time to Failure (mos)</th>
<th>Symptoms at Local Failure</th>
<th>Treatment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>lung</td>
<td>cerebellar</td>
<td>0.94</td>
<td>12</td>
<td>none</td>
<td>repeat GKS (failed), then resection, then WBRT</td>
</tr>
<tr>
<td>1†</td>
<td>lung</td>
<td>occipital</td>
<td>0.74</td>
<td>9</td>
<td>none</td>
<td>repeat GKS (failed), then resection (failed), then WBRT</td>
</tr>
<tr>
<td>1†</td>
<td>lung</td>
<td>occipital</td>
<td>0.55</td>
<td>9</td>
<td>none</td>
<td>repeat GKS (failed), then resection (failed), then WBRT</td>
</tr>
<tr>
<td>2</td>
<td>lung</td>
<td>occipital</td>
<td>3.2</td>
<td>7.5</td>
<td>vision complaints‡</td>
<td>resection</td>
</tr>
<tr>
<td>3</td>
<td>lung</td>
<td>lateral ventricle</td>
<td>0.19</td>
<td>9</td>
<td>none</td>
<td>died of systemic disease before treatment</td>
</tr>
<tr>
<td>4</td>
<td>lung</td>
<td>cerebellar</td>
<td>0.52</td>
<td>15</td>
<td>none</td>
<td>repeat GKS</td>
</tr>
<tr>
<td>5</td>
<td>lung</td>
<td>cerebellar</td>
<td>2.60</td>
<td>20</td>
<td>headache, ataxia</td>
<td>resection</td>
</tr>
<tr>
<td>6a</td>
<td>lung</td>
<td>frontal</td>
<td>0.55</td>
<td>16.2</td>
<td>none</td>
<td>resection</td>
</tr>
<tr>
<td>7</td>
<td>lung</td>
<td>temporal</td>
<td>0.61</td>
<td>6.74</td>
<td>none</td>
<td>resection</td>
</tr>
<tr>
<td>8</td>
<td>melanoma</td>
<td>basal ganglia</td>
<td>0.13</td>
<td>3</td>
<td>none</td>
<td>WBRT (resection cavity recurrence)</td>
</tr>
<tr>
<td>8</td>
<td>melanoma</td>
<td>temporal</td>
<td>0.21</td>
<td>3</td>
<td>none</td>
<td>WBRT (resection cavity recurrence)</td>
</tr>
<tr>
<td>9</td>
<td>melanoma</td>
<td>temporal</td>
<td>NA</td>
<td>6</td>
<td>none</td>
<td>resection twice, then WBRT for recurrence</td>
</tr>
<tr>
<td>10</td>
<td>melanoma</td>
<td>parietal</td>
<td>1.80</td>
<td>4</td>
<td>none</td>
<td>partial field radiation therapy</td>
</tr>
<tr>
<td>11</td>
<td>melanoma</td>
<td>temporal</td>
<td>0.45</td>
<td>7.25</td>
<td>aphasia recurred</td>
<td>WBRT (new lesions)</td>
</tr>
<tr>
<td>12</td>
<td>breast</td>
<td>parietal</td>
<td>0.18</td>
<td>26</td>
<td>none</td>
<td>repeat GKS</td>
</tr>
<tr>
<td>13</td>
<td>breast</td>
<td>cerebellar</td>
<td>0.49</td>
<td>5</td>
<td>none</td>
<td>WBRT (new lesions)</td>
</tr>
<tr>
<td>14</td>
<td>renal</td>
<td>CPA</td>
<td>0.50</td>
<td>29</td>
<td>facial weakness recurred</td>
<td>repeat GKS</td>
</tr>
</tbody>
</table>

* CPA = cerebellopontine angle; NA = not available.

† Lesions treated at subsequent sessions (salvage GKS).
‡ Complained of flashes of light and “floaters” in contralateral visual field but had no new deficits.
WBRT had further distant failures and were treated using salvage GKS.

On uni- and multivariate Cox proportional hazard analyses, the primary pathology of melanoma was the only risk factor for distant failure (HR 4.08 [95% CI 1.28–12.96], p < 0.0001). No risk factors were associated with early failures (≤ 3 months from GKS) or need for WBRT.

Comparison of Primary Versus Salvage GKS

A total of 274 brain metastases were treated via primary (in 164 cases) or salvage (in 110 cases) GKS. Twenty Gy was given to 255 lesions, and 19 lesions received less than 20 Gy. Excluding lesions retreated with GKS for local failure (5 lesions) and 4 lesions in 4 patients who died before adequate follow-up imaging (primary GKS in 3 and salvage GKS in 1), 265 metastases were included in local PFS analyses. There was an insignificant trend toward a higher proportion of metastases failing initial GKS (14 [8.7%] of 161) compared with salvage GKS (3 [2.9%] of 104, p = 0.07). Figure 4 illustrates improved local PFS for metastases treated with salvage compared with primary GKS (p = 0.036). The 6-, 12-, 24- and 36-month actuarial rates of local PFS from initial GKS were 93%, 90%, 88%, and 82%, respectively. The 6-, 12-, 24-, and 36-month ac-

Fig. 2. Flow diagram illustrating the management of 109 patients after GKS for brain metastases. One patient who experienced local failure of a metastasis treated with GKS died of systemic progression prior to salvage therapy (A). The indication for WBRT in this patient was diffuse recurrence in the cavity of metastasis that was resected prior to GKS. Indications for surgery in 3 patients were local failure, intracerebral hematoma, and radiation necrosis (in 1 patient each) of metastases treated with GKS (B). Planned salvage therapy included GKS in 2 patients with new single lesions and WBRT in 2 patients with numerous metastases. One of the latter patients refused WBRT and all further treatment (C). Twenty-eight patients were treated with 1 or more sessions of salvage GKS without surgery or WBRT. Five patients underwent resection for local failure (3 patients), resection site recurrence (1 patient), and concomitant distant and local failure (1 patient). Pathology confirmed the presence of cancer in all 5 patients (D). Indications for WBRT included development of numerous brain metastases (in 10 patients), leptomeningeal disease (in 2), onset of numerous metastases and local failure of lesion treated with GKS (in 2), and diffuse resection cavity recurrence and new metastases (in 2). Four patients in this group had one or more surgeries for resection cavity recurrence (2 patients), local failure (1 patient), and radiation necrosis (1 patient). Two patients had further GKS following WBRT for new metastases (E).

Fig. 3. Bar graph showing that the majority of patients required only a single session of GKS to successfully treat their distant-site brain disease.
Actuarial rates of local PFS from salvage GKS treatment were 97%, 95%, 95%, and 95%, respectively.

**Overall Survival**

The median OS was 13.8 months (mean 18.7 ± 17.5 months, range 1 week to 7.6 years). Actuarial survival was 54%, 45%, 26%, and 11% at 6, 12, 24, and 36 months, respectively. Twenty-six patients (23.9%) are still alive at a median of 29.9 months. The causes of death are summarized in Table 3. Thirteen patients (11.9%) died with or of active neurological disease.

Table 3 summarizes the univariate and multivariate risk factors for decreased OS following GKS. On multivariate analysis, melanoma as primary tumor (HR 3.37, p < 0.0001), increasing RPA class (HR 2.06, p = 0.005), and active primary disease (HR 1.63, p = 0.048) predicted worse OS (Fig. 5).

Neither distant nor local failure negatively impacted

<p>| TABLE 3: Univariate and multivariate risk factors for shorter OS following radiosurgery for 109 patients with 1–3 brain metastases* |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>melanoma vs others</td>
<td>2.98 (1.73–5.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>lung cancer vs others</td>
<td>0.94 (0.61–1.44)</td>
<td>0.76</td>
</tr>
<tr>
<td>breast cancer vs others</td>
<td>0.49 (0.27–0.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>RPA</td>
<td>2.55 (1.57–4.14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>KPS score</td>
<td>0.97 (0.95–0.99)</td>
<td>0.003</td>
</tr>
<tr>
<td>KPS score ≥80</td>
<td>0.48 (0.28–0.84)</td>
<td>0.009</td>
</tr>
<tr>
<td>age (yrs) at GKS</td>
<td>1.01 (0.99–1.03)</td>
<td>0.25</td>
</tr>
<tr>
<td>cancer diagnosis-brain metastases interval</td>
<td>1.00 (0.99–1.00)</td>
<td>0.11</td>
</tr>
<tr>
<td>active primary disease</td>
<td>1.70 (1.09–2.65)</td>
<td>0.02</td>
</tr>
<tr>
<td>extracranial metastases</td>
<td>2.40 (1.39–4.16)</td>
<td>0.004</td>
</tr>
<tr>
<td>no. of metastases at initial GKS</td>
<td>1.30 (0.96–1.75)</td>
<td>0.09</td>
</tr>
<tr>
<td>solitary brain metastasis vs single or multiple</td>
<td>0.30 (0.12–0.74)</td>
<td>0.009</td>
</tr>
<tr>
<td>total vol of brain metastases at initial GKS</td>
<td>0.98 (0.77–1.25)</td>
<td>0.87</td>
</tr>
<tr>
<td>female sex</td>
<td>0.67 (0.43–1.05)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* — = multivariate analysis was performed but was not significant (NS).
OS, and both correlated with longer OS. There was a trend toward a higher proportion of patients with melanoma dyeing of brain disease compared with other primary cancers (531% of 16 vs 811% of 64, p = 0.055). Otherwise, no risk factors for death due to progressive brain disease were identified.

Neurological Outcomes and Complications

Of the 17 patients with deficits from active metastases at GKS, 5 patients (29.4%) had complete resolution of their deficits, 7 (41.2%) improved, 4 (23.5%) remained stable, and 1 patient (5.9%) with mild hemiparesis worsened (moderate hemiparesis at follow-up). Transient neurological worsening due to edema occurred in 4 patients (3.7%) and was due to hemorrhage in 1 patient (0.9%). Permanent neurological worsening occurred in 3 patients (2.8%), all from treated lesions and not from distant failures. Neurological symptom-free survival at 6, 12, 24, and 36 months was 80%, 85%, 86%, and 75%, respectively.

Radiation necrosis occurred in 3 patients; it was confirmed after resection in 2 cases and was radiographically suspected in the remaining patient who was successfully treated with a course of corticosteroids. The incidence of radiation necrosis was 2.8% (3 of 106 patients with follow-up) and in 1.1% (3 of 270) of brain metastases treated with GKS.

Discussion

Using a protocol of 20-Gy GKS alone for a consecutive series of functionally independent patients with 1–3 brain metastases 2 cm or smaller, close follow-up, and preferentially using additional GKS for new metastases, LC was achieved in more than 93% of treated metastases and median OS was 13.8 months from treatment. The use of WBRT and death due to neurological disease were avoided in almost 85% of patients. More than 75% of patients who developed new lesions were treated successfully with additional GKS. Salvage therapy was effective in providing LC with minimal morbidity. Neither local nor distant failure negatively impacted OS. With frequent follow-up imaging, new metastases were typically diagnosed while small, few in number, asymptomatic, and readily treatable with GKS.

Whole-Brain Radiation Therapy for Brain Metastases

The treatment of brain metastases has evolved considerably since radiotherapy and glucocorticoids were introduced in the 1950s when patients were often diagnosed with large, symptomatic lesions before CT scanning.12,38 Although WBRT is effective in palliating symptoms (70%) and extends survival by several months, it has relatively high rates of local failure and neurological death.9,10,18,21,40,43,53,55 The Pittsburgh group40 contended, “WBRT alone does not provide lasting and effective care for most patients.”

Moreover, adverse events and decreased QOL have been reported in many long-term survivors who have undergone WBRT.1,7,8,17–20,24,25,29,32,39,42,44,46,48,65,68,69,71 Acute side effects of irradiation include fatigue, dermatitis, and alopecia, and WBRT often requires interruption of systemic chemotherapy. Chronic sequelae of irradiation can include cognitive decline, apathy, dementia, white matter signal change, cerebral atrophy, encephalomalacia, gait disturbance, ataxia, visual loss, and radiation necrosis.79,88

While WBRT continues to be the most commonly used treatment for brain metastases, numerous centers have reported diminished QOL following treatment. Bezjak et al.7 prospectively analyzed palliation of symptoms and QOL in 85 patients who received WBRT for brain
metastases. Of the 52 patients who underwent pre- and posttreatment evaluations, 40% of patients worsened neurologically and 50% experienced deterioration in their performance status at 1 month. While 84% of patients in this series experienced symptom improvement with steroids, only 19% improved neurologically after WBRT. Doyle et al. prospectively studied QOL in 60 patients before and after WBRT for brain metastases. Two months after treatment there were trends toward worsening overall and brain-specific QOL indices. In a prospective assessment of QOL parameters in 170 patients, Chow et al. noted significant declines from pretreatment baselines in the following domains after WBRT: fatigue, drowsiness, and appetite. In a review of 42 studies on the side effects of cranial irradiation, Crossen et al. reported that delayed adverse effects were dependent on patient age, timing of chemotherapy, fraction sizes, and total dose. They contend that neurobehavioral sequelae for patients living longer than 6 months are likely underestimated by current reports in the literature. We concur given the lack of standardized metrics and the confounding influences of chemotherapy, cancer progression, and malnutrition.

Multiple studies have consistently found the peak onset of neurocognitive decline after WBRT to be between 6 and 24 months. Hence, many patients with cancer and brain metastases may be exposed to the adverse effects of WBRT unnecessarily and suffer poor QOL during their remaining survival time. With these considerations of WBRT in mind, our protocol centers on GKS as stand-alone treatment for patients with a limited number of brain metastases, and we preferentially treat them with additional GKS should new lesions arise.

Radiosurgery for Brain Metastases

In contrast to WBRT, radiosurgery delivers highly conformal radiation to small target volumes with minimal exposure to the surrounding brain to the deleterious effects of ionizing radiation. It can be safely used to treat multiple lesions in the same setting, is repeatable without increased morbidity, and avoids almost all WBRT side effects. Rates of LC with SRS range from 70% to more than 90% and OS varies from 7.6 to 10.3 months in prospective studies. Given its efficacy, low morbidity and comparable OS to WBRT, many centers use SRS as the sole treatment for brain metastases when appropriate. In our experience with the patient population we described, 85% of patients meeting our criteria for treatment never received WBRT.

Kondziolka et al. prospectively surveyed QOL parameters in 200 consecutive patients who underwent SRS with or without WBRT, 104 of whom completed the questionnaire. Overall, patients who received WBRT reported significantly more side effects (63% vs 36%). Specifically, patients who underwent only SRS reported significantly less fatigue, hair loss, depression, short- and long-term memory difficulties, and concentration problems. Vargas et al. retrospectively reported on 54 patients who received SRS and noted no morbidity, mortality, or decrease in KPS score following treatment. In 2 large, retrospective series (504 and 804 patients) by Gerosa et al. the median functionally independent survival was preserved for 12–13 months following SRS. In our series, we did not assess neurocognition in a standardized manner but did find excellent preservation of neurological function with neurological symptom-free survival of 85% at 1 and 2 years following GKS.

One argument for combining adjuvant WBRT with SRS is to decrease the incidence of new lesions and the need for salvage therapy. Some assume that this is due to the treatment “micrometastases” that are too small to be visualized at initial treatment. However, new lesions still arise after WBRT, occurring in nearly 50% of patients in some series similar to the rate we observed. Karlsson et al. reported that 52% of 215 patients observed for more than 2 years after GKS developed new metastases; 87% occurred after 6 months and 49% after 1 year. They suggest that reseeding is the most likely etiology of the majority of new lesions. They also reported a similar proportion of patients undergoing salvage GKS as we do (50% by 2 years).

Although some may challenge our decision to proceed with GKS in lieu of WBRT at the time of initial distant failure, we report excellent success of salvage GKS therapy, and most patients required only 1 session of salvage GKS for durable disease control. The minority of patients who experienced additional distant failures did so at an extended time interval, and only fewer than 20% of new instances of distant failures occurred within 3 months following salvage therapy. We contend that many of these patients would have experienced distant failures after WBRT as well. Whether new lesions are due to micrometastases present at initial GKS or reseeding, the outcomes of GKS alone upfront are similar to those with WBRT but can spare most patients the need for weeks of radiation treatments, its morbidity, and the interruption of systemic chemotherapy.

Another rationale for upfront WBRT is preservation of neurological function due to fewer new metastases. Regine et al. reported new symptoms (71%) or neurological deficits (59%) in 17 of 36 patients from combined new metastases and local failures after SRS. This contrasts dramatically with our results; only 7% of patients with new lesions were symptomatic, and only 2.3% developed neurological deficits. Similarly, the majority of patients who had local failure were asymptomatic and few developed neurological deficits. These disparities may be due to our regular imaging protocol that diagnoses new metastases earlier, as opposed to varying intervals of 2–5 months in the latter study.

Three well-designed prospective trials have assessed the impact of SRS with or without WBRT on functional and oncological outcomes. Aoyama et al. prospectively compared SRS with or without WBRT in 132 patients with 1–4 brain metastases and found no improvement in overall or high-functioning survival with the addition of WBRT. While there was a higher incidence of new metastases (51% vs 32%) and an increased need for salvage therapy in the SRS-only group, there was no difference in the rate of death due to neurological disease (19.3% vs 22.8%). In a follow-up study in this cohort of patients examining sustained neurocognitive function, Aoya-
Gamma Knife surgery for brain metastases

ma et al.3 reported that the addition of WBRT provided short-term prevention of the decrement in neurocognitive function (as measured using the mini-mental state examination) that often accompanied disease progression but resulted in continual deterioration in function over time. With ongoing improvements in systemic cancer therapies and improved survival and, more importantly, high-functioning survival, these long-term side effects become more critical in the assessment of overall outcome.

Kocher and colleagues37 published their results from the EORTC (European Organisation for Research and Treatment of Cancer) Study (22952–26001), which randomized 359 patients with 1–3 brain metastases to treatment with resection followed by observation or WBRT or SRS followed by observation or WBRT. Those authors found that adjuvant WBRT reduced the incidence of local (31% vs 19%) and distant-site (48% vs 33%) intracranial relapse and neurological deaths (28% vs 44%), but they noted similar OS with or without WBRT (10.9 vs 10.7 months) and no difference in duration of functional independence following initial treatment (10 vs 9.5 months). Similar to our results, they concluded that improved PFS did not translate into improved overall or highly functional survival and that WBRT can be withheld after SRS until relapse. Differences in our studies, however, do exist. Although 20 Gy was the median dose, dosing ranged from 14 to 25 Gy, and the size of the lesions treated with radiosurgery had a median size of 2 cm and were as large as 4 cm. We rarely treat metastases larger than 3 cm with radiosurgery and perhaps the higher rate of local failure (compared with our results) may have been reduced with higher doses or better patient or lesion selection. While their conclusion supports our approach, their data highlight the notion that WBRT was perhaps unnecessarily administered to more than half of the patients.

Chang and colleagues41 prospectively randomized patients with 1–3 brain metastases to receive either SRS alone or SRS plus WBRT and studied neurocognitive decline and need for salvage therapy. The trial was halted after enrolling 58 patients because of significantly greater decline in learning and memory function evident at 4 months following treatment in the group that received WBRT (52% vs 25%). Significantly more patients in the SRS-alone group required salvage therapies but, in contrast to the results of Aoyama et al.,4,5 they had longer OS and better maintenance of cognitive function. While other studies attributed neurocognitive decline to disease progression,5,38 Chang et al.11 showed that WBRT has a more deleterious impact on learning and memory than on the development of new metastases. These findings agree with the interpretation of our data given that most new lesions were asymptomatic, discovered on surveillance imaging and, with the success of salvage therapy, did not cause undue harm.

In the aforementioned series, it becomes apparent that the rationale for using immediate, adjuvant WBRT after SRS is to decrease intracranial recurrence. This appears to be a philosophical choice that is institution-dependent and one that comes with a price to pay, both in terms of the probable cognitive effects as well as the actual cost in dollars. Although our protocol may not be ideal for many areas with limited access to sophisticated medical care or economic constraints, we believe that the results of our study and others have demonstrated that immediate, adjuvant WBRT after SRS for limited brain metastases may not be warranted.

Importantly, neither local nor distant failure diminished OS in our series (relative to patients who did not have failure)—emphasizing the success of surveillance and salvage treatment. Diagnosis of new lesions while few and small in size allowed for effective secondary GKS with a crude local control rate of 97%. Thus, most patients were successfully treated with additional GKS without subsequent surgery or WBRT. These data agree with the findings of other centers that withholding upfront WBRT, but using close follow-up and salvage treatment, does not compromise QOL.14,66

Whole-brain radiation therapy, however, does have an instrumental role in the management of brain metastases. We recommend WBRT initially for numerous lesions or large, unresectable lesions or as salvage therapy for disease not amenable to focal treatments (numerous lesions, leptomeningeal disease, or diffuse resection cavity recurrence). Ultimately, only 15% of these patients were given WBRT, which is comparable with the results of other centers. In 10 studies that reported the need for WBRT after SRS alone, 64%–98% of patients were spared WBRT.13,15,27,28,45,47,49,56,61,66,67 Moreover, limiting the use of WBRT to such indications did not, however, compromise neurological survival. Only 12% of patients in our series died of progressive neurological disease, which is comparable to the reported rates from other SRS series (4%–43%).2–4,6,13,15,16,25,27–31,33,35,36,52,56,59,61,63,64,66

Comments on Our Study

Limitations of this study include its retrospective methodology, the lack of neurocognitive assessments, lack of cost comparison analysis, and that follow-up is absent in 5 patients. However, it provides data on a relatively large series of consecutive patients with well-defined selection criteria, treated with an identical radiosurgical protocol. Standardized posttreatment imaging was performed, and focal treatments were preferentially used for new metastases. Moreover, strict indications for WBRT were used. Such uniform selection, standardized primary and secondary treatment, and close follow-up of these patients make these data useful for guiding clinical practice as the detection and treatment of brain metastases evolve concurrently with changes in systemic therapies.

Conclusions

For patients with limited brain metastases and functional independence, 20-Gy GKS provides excellent disease control and high-functioning survival with minimal morbidity. New metastases developed in almost 50% of patients, but additional GKS when appropriate was extremely effective in controlling disease. Close clinical follow-up and frequent imaging seem paramount to early detection of new lesions and their successful treatment. This protocol resulted in the majority of patients being
spared the morbidity of WBRT, symptomatic recurrence, and neurological death due to uncontrolled brain metastases.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Elliott, Rush. Acquisition of data: Elliott, Morsi, Mehta, Spreit. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Elliott, Rush, Narayana, Donahue, Parker, Golfinos. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Elliott. Administrative/technical/material support: Rush, Golfinos. Study supervision: Rush, Narayana, Donahue, Golfinos.

References

Gamma Knife surgery for brain metastases


J Neurosurg / Volume 115 / July 2011


Manuscript submitted October 9, 2010. Accepted February 14, 2011. Please include this information when citing this paper: published online March 18, 2011; DOI: 10.3171/2011.2.JNS101724.

Address correspondence to: Stephen Rush, M.D., Departments of Radiation Oncology and Neurosurgery, New York University Langone Medical Center, 530 First Ave, Suite 8R, New York, New York 10016. email: stephencrush@aol.com.