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Clinical Study

Outcomes and cost-effectiveness of gamma knife radiosurgery and whole brain radiotherapy for multiple metastatic brain tumors

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ABSTRACT

We aimed to analyze the outcomes and cost-effectiveness of gamma knife radiosurgery (GKRS) and whole brain radiotherapy (WBRT) for multiple metastatic brain tumors. Over a period of 5 years, 156 patients with multiple metastatic brain tumors were enrolled and freely assigned by the referring doctors to either gamma knife radiosurgery (GKRS, Group A, $n = 56$), or to whole brain radiotherapy (WBRT, Group B, $n = 100$). The follow-up time was set at 1200 days (3.3 years) post-treatment. The number of tumors, patient age, extent of systemic disease and Karnofsky performance scale (KPS) score, were recorded and recursive partitioning analysis used. The outcomes analyzed were: mortality, survival time, neurological complications, post-treatment KPS score, quality-adjusted life years (QALY), and cost-effectiveness. A paired *t*-test was used for statistical analysis. Mortality rates for patients receiving GKRS and WBRT were 81.1% and 93.0%, respectively ($p = 0.05$). The mortality rate was lower for GKRS (74.4%) than for WBRT (97.1%) in patients with initial KPS $\geqslant$ 70 ($p = 0.02$). The mortality rate was also significantly lower for GKRS (78.9%) than WBRT (95.5%) in patients with 2–5 tumors ($p < 0.05$). Post-treatment KPS score (mean ± standard deviation [s.d.] was higher for patients receiving GKRS (73.8 ± 13.2) than for those receiving WBRT (45.5 ± 26.0), $p < 0.01$. The median survival time for GKRS and WBRT was 9.5 months and 8.3 months, respectively, $p = 0.72$. The mean (± s.d.) QALY was 0.76 ± 0.23 for GKRS and 0.59 ± 0.18 for WBRT, respectively ($p < 0.05$). The cost-effectiveness per unit of QALY was better for the GKRS treatment (US$10,381/QALY) than in the WBRT treatment (US$17,622/QALY), $p < 0.05$. The cost-effectiveness per KPS score was also higher for the GKRS treatment (US$139/KPS score) than for WBRT (US$229/KPS score), $p < 0.01$. Thus, the mortality rate for multiple metastatic brain tumors treated by GKRS is significantly better with a good initial KPS score and when the tumor number is 2–5. GKRS results in a better post-treatment KPS score, QALY, and higher cost-effectiveness than WBRT for treating multiple metastatic brain tumors.

1. Introduction

Patients with multiple metastatic brain tumors have a poor prognosis.[1–9] Brain tumor metastasis occurs in 20% to 40% of patients with cancer and its frequency has increased over time.[10–12] Intracranial metastasis is the most common brain tumor malignancy, affecting an estimated 1 million to 1.7 million people annually in the USA.[11] Based on the results of MRI examinations, 66% to 75% of brain metastases involve multiple lesions.[5] The mortality rate for multiple brain metastases is usually worse than for a single brain metastasis, and quality of life is also worse.[13] The mainstay of treatment for single and multiple brain metastases is whole brain radiotherapy (WBRT) plus steroids.[14,15] However, 50% of patients with multiple brain metastases who undergo WBRT still die due to persistent or recurrent brain metastases.[16] In addition, late neurotoxicity after WBRT treatment is common in long-surviving patients.[17] Thus, WBRT theoretically may decrease distant brain failure but it does not affect overall survival.

The treatment objective for multiple brain metastases is not only to increase survival time but also to improve the quality of life. Accordingly, we considered the outcomes and cost-effectiveness of gamma knife radiosurgery (GKRS) for brain metastases. GKRS is an effective modality for treating a single metastatic brain tumor; it has shown a high rate (80–92%) of tumor control.[18,19] However, compared with the literature discussing a single metastatic brain tumor, only a few reports have examined GKRS in the treatment of multiple metastatic brain tumors.[13,20–25] GKRS may also be valuable because of its effects on quality of life and its cost-effectiveness.[9,26,27] Given the above, we evaluated

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outcomes and cost-effectiveness for GKRS compared to WBRT in the treatment of multiple brain metastases.

2. Methods

Over the past 5 years, we treated 156 patients with metastatic brain tumors. The patients were not randomly allocated to each treatment group but were "freely" assigned to one of two treatment groups according to the preference of the referring doctor. The referring doctors (30) included 5 oncologists, 12 medical doctors and 13 surgeons. The authors were not involved in the selection of patients. We could not perform randomized trials with these patients with many different metastases in the terminal stage of their illness because of ethical and technical difficulties. Overall, patients were enrolled in the study with an approximate ratio of 1:2 for GKRS and WBRS. Although we did not assign patients randomly, it was still a prospective study. Group A ($n = 56$) underwent GKRS; group B ($n = 100$) underwent WBRT. Patients were enrolled in the study if they were 18 to 80 years old, had multiple metastatic brain tumors and a pre-operative Karnofsky performance scale (KPS) score of 50 to 100. Primary lesions and systemic metastatic lesions were evaluated by MRI, CT scan, single photoemission tomography (SPECT) or positron emission scan (PET) with fluoride deoxyglucose (FDG). If the tumor was more than 3 cm, caused mass effect and was accessible, an additional craniotomy was performed. To simplify the outcome evaluation, data from patients who were treated with combined GKRS and WBRT were excluded from this study.

2.1. Gamma knife radiosurgery

The neurosurgeons (Drs Lee and Cho) used a type C gamma knife (Leksell, Stockholm, Sweden) to excise metastatic brain tumors. We used its automatic positioning system (APS) for efficiency, accuracy and convenience. A head ring was set under local anesthesia on the morning of surgery and we completed the radiosurgical procedure by the afternoon. Usually patients were discharged on the morning of the next day. If brain swelling occurred, a low dose of steroid (dexamethasone, 0.5 mg) was administered for 2 to 4 weeks.

2.2. Whole brain radiotherapy

The radiation oncologists (Drs Yang and Liang) applied WBRT using a linear-accelerator. A total dose of 20 Gy to 50 Gy (median 30 Gy) was applied over 2 to 5 weeks. The radiation dose depended on tumor number, the presence of brain edema, and the patient's treatment tolerance. For example, the radiation dose was increased with the tumor number, but it was reduced, or even stopped, if there was local brain edema or poor patient tolerance.

2.3. Imaging examinations and follow-up

Tumor markers, whole-body bone scans, CT scans of the abdomen and chest, and single photon emission tomography (SPECT) or positron emission tomography (PET) were performed routinely. Regular follow-up was performed in the outpatient department (OPD). An MRI was arranged every 3 months during the first year and every 6 months thereafter. The follow-up time was set at 1200 days after treatment.

2.4. Clinical assessments

To classify the patients' pre-treatment status, we used a recursive partitioning analysis (RPA) system.[28] According to the Radiation Therapy Oncology Group (RTOG), the following criteria apply: Class I - KPS score $\geqslant$ 70, age < 65 years, control of primary origin, and no extracranial metastases; Class II - KPS score $\geqslant$ 70, age $\geqslant$ 65 years, poor control of primary origin or positive for extracranial metastases; Class III - KPS score < 70. Outcome analysis included mortality, survival time, neurological complications, post-treatment KPS score, quality-adjusted life years (QALY), total length of hospital stay, medical costs, and cost-effectiveness. The post-treatment KPS score was evaluated 6 months after treatment. The QALY score was assessed 1 years post-treatment by nursing specialist Miss Ho. The QALY score was measured as: normal life, score, 1; mild disability, 0.8; moderate disability, 0.5; severe disability, 0.3; vegetative state, 0.2, and mortality, 0.[26,29] The KPS score was measured as: normal life, 100; independent life, 70; and total disability, 0. Cost-effectiveness was measured as the medical cost divided by the QALY or KPS scores (Fig. 1). The medical cost included costs of the hospital stay and the OPD, which included the OPD imaging examinations. The cost of the hospital stay included the combined cost of the intensive care unit (ICU), the ordinary wards, and treatments (WBRT, GKRS and craniotomy).

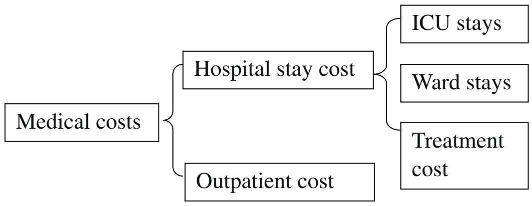

Fig. 1. The total medical cost comprised the cost of the hospital stay and outpatient treatment. The costs of the hospital stay included the intensive care unit costs (ICU), the ordinary ward costs, and treatment costs. The cost-effectiveness is equal to the medical costs divided by the number of quality-adjusted life years (QALY) (or post-operative Karnofsky performance scale, KPS, score).

The neurological complications were defined by the common terminology criteria (CTC) of adverse effect (version 3.0)[30], including mental status, cognition disturbance, speech impairment, motor or sensory neuropathy, cranial nerve neuropathy, CNS hemorrhage, and ischemia or necrosis, neuropathic pain, headache, dizziness, ataxia, tremor, seizures, hydrocephalus, and psychosis.

2.5. Statistical analyses

We used a paired t-test for comparisons. Survival time and survival rate were plotted by the Kaplan-Meier method and compared by a chi-squared (χ^2) test. The level of statistical significance was defined at $p < 0.05$.

3. Results

Table 1 shows the demographics of patients from both groups. The mean age (±standard deviation [s.d.]) of patients in the GKRS group was 58.8 ± 11.84 years; in the WBRT group it was 61.8 ± 13.46 years ($p = 0.24$). The most common tumors originated in the lungs, breast, and colon. The mean number (±s.d.) of tumors was 5.24 ± 3.10 for the GKRS group and 5.42 ± 3.80 for the WBRT group ($p = 0.73$). The median radiation dose was 28 Gy for the GKRS group and 30 Gy for the WBRT group ($p = 0.56$). The mean RPA grade was 2.09 for the GKRS group and 2.22 for the WBRT group ($p = 0.54$).

3.1. Mortality rate and survival time

Table 2 shows the outcomes for patients with multiple metastatic brain tumors in the GKRS and WBRT groups. The mortality

Table 1
Demographic data of 156 patients with multiple metastatic brain tumors treated with either GKRS or WBRT

	GKRS (n = 56)	WBRT (n = 100)	Probability (p =)
Age (mean ± s.d.)	58.8 ± 11.84	61.8 ± 13.46	0.24
M/F	20/36	42/58	0.11
GKRS/ WBRT (median) dose (Gy)	28	30	0.56
Tumor no. (mean)	5.24 ± 3.10	5.42 ± 3.80	0.73
2	18 (32.2%)	27 (27.0%)	–
3–5	20 (35.6%)	40 (40.0%)	–
⩾6	18 (32.2%)	33 (33.0%)	–
RPA (mean)	2.09	2.22	0.54
1	13 (23.2%)	18 (18.0%)	–
2	25 (44.6%)	42 (42.0%)	–
3	18 (32.2%)	40 (40.0%)	–
Pre-treatment KPS score (mean)	69.1	65.3	0.47
⩾70 (no.)	43 (76.8%)	68 (68.0%)	
<70 (no.)	13 (23.2%)	32 (32.0%)	
Tumor origins			
Lung	35 (62.5%)	64 (64.0%)	–
Breast	11 (19.6%)	7 (7.00%)	–
Colon–rectum	3 (5.35%)	9 (9.00%)	–
Kidney	4 (7.14%)	8 (8.00%)	–
Others	3 (5.35%)	10 (10.0%)	

F = female, GKRS = gamma knife radiosurgery, KPS = Karnofsky performance scale (KPS) score, M = male, RPA = recursive partitioning analysis, s.d. = standard deviation, WBRT = whole brain radiotherapy.

Table 2
Outcomes of 156 patients with multiple metastatic brain tumors treated with either GKRS or WBRT

	GKRS (n = 56)	WBRT (n = 100)	Probability (p =)
	Mean ± s.d.	Mean ± s.d.	
Mortality (n/total n)	45/56 (81.1%)	93/100 (93.0%)	0.05
Median survival time (months)	9.5	8,3	0.72
Neurological complications (n/total n)	3/56 (5.4%)	7/100 (7%)	0.73
Post-treatment KPS score	73.8 ± 13.2	45.5 ± 26.0	<0.01
QALY	0.76 ± 0.23	0.59 ± 0.18	<0.05
Length of stay (days)	26.4 ± 21.1	62.3 ± 52.5	<0.01
OPD (times)	16.0 ± 15.9	22.2 ± 22.7	0.55
Treatment cost (US$)	4,688 ± 2,201	2,799 ± 1,784	<0.05
OPD cost (US$)	1,104 ± 560	2,688 ± 1,836	0.54
Hospital stay cost (US$)	2,531 ± 1,596	4,910 ± 2,522	<0.05
All costs (US$)	8,323 ± 3,683	10,397 ± 4,782	0.32
Cost-effectiveness			
(US$/QALY)	10,831	17,622	<0.05
(US$/KPS)	139	229	<0.01

F = female, GKRS = gamma knife radiosurgery, KPS = Karnofsky performance scale score, M = male, OPD = outpatient department, QALY = quality-adjusted life years, RPA = recursive partitioning analysis, s.d. = standard deviation, WBRT = whole brain radiotherapy.

rate for patients in the group receiving the GKRS was 81.1%; for patients in the WBRT group it was 93.0% (p = 0.05). Extracranial causes of mortality occurred in 73.3% of patients in the GKRS group and 66.7% in the WBRT group. The mortality rate was significantly lower for patients in the GKRS group (74.4%) than in the WBRT group (97.1%) in patients with initial KPS scores ⩾ 70 (p = 0.02; Table 3). There were no significant between-group differences in mortality rates for patients with initial KPS scores < 70 (p = 1.00). The median survival time for patients receiving GKRS and WBRT was 9.5 months and 8.3 months, respectively (p = 0.72). The survival rate was plotted against survival time by the Kaplan-Meier method. There were no significant differences between patients in the GKRS and WBRT groups (p = 0.260; Fig. 2).

Table 3
Mortality rate associated with tumor number, KPS and RPA for multiple metastatic brain tumors in patients receiving either GKRS or WBRT

	GKRS (n = 56)	WBRT (n = 100)	Probability (p =)
	(Mortality%)	(Mortality%)	
Pre-treatment			
KPS < 70	13/13 (100%)	29/32 (90.6%)	1.00
KPS ⩾ 70	32/43 (74.4%)	66/68 (97.1%)	0.02
Tumor no.			
2–5	30/38 (78.9%)	64/67 (95.5%)	<0.05
⩾ 6	15/18 (83.3%)	29/33 (87.9%)	0.33
RPA			
1	11/13 (84.6%)	18/18 (100%)	0.43
2	16/25 (80.0%)	40/42 (95.2%)	0.09
3	18/18 (100%)	37/40 (92.5%)	1.00

F = female, GKRS = gamma knife radiosurgery, KPS = Karnofsky performance scale score, M = male, RPA = recursive partitioning analysis, WBRT = whole brain radiotherapy.

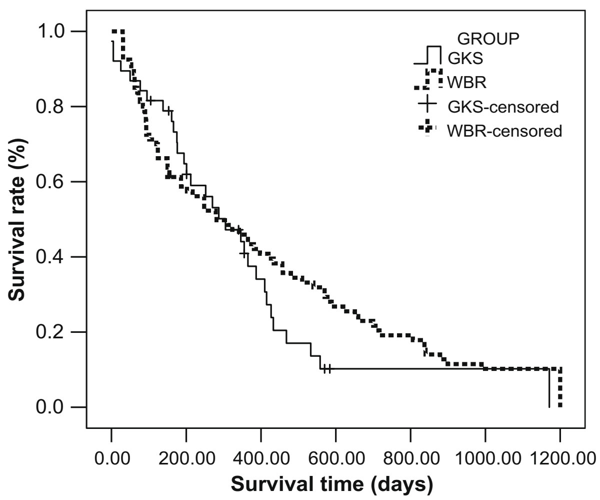

Fig. 2. The survival rate plotted against the survival time by the Kaplan-Meier method for patients receiving gamma knife radiosurgery (GKRS) and whole brain radiation therapy (WBRT). There were no statistical differences between the GKRS and WBRT groups [chi-squared (χ^2) test; p = 0.26). Solid line = GKRS, dotted line = WBRT; a vertical line through the plot indicates censored data.

However, in patients with 2 to 5 tumors, mortality was significantly lower for patients in the GKRS group (78.9%) than in the WBRT group (95.5%) ($p < 0.05$). There were no statistical differences between the GKRS and WBRT groups in RPA grading.

3.2. Surgical salvage

One patient with three metastatic lesions receiving GKRS needed a craniotomy to remove a frontal tumor. Only two patients receiving WBRT with multiple lesions needed craniotomy for decompression. There were no statistical differences in surgical salvage rate between groups.

3.3. Neurological complications

Three patients (5.4% of patients) receiving GKRS developed neurological complications: 1 had a severe headache and brain edema, 1 had mental confusion, and 1 had motor weakness, which were relieved by steroid treatment. Seven patients (7% of patients) receiving WBRT developed neurological complications: 3 patients had headaches and increased intracranial pressure, 1 had mental confusion, 1 had motor weakness, 1 had seizures, and 1 developed hydrocephalus. Except for the patient in the WBRT group with hydrocephalus who underwent subsequent shunt surgery, the remaining 6 patients with neurological complications were treated with steroids. There were no statistical differences in neurological complications ($p = 0.73$) between the GKRS and WBRT groups.

3.4. Post-treatment KPS score, QALY, hospital cost, and cost effectiveness

The mean (±s.d.) post-treatment KPS score was higher for the patients receiving GKRS (73.8 ± 13.2) than for patients receiving WBRT (45.5 ± 26.0) ($p < 0.01$). The QALY (mean ± s.d.) was 0.76 ± 0.23 for the GKRS group and 0.59 ± 0.18 for the WBRT group ($p < 0.05$; Table 2). The hospital stay was significantly shorter for patients in the GKRS group (26.4 ± 21.1 days) than in the WBRT group (62.3 ± 52.5 days) ($p < 0.05$). The mean medical cost was lower (US$8,323 ± US$3,683) for patients in the GKRS group than in the WBRT group (US$10,397 ± US$4,782) ($p = 0.032$). Furthermore, based on the QALY, the GKRS treatment was also more cost-effective (US$10,831/QALY) than WBRT (US$17,622/QALY), ($p < 0.05$). The cost-effectiveness based on the KPS score was also better in the GKRS group (US$139/KPS score) than in the WBRT group (US$229/KPS score) ($p < 0.01$).

4. Discussion

For patients with 2 to 5 tumors and who had an initial KPS score ⩾ 70, the mortality rate from multiple metastatic brain tumors was significantly lower for those patients receiving GKRS than WBRT. The post-treatment KPS score was also higher for patients who had received GKRS. The overall cost-effectiveness for the patients in the GKRS group was significantly higher than for patients in the WBRT group.

4.1. Mortality rate and survival time for GKRS and WBRT

Since 1954, external beam radiation has become the cornerstone of treatment for metastatic brain tumors.[1,9,31,32] For a single brain metastasis, the mean survival time after WBRT is only 4–7 months, whereas the mean survival time after GKRS is 6–11 months.[33] More than half the patients treated with WBRT die as a direct result of progressive systemic disease rather than from brain metastasis. However, the survival time for tumor resection after WBRT (8.7 months) is similar to that after GKRS (11 months).[10,18,19,34]

The median survival time for a multiple brain metastases is usually less than for single brain metastasis. Bhatagar et al. reported that the median survival time after GKRS for four or more intracranial metastasized tumors, with or without WBRT, was 8 months.[4] Jawahar et al. reported that the median survival time for a patient with 3–6 tumors was 12 months, and the period that the brain disease was controlled was 19 months.[31]

The difference in survival times between WBRT and WBRT plus GKRS is controversial. Hazard et al. reported that WBRT with additional GKRS did not increase the survival time for single or multiple metastases.[33] Varlotto et al. reported that WBRT given in addition to GKRS is associated with an improved local control rate for patients who have a tumor volume of > 2 mL, at a peripheral dose < 16 Gy, for a single brain tumor metastasis, radio-resistant tumors and especially for lung cancer metastasis.[12] However, in our study, we did not enrol patients who required combined GKRS and WBRT treatment.

Koal et al. reported that the median survival time for patients with RPA class I, II and III was: 7.1 months (single tumor metastasis 13.5 months vs. multiple tumor metastases 6.0 months); 4.2 months (single 8.1 months vs. multiple 4.1 months); and 2.3 months, respectively.[35] However, in our study, there was no statistical difference between the mortality rate associated with GKRS and WBRT treatments in each RPA classification. Local GKRS or WBRT treatment of metastatic brain tumors is not the only factor influencing outcomes: 50% of patients with metastatic brain tumors died from extracranial lesions.[18,19] In our study, an extracranial cause of mortality occurred in 73.3% of the GKRS group and 66.7% of the WBRT group.

Hasegawa et al. report that WBRT should not be part of the initial treatment for patients with one or two metastases, high KPS score, young age, and good control of the primary tumor, and they suggested that delaying WBRT treatment might improve quality of life.[36] In our study of patients with multiple brain metastases with an initial KPS score ⩾ 70 and between 2 and 5 tumors, the mortality rate was significantly lower for patients receiving GKRS than WBRT. The lower number of metastatic tumors means that the chance of metastasis spreading through the blood is reduced, thus increasing the survival time.[34] However, the radiation dose and side effects of GKRS for patients with > 5 tumors approaches those for WBRT.[24] In addition, Joseph et al. claimed that WBRT for 3 or 4 lesions was no more effective than GKRS.[37] An initial KPS score ⩾ 70 means that the brain disease was under control at that time.[27] It means that local treatment with GKRS is enough.

4.2. KPS, QALY, and cost effectiveness

In our study the post-treatment KPS scores were better for patients in the GKRS group than for the WBRT group because GKRS is a minimally invasive treatment for metastatic brain tumors, resulting in less focal edema than WBRT. Therefore, the functional outcome is also better for QALY in GKRS. The length of stay is longer in WBRT (62 days) then GKRS (26 days). Several reasons were proposed. First, in our study the WBRT course takes 2 weeks to 5 weeks (median 3 weeks). Inpatient treatment is preferred to reduce the transport burden for patients with multiple brain metastases due to advanced cancer or for those who are bed-ridden. Second, a worse post-treatment KPS score or QALY for patients receiving WBRT rather than GKRS may prolong the length of stay. In another study of single metastatic brain tumors, the costs of GKRS with WBRT and of a resection with WBRT were US$13,729 and US$27,523, respectively. The average cost-effectiveness, evaluated by US$/QALY was US$1,454 and US$5,102, respectively. In our study, the cost for GKRS was slightly lower than for WBRT, due to a shortened hospital stay. However, the overall cost-effectiveness was also greater for GKRS than for WBRT, primarily due to better post-treatment KPS scores and better QALY scores in the GKRS group.

4.3. Weakness and limitations

The main weakness of this study is patient selection. We attempted to "relatively randomize" patients by using the referring doctors' "free assignment" of patients to either GKRS or WBRT to reduce our study biases. The referring clinical doctors decide the entire treatment course, including surgery, medical treatment and chemotherapy. Although the demographics of both groups is similar when compared by univariate analysis, accumulative biases may exist in our study; for example, patients in the WBRT group are older, less likely to have 2 metastases, be in RPA class III and have a lower pre-treatment KPS score. Our comparison of cost-effectiveness of both treatments has limited application because different countries have different medical costs.

5. Conclusions

The mortality rate associated with multiple metastatic brain tumors is significantly lower for patients treated with GKRS than for those treated with WBRT (for patients with a good initial KPS score and between 2 and 5 tumors). Relative to WBRT, GKRS improves post-treatment KPS and, QALY, and increases treatment cost-effectiveness for multiple metastatic brain tumors.

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