OUTCOME AFTER RADIOSURGERY FOR BRAIN METASTASES IN PATIENTS WITH LOW KARNOFSKY PERFORMANCE SCALE (KPS) SCORES

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Purpose: The objective of this retrospective study was evaluation of the outcome after stereotactic radiosurgery (SRS) in patients with intracranial metastases and poor performance status.

Methods and Materials: Forty consecutive patients with metastatic brain tumors and Karnofsky performance scale (KPS) scores <50 (mean, 43 ± 8; median, 40) treated with SRS were analyzed. Poor performance status was caused by presence of intracranial metastases in 28 cases (70%) and resulted from uncontrolled extracerebral disease in 12 (30%).

Results: Survival after SRS varied from 3 days to 11.5 months (mean, 3.8 ± 2.9 months; median, 3.3 months). Survival probability constituted 0.50 ± 0.07 at 3 months and 0.20 ± 0.05 at 6 months posttreatment. Cause of low KPS score (p = 0.0173) and presence of distant metastases beside the brain (p = 0.0308) showed statistically significant associations with overall survival in multivariate Cox proportional hazards regression analysis. Median survival was 6.0 months if low KPS score was caused by cerebral disease and distant metastases in regions beyond the brain were absent, 3.3 months if low KPS score was caused by cerebral disease and distant metastases in regions beyond the brain were present, and 1.0 month if poor performance status resulted from extracerebral disease.

Conclusions. Identification of the cause of low KPS score (cerebral vs. extracerebral) in patients with metastatic brain tumor(s) may be important for prediction of the outcome after radiosurgical treatment. If poor patient performance status without surgical indications is caused by intracranial tumor(s), SRS may be a reasonable treatment option. © 2007 Elsevier Inc.
prognostic variables besides KPS score, such as patient age, ambulatory performance status, multiplicity of brain metastases, response to steroids, control of primary cancer, and presence and location of extracranial metastases may significantly influence the treatment outcome (4, 9, 21–25). Moreover, poor performance status in a patient with brain metastases may result either from presence of intracranial tumor(s) or uncontrolled somatic disease. The cause of low KPS score (cerebral vs. extracerebral), however, was not previously taken into account for determination of patient prognosis after irradiation of brain metastases. The objective of this study was evaluation of SRS in patients with metastatic brain tumors and KPS score ≤50 with a particular emphasis on prognostic significance of the determined cause of poor performance status.

METHODS AND MATERIALS

In 2002–2003, 474 patients with metastatic brain tumors underwent Gamma Knife radiosurgery in the Department of Neurosurgery of the Tokyo Women’s Medical University. At the time of treatment, 40 of these patients (8.5%) had KPS scores ≤50 and were included in retrospective analysis. All clinical and radiosurgical data were extracted from prospectively maintained computer database.

Clinical characteristics

Included in the study were 22 men and 18 women with a mean age 62.1 ± 12.0 years (median, 64.5 years). The primary cancer was located in the lungs (18 cases), breast (5 cases), prostate (3 cases), colon (3 cases), skin (malignant melanoma), and bile duct, esophagus, ovary, stomach, thyroid (1 each). The source of brain metastases remained unknown in five cases. Progression of the local disease was marked in 14 cases (35%). Twenty patients (50%) had distant metastases beyond the brain.

Single intracranial tumors were encountered in 12 patients (30%) and multiple tumors in 28 (70%). The number of multiple metastases remained unknown in 55% and significant in 45%. Midline shift was absent or considered nonsignificant in 22 cases (55%) and significant in 18 cases (45%). Midline shift was marked in four cases (10%) and direct brainstem compression by the tumor in eight (20%). Twenty patients (50%) had moderate-to-severe hemiparesis, which was the most common neurologic sign. Thirteen patients (33%) received previous treatment for metastatic brain disease, which included SRS (three cases), WBRT (two cases), surgery (three cases), chemotherapy (one case), or a combination of these (four cases).

Performance status

The final evaluation of the performance status was done by the treating neurosurgeon on the day before SRS. KPS score was 50 (“complete dependence on relatives in daily life”) in 16 patients, 40 (“need for regular medical assistance on the outpatient basis”) in 20 patients, 30 (“need for medical treatment on inpatient basis”) in 2 patients, and 20 (“need for intensive therapy”) in 2 patients. Although the definitions of KPS values are different from those that are usually used, this did not seem to cause bias in the evaluation of the performance status. Mean KPS score was 43 ± 8, and median was 40. The score index for radiosurgery (SIR) in brain metastases (7) varied from 0 to 7 (mean, 3 ± 2; median, 3).

Cause of declined performance status (cerebral vs. extracerebral) was defined by the treating neurosurgeon based on the correspondence of the neurologic status to poor general condition. Low KPS score was caused by presence of intracranial metastases in 28 cases (70%) and resulted from uncontrolled extracerebral disease in 12 (30%). Comparison of main neurologic symptoms and signs in the two groups are shown in Table 1.

Radiosurgery

At the time of radiosurgery, patients either had no indications for surgical removal of metastatic brain tumors or had significant contraindications including rejection of proposed intervention by the individual and his or her family. Informed consent was obtained before treatment in each case. All patients received steroid therapy, which was initiated either before or immediately after SRS. In all cases with significant mass effect, maximal management with steroids was done before radiosurgery session.

Leksell Gamma Knife Models B and (later) C were used. On the day of treatment, the stereotactic frame was fixed under local anesthesia. The axial slices of the contrast-enhanced CT and single-dose gadolinium MRI were obtained at every 2 mm. Treatment planning and dose calculation were performed using Leksell GammaPlan. In each case, all identified intracranial metastases were treated. The target volume was defined as an area of contrast enhancement, without inclusion of the surrounding brain tissue. The treatment parameters of the tumor, or of the largest tumor in cases of multiple metastases, were as follows: maximal dose, 24–50 Gy (mean, 37.8 ± 6.3 Gy; median, 38 Gy), marginal dose, 12–25 Gy (mean, 19.0 ± 3.4 Gy; median, 19 Gy), energy delivered to tumor, 6.4–495.7 mJ (mean, 144.2 ± 112.7 mJ; median, 136 mJ), unit energy delivered to tumor, 14.0–444.4 mJ/mL (mean, 26.0 ± 7.1 mJ/mL; median, 24.3 mJ/mL), conformity index, 0.43–1.00 (mean, 0.88 ± 0.15; median, 0.94), selectivity index, 0.12–0.97 (mean, 0.74 ± 0.19; median, 0.78). In the vast majority of cases, the marginal dose corresponded to 50% prescription

<table>
<thead>
<tr>
<th>Cause of low KPS score</th>
<th>Cerebral (n = 28)</th>
<th>Extracerebral (n = 12)</th>
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</thead>
<tbody>
<tr>
<td>Moderate-to-severe hemiparesis</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Increased intracranial pressure</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ataxia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Aphasia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cranial nerves palsy</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dementia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No neurologic symptoms</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>
isodose line. No early complications or adverse reactions of the treatment were marked in any case. Patients were discharged or transferred to another hospital after overnight observation.

**Further treatment**

The decision to taper or continue glucocorticoids after radiosurgery was done by the referring physician, and no information in this regard was available. Eight patients (20%) underwent additional treatment for brain metastases during further follow-up, which included WBRT (four cases), SRS (three cases), and a combination of these (one case). The data considering efficacy of treatment of the progressive extracerebral disease were not available at the time of this analysis.

**Outcome**

Outcome was evaluated by direct phone calls to patients' family, and/or the referring physician. The emphasis was put on the survival calculated from the time of SRS and improvement of the patient condition after treatment. At the time of the outcome evaluation, all patients were dead. The cause of death was not identified.

**Statistics**

Dependence of the overall survival on clinical variables was evaluated by log-rank test after construction of Kaplan-Meier survival curves. Survival probabilities at 3 and 6 months and probability of clinical improvement after treatment were compared using Z tests. Multivariate analysis regarding prognostically important variables was done using Cox proportional hazards method. Level of significance was $p < 0.05$ (27).

**RESULTS**

Overall survival after SRS in patients with brain metastases and low KPS score was evaluated by log-rank test from 3 days to 11.5 months; mean survival was 3.8 ± 2.9 months, median was 3.3 months (95% confidence interval [CI], 2.0–4.0) (Fig. 1). Survival probability at 3 months after treatment was 0.50 ± 0.07 (95% CI, 0.36–0.64), and at 6 months it was 0.20 ± 0.05 (95% CI, 0.09–0.31).

The patients’ survival was significantly longer if at the time of radiosurgery low KPS score was caused by an intracranial metastases (log-rank test, 10.554; $p = 0.0012$), if distant metastases beyond the brain were absent (log-rank test, 6.329; $p = 0.0117$), if presence of the largest metastatic brain tumor was associated with significant mass effect (log-rank test, 4.316; $p = 0.0375$), and if additional SRS and/or WBRT for metastatic brain tumors was performed during further follow-up after treatment (log-rank test, 3.920; $p = 0.0477$). Cause of low KPS score (Z = 2.38; $p = 0.0173$) and presence of distant metastases beyond the brain (Z = 2.16; $p = 0.0308$) preserved their statistically significant associations with overall survival in the multivariate Cox proportional hazards regression analysis (Table 2).

On the basis of the results of multivariate analysis, three groups of patients were defined: those with cerebral cause of low KPS score and absence of distant metastases beyond the brain (Group I), those with cerebral cause of low KPS score and presence of distant metastases beyond the brain (Group II), and those with extracerebral cause of low KPS score (Group III). The survival characteristics in the three groups are presented in Table 3. The overall survival was significantly different among the three groups (log-rank test, 12.920; $p < 0.01$; Fig. 2). This difference reached borderline statistical significance when Groups I and II were compared (log-rank test, 3.720; $p = 0.0536$) and was significant when Groups I and III (log-rank test, 12.451; $p = 0.0004$) and Groups II and III (log-rank test, 9.669; $p = 0.0019$) were compared. Survival probability at 3 months did not differ significantly between Groups I and II (Z = 1.39; $p = 0.1645$) and between Groups II and III (Z = 1.83; $p = 0.0672$) but was significantly different between Groups I and III (Z = 3.79; $p = 0.0001$). The survival probability at 6 months was significantly different between Groups I and II (Z = 2.45; $p = 0.0143$) and between Groups I and III (Z = 3.55; $p = 0.0003$) but was not significantly different between Groups II and III (Z = 1.02; $p = 0.3077$).

Clinical improvement after SRS was marked by patient family members or the referring physician in 24 cases (60%). It had a strong association with longer survival: the latter constituted 5.6 ± 2.4 months for those individuals who improved after SRS, compared with 1.1 ± 0.8 months for those who did not improve (median test, 26.667; $p < 0.0001$). In all patients who survived more than 3 months after SRS, clinical improvement was marked.

**DISCUSSION**

Management options of intracranial metastases in patients with low KPS score are scarce (28). Many propose withholding active treatment in such cases, particularly with
an active systemic disease and provide only symptomatic therapy with steroids or anticonvulsants (19). Steroids can result in dramatic improvement of the general condition, and response to dexamethasone may be predictive of survival (19, 22), but duration of such an effect is usually short, and significant complications may accompany prolonged high-dose therapy (19, 20, 28, 29). Whole-brain radiation therapy, which is considered as a standard option for management of intracranial metastases not amenable to surgery or radiosurgery, can provide only limited prolongation of survival of RPA Class III patients (21, 22, 24, 25, 30, 31). In approximately two thirds of cases with serious neurologic dysfunction, clinical improvement within 1–2 weeks can be expected (30), but the treatment may be associated with significant toxicity, which may result in further patient impairment (19, 30, 32). Chemotherapy can be effective in some patients with brain metastases (19, 21, 33); however, its survival benefit has not been demonstrated to date, and on the basis of current evidence, this treatment is not considered for the RPA Class III cohort (34). Finally, good performance status is one of the main selection criteria of the Radiation Therapy Oncology Group results in each RPA class. Addition of SRS to WBRT resulted in a statistically significant increase of the median survival from 7.1 to 16.1 months in the RPA Class I cohort, from 4.2 to 10.3 months in the RPA Class II cohort, and from 2.3 to 8.7 months in the RPA Class III cohort. Addition of local treatment, either surgery or radiosurgery, to WBRT increases the probability of neurologic improvement and its duration (1, 14, 21, 31, 39). Radiosurgery can be easily done as a 1-day treatment on an outpatient basis, which offers more opportunities for active treatment of systemic disease and avoids protracted fractionated radiotherapy, which may be important in patients with lim-

<table>
<thead>
<tr>
<th>Patient characteristics and number of cases (n)</th>
<th>Median survival in months (95% CI)</th>
<th>Survival probability (mean ± SE) and 95% CI At 3 months</th>
<th>At 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (n = 16): cerebral cause of low KPS and absence of distant metastases beyond the brain</td>
<td>6 (3.0–8.0)</td>
<td>0.75 ± 0.10 (0.55–0.95)</td>
<td>0.44 ± 0.11 (0.22–0.66)</td>
</tr>
<tr>
<td>Group II (n = 12): cerebral cause of low KPS and presence of distant metastases beside the brain</td>
<td>3.3 (1.5 – 4.0)</td>
<td>0.50 ± 0.13 (0.26–0.75)</td>
<td>0.08 ± 0.05 (0.00–0.19)</td>
</tr>
<tr>
<td>Group III (n = 12): extracerebral cause of low KPS</td>
<td>1.0 (0.5–3.0)</td>
<td>0.17 ± 0.08 (0.02–0.32)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; KPS = Karnofsky performance scale.
The proportion of RPA Class III patients in the tumors who are in poor general condition (2, 4, 8, 11, 14, 16), those with cerebral cause of poor performance status and no distant metastases beyond the brain (Group I; \( n = 16 \)), those with cerebral cause of poor performance status and distant metastases beyond the brain (Group II; \( n = 12 \)), and those with extracerebral cause of poor performance status (Group III; \( n = 12 \)). Median survival was 6.0 (95% confidence interval [CI], 3.0–8.0), 3.3 (95% CI, 1.5–4.0), and 1.0 (95% CI, 0.5–3.0) months for the three groups, respectively.

Results of our study demonstrate that SRS may be considered a reasonable option for some patients with low KPS scores and without urgent surgical indications. Mean and median survival after treatment were 3.8 and 3.3 months, respectively, which is comparable to previously published outcomes in RPA Class III cohorts (Table 4). The probability of 6-month survival was 0.20 \( \pm \) 0.05, and the longest survival was 11.5 months. No significant complications or side effects were noted. Moreover, referring physician or patients’ family members noted some clinical improvement after SRS treatment might not have enough time to enjoy its potential benefits” and concluded that “although radiosurgery may offer some improvement in quality of life, and perhaps in survival time, for patients with a very poor prognosis, [it] may not justify the stress, cost, and risk involved.” Such a statement, however, seems arbitrary to us.

Table 4. Outcome after irradiation of metastatic brain tumors in patients with KPS score <70 (RPA Class III)

<table>
<thead>
<tr>
<th>Reference (No.)</th>
<th>Treatment method</th>
<th>Median survival after treatment (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaspar et al. (1997) (17)</td>
<td>WBRT ± local boost</td>
<td>2.3</td>
<td>KPS ≥30</td>
</tr>
<tr>
<td>Cho et al. (1998) (4)</td>
<td>LINAC ± WBRT</td>
<td>6.6</td>
<td>KPS ≥40</td>
</tr>
<tr>
<td>Weltman et al. (2000) (7)</td>
<td>LINAC ± WBRT</td>
<td>3.4</td>
<td>KPS ≥50</td>
</tr>
<tr>
<td>Nieder et al. (2000) (24)</td>
<td>WBRT ± surgery</td>
<td>2.0</td>
<td>KPS ≥30</td>
</tr>
<tr>
<td>Kim et al. (2000) (6)</td>
<td>GKR ± WBRT</td>
<td>1.3</td>
<td>KPS ≥50</td>
</tr>
<tr>
<td>Noel et al. (2001) (8)</td>
<td>LINAC</td>
<td>1.6</td>
<td>Recurrent cases after WBRT; KPS score 60 and more</td>
</tr>
<tr>
<td>Sanghavi et al. (2001) (9)</td>
<td>WBRT ± SRS boost</td>
<td>8.7</td>
<td>Detailed KPS information not provided</td>
</tr>
<tr>
<td>Ford et al. (2002) (11)</td>
<td>LINAC ± WBRT</td>
<td>6.0</td>
<td>Detailed KPS information not provided</td>
</tr>
<tr>
<td>Lutterbach et al. (2002) (25)</td>
<td>WBRT</td>
<td>1.8</td>
<td>Detailed KPS information not provided</td>
</tr>
<tr>
<td>Lutterbach et al. (2003) (13)</td>
<td>LINAC</td>
<td>1.5</td>
<td>KPS score ≥50</td>
</tr>
<tr>
<td>Chang et al. (2003) (12)</td>
<td>LINAC ± WBRT</td>
<td>6.4</td>
<td>KPS score ≥60</td>
</tr>
<tr>
<td>Chang et al. (2005) (15)</td>
<td>LINAC ± WBRT</td>
<td>3.0</td>
<td>KPS score ≥40</td>
</tr>
</tbody>
</table>

Abbreviations: GKR = Gamma Knife radiosurgery; KPS = Karnofsky performance scale; LINAC = linear accelerator radiosurgery; RPA = Recursive partitioning analysis.
statistical analysis: the presence of distant metastases beyond the brain and the cause of the poor performance status of the patient. In fact, extracranial disease status, defined as a control of the primary cancer, presence of extracranial metastases, or both, consistently showed statistically significant associations with the outcome after radiosurgical or radiotherapeutic management of brain metastases (3–6, 9, 10, 12–14, 17, 22–24, 31, 36, 39, 41, 42), and therefore it was included in the majority of existing prognostic schemes (4, 7, 17, 22). At the same time, despite the fact that poor performance status in a patient with brain metastases may result from either presence of intracranial tumor(s) or uncontrolled somatic disease, the cause of low KPS score (cerebral vs. extracerebral) has not previously been taken into account for determination of the patient prognosis.

In this study, the cause of low KPS score had the strongest association with the overall survival in both univariate and multivariate statistical analyses. It was shown that radiosurgery might be effective for patients with KPS score ≤50 if poor performance status is due to the presence of intracranial metastases, especially if distant metastases beyond the brain were absent. In such cases, despite relatively large-sized tumors, frequent presence of significant mass effect, and midline shift or direct brainstem compression, the median survival constituted 6 months, and survival proportions at 3 and 6 months were 0.75 and 0.44, respectively. In contrast, if poor performance status was caused by uncontrolled extracerebral disease, median survival was just 1 month, survival proportion at 3 months was 0.17, and no patient was alive at 6 months posttreatment. Therefore, determined cause of low KPS score may be used as a selection criterion for radiosurgery, which may be prognostically important not only in patients with KPS scores ≤50 but in the whole RPA Class III cohort.

In conclusion, this retrospective analysis shows that the outcome after SRS for brain metastases in patients with KPS ≤50 and without urgent surgical indications is comparable to previously reported results of radiosurgery or WBRT in the RPA Class III cohort. Selection of patients with poor performance status for radiosurgical treatment should be based on identification of the cause of low KPS score (cerebral vs. extracerebral) and presence of distant metastases beyond the brain. Stereotactic radiosurgery can be considered a reasonable option if patients’ low KPS score is caused by intracranial tumor(s), if there are no indications for urgent surgical tumor removal, and if activity of extracranial disease is limited.

REFERENCES