J Neurosurg (Suppl) 102:262–265, 2005

Prolonged survival in a subgroup of patients with brain metastases treated by gamma knife surgery

C. P. Yu, M.D., Joel Y. C. Cheung, Ph.D., Josie F. K. Chan, B.N., Samuel C. L. Leung, M.D., and Robert T. K. Ho, M.D.

Gamma Knife Centre, Canossa Hospital, Hong Kong, China

Object. The authors analyzed the factors involved in determining prolonged survival (≥ 24 months) in patients with brain metastases treated by gamma knife surgery (GKS).

Methods. Between 1995 and 2003, a total of 116 patients underwent 167 GKS procedures for brain metastases. There was no special case selection. Smaller and larger lesions were treated with different protocols. The mean patient age was 56.9 years, the mean number of initial lesions was 3.15, and the mean lesion volume was 10.45 cm.^{3} The mean follow-up time was 9.2 months.

The median patient survival was 8.68 months. One-, 2-, 3-, 4-, and 5-year actuarial survival rates were 31.8%, 19.8%, 14.6%, 7.7%, and 6.9%, respectively. Patient age, number of lesions at presentation, and lesion volume had no influence on patient survival. Twenty-three (19.8%) patients survived for 24 months or more. Certain factors were associated with increased survival time. These were stable primary disease (21 of 23 patients), a long latency between diagnosis of the primary tumor and the occurrence of brain metastases (mean 28.4 months, median 16 months), absence of third-organ involvement, and repeated local procedures. Ten patients underwent repeated GKS (mean 3.4 per patient). Seven patients required open surgery for local treatment failures (recurrence or radiation necrosis). Two patients had both. Fifteen patients underwent repeated procedures.

Conclusions. Aggressive local therapy with GKS, repeated GKS, and GKS plus surgery can achieve increased survival in a subgroup of patients with stable primary disease, no third-organ involvement, and long primary-brain secondary intervals.

Key Words • gamma knife surgery • brain metastasis • radiosurgery • survival

Survival of patients with brain metastases has traditionally meant a dismal prognosis;[9] however, authors of several studies have reported a more prolonged survival (≤ 2 years) in a subgroup of patients.[5,12] Gamma knife surgery is now an established treatment modality for brain metastases. In this study, we aim as far as possible to analyze the characteristics of the patients, tumors, and treatment parameters associated with prolonged survival in patients with brain metastases.

Clinical Material and Methods

There were no predetermined patient selection criteria. We used two treatment protocols. The first was for patients with brain metastases with a volume less than 10 cm^3, whose lesions received 18 to 20 Gy to the 50% isodose line at the margin with a maximum dose of 36 to 40 Gy. The second protocol was for patients with lesions of 10 cm^3 or more. These lesions received 16 to 18 Gy at the 30% isodose line with a central dose of 53 to 60 Gy. For multiple lesions that could not be treated within one frame position, we treated one side first, removed the frame, and treated the other side on another date with a different frame position; usually 24 hours later. All patients received steroid agents, which consisted of dexamethasone 4 mg intravenously 30 minutes before frame placement, followed by an oral course of dexamethasone in decreasing dosages for 2 weeks. All patients underwent sequential magnetic resonance imaging follow up at 2- to 3-month intervals. We collected all patient data prospectively. We defined survival as the time from the initial GKS to time of death. Survivors living 2 years or more were then analyzed retrospectively to identify factors associated with their proven favorable prognosis.

Abbreviation used in this paper: GKS = gamma knife surgery.

Results

Between March 1995 and December 2003, a total of 116 patients underwent 167 GKS procedures for brain metastases. The mean age of patients at diagnosis was 56.9 years. The mean numbers of brain metastases per patient was 3.15. The mean volume of each brain metastasis was 10.45 cm^3. The median patient survival based on the Kaplan–Meier method was 8.68 months. Table 1 shows the 1-, 2-, 3-, 4-, and 5-year actuarial survival results. Twenty-three patients (19.8%) met our criteria for better/prolonged survival, that is 24 months or more. Table 2 shows a comparison of the differences in mean age, mean number of brain metastases per patient, and mean volume per lesion among three

TABLE 1

Actuarial survival rates for patients undergoing GKS

Survival (yrs)	No. of Patients	Percentage of Total
≥1	37	31.8
≥2	23	19.8
≥3	17	14.6
≥4	9	7.7
≥5	8	6.9

groups of patients. The groups were: poor survivors (< median), average survivors (> median), and the long-term survivors (> 2 years).

The primary cancers in the long-term survivors consisted of 14 lung, four breast, two kidney, two unknown, and one esophagus. There was no statistical difference in the relative incidence of primary tumor between the long-term and short-term survivors.

All long-term survivors had the following characteristics. 1) Twenty-two of 23 patients' primary cancer received curative resection and the patients remained free of local recurrence. The remaining patients' primary showed excellent response to chemotherapy. 2) There was a long latency period between the diagnosis of the primary tumor and the development of brain metastases (mean 28.4 months, median 16 months). 3) Twenty-two of these 23 patients showed no third-organ involvement. The remaining patient (primary from kidney) had a suspicious lung shadow, which remained stable for 6 years and may never have been a lung metastasis. 4) Repeated GKS was necessary for new brain metastases in 10 patients, with a mean of 3.4 procedures per patient. Open surgery was required for either local failure or radiation necrosis in seven patients, with no mortality or morbidity. Two patients required repeated GKS and open surgery. Both lived longer than 5 years. Overall, 15 (65%) of 23 underwent repeated local procedures.

Discussion

Which Factors Predict Better Survival?

The overall management of cancer patients with brain metastases has been advancing and improving with the evolution of medical technology. Gamma knife surgery is now an established treatment option.[2,6,7,9] Although active systemic disease is always associated with a poor outcome,

TABLE 2

Comparison among different survivors of age, number, and volume of brain metastases

Characteristic	Duration of Survival		
	< Median (8.69 mos)	> Median (8.69 mos)	≥ 2 Yrs
mean age	58.1	55.7	55
mean no. of brain metastases	3.2	3.0	3.0
mean vol of brain metastases	10.6	10.3	12.1

several reports have identified a subgroup of patients who are candidates for prolonged survival.[5,12,17,18] Our data confirm that controlled or inactive primary disease is important in long-term survival. The association of a long latency period between the initial diagnosis and development of a brain metastasis also agrees with the findings of other studies on metachronous compared with synchronous metastases.[4,19] Recent evidence also suggested that single-site metastasis can be a favorable factor.[1,11,14] None of our long-term surviving patients had third-organ involvement, which is equivalent to single-site metastasis. Why some cancers metastasize only to a single-site remains unknown.

Do Multiple Brain Metastases and/or Large Volume Brain Metastases Preclude Better Survival?

Thus far, the results of most radiosurgical series have indicated that solitary brain metastases and small tumor volumes were predictors of better survival.[3,9,10,13,15] In our series, the long-term survivors had a mean of three lesions, and the mean volume of the largest single lesion was 12 cm^3. The latter is equivalent to a 28-mm-diameter sphere. The high success rate with the larger tumors in this series may be related to a treatment protocol in which a higher central dose (up to 60 Gy) was used for the large volume because it was effective in gaining tumor shrinkage as well as in achieving better survival (our unpublished data) (Figs. 1 and 2).

Aggressive Local Therapy

Repeated local procedures were necessary for sustaining prolonged survival in patients in this series. This agrees with other Gamma Knife centers' experience.[16,20] Overall, 15 (65%) of the 23 long-term survivors required repeated GKS, surgery, or both as local therapy. Such data are impor-

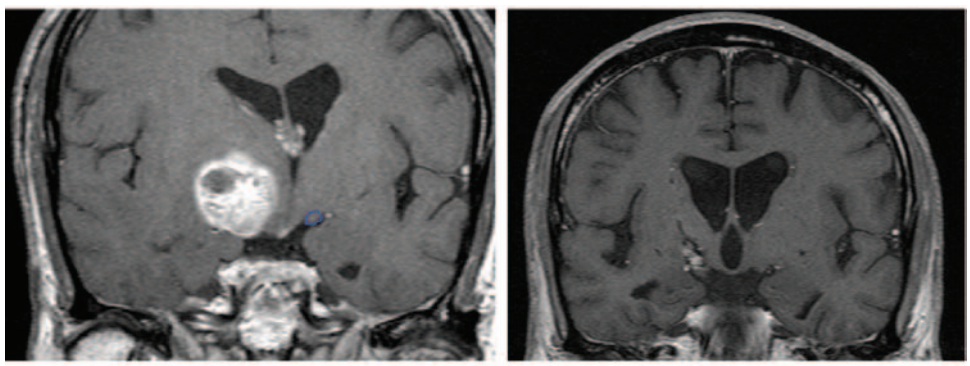

FIG. 1. *Left:* Magnetic resonance image revealing a large basal ganglia metastasis from lung carcinoma before treatment. *Right:* Rapid shrinkage of the tumor is seen at 3 months after GKS.

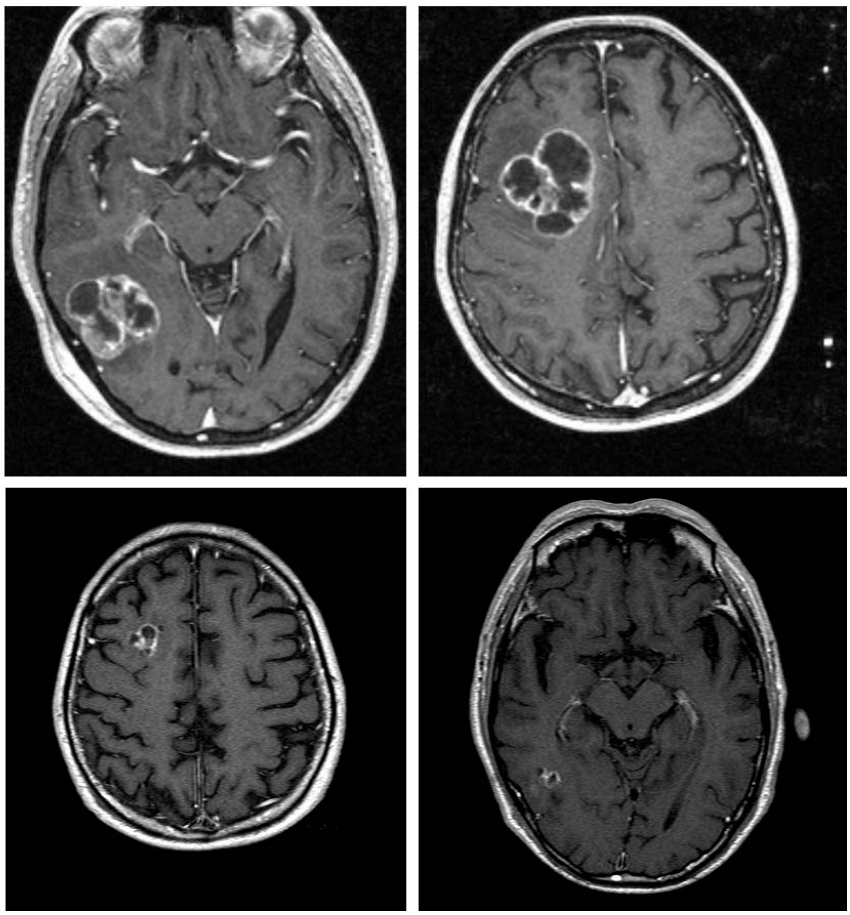

FIG. 2. *Left:* Magnetic resonance image revealing large right frontal and posterior temporal metastases from carcinoma of the esophagus before treatment. *Right:* Excellent volume shrinkage of both metastases is seen 3 months after GKS.

tant in advising the patient during the informed consent interview. For the potential long-term survivor candidates, the clinician must warn them that aggressive and repeated local therapy is to be expected.

Conclusions

This retrospective study with no sophisticated statistical analysis has its limitations; however, certain preliminary conclusions may be drawn. This study confirms the findings of others that patients with brain metastases who lived 24 months or longer after GKS were characterized by primary tumor control, single organ metastasis, and a long latency between primary diagnosis and development of metastases. It is suggested that aggressive local therapy can overcome the negative prognostic influence of multiple or large lesions. Intensive local therapy includes a higher integral radiation dose to larger lesions and a planned regimen of repeated local treatment when needed.

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Address reprint requests to: C. P. Yu, M.D., Gamma Knife Centre, Canossa Hospital, 1, Old Peak Road, Hong Kong, SAR, China. email:cpyu@thebraincentre.org.