In 1975, the first patient underwent GKS for a cerebral metastasis at the Karolinska Hospital, and the first reports from that group indicating good results on survival were published in 1989 and 1991. Prior to the advent of GKS, survival in patients with metastatic tumors to the brain was measured in weeks rather than months or years. Treatment on a larger scale of patients with brain metastases was started in 1988. At that time only CT scanning was available for tumor detection and dose planning. Delattre et al. reported that 89% of patients with secondary brain tumors had < 4 tumors visualized on CT when they first presented with neurological symptoms. Based on their findings, we therefore set an upper limit of 4 lesions for a patient to be a candidate for GKS and only in exceptional cases did patients harboring > 4 tumors receive treatment in the first years.

Time has proven radiosurgery to be a very useful tool in the management of brain metastases, yielding a high local tumor control rate. However, the fact that radiosurgery results in a high local tumor control rate does not necessarily translate into a prolonged survival time. The authors of a prospective randomized study concluded that a prolonged median survival time will result should single metastases to the brain be treated with radiosurgery and WBRT compared to using WBRT alone. A better quality of life (but not a prolonged survival) was shown in the same study in patients with 2–3 brain metastases. It has also been shown that the median survival time is similar in patients with ≤ 4 brain metastases, independent of having received radiosurgery alone compared to

Abbreviations used in this paper: GKS = Gamma Knife surgery; WBRT = whole-brain radiation therapy.
radiosurgery and WBRT. In their recently published paper, DiLuna and colleagues compared patients with 1–3 lesions to those with ≥ 4 lesions, and concluded that there was a significant difference in median survival time between the 2 groups.

The above studies conclude that radiosurgery should be considered in patients with ≤ 3–4 brain metastases. The issue of how to treat patients with > 4 metastases has not been addressed. Although the number of secondary tumors in the brain may be indicative of the aggressiveness of the primary disease, it seemed unlikely to us that a certain magic number of brain lesions would be more important in the prognosis than control of the primary tumor itself. This is, of course, provided that an effective treatment of metastases is available. We therefore hypothesized that control of the primary disease is much more important to survival than the number of metastases treated, and that repeated GKS is more effective than the addition of WBRT. We tried to resolve these issues in this long-term retrospective study with a large patient cohort.

Methods

Patient Population and Data Collection

Patient data were collected from a consecutive series of patients with metastases to the brain. The patients underwent GKS at 4 institutions: Karolinska Hospital in Stockholm, Sweden; St. Elisabeth Ziekenhuis, Tilburg, The Netherlands; Gamma Knife Zentrum, Frankfurt am Main, Germany; and West Virginia University. The data were obtained from telephone interviews, patient’s charts, and clinical visits. Computed tomography was used as the imaging technique until the late 1980s when we began to use MR imaging with high-dose (0.3 mmol/kg) Gd enhancement.25 The treatment protocol used was developed at Karolinska and transferred to the other institutions by 1 author (B.K.), who worked in all centers. All participating institutions used multiple isocenters for a highly conformal dose distribution, and defined the prescription dose as the dose covering at least 90–95% of the target volume. The prescription dose was 20–25 Gy for small-to-medium tumors, and lower for large tumors to avoid complications. The follow-up schedule was the same for all patients—an MR imaging examination and clinical evaluation was performed every 3 months after the treatment unless the patient’s deteriorating clinical condition made further treatments or diagnostic procedures meaningless.

The years of treatments were as follows: 1975–2001 at Karolinska (868 patients); 2001–2003 at Gamma Knife Zentrum (117 patients); 2002 to June 30, 2007, at St. Elisabeth Ziekenhuis (699 patients); and 2002–2007 at West Virginia University (237 patients), for a total of 1921 patients. No follow-up information was available in 58 patients, and in 8 patients not all cerebral lesions were treated, leaving 1855 patients (97%) eligible for inclusion in the study.

The patients included 977 women (53%), and 878 men. Based on the latest available information, 1655 patients (89%) have died. The most recent information on survivors is from earlier than January 1, 2007, in 57 patients and later than January 1, 2008, in 102 patients. Primary tumor control was defined by the referring physician, either based on a PET scan or other clinical, radiological, or laboratory data. If the intra- and extracerebral disease were simultaneously diagnosed, primary tumor control was defined based on the tumor response to subsequent treatment. Primary tumor control data were unavailable for the patients who underwent treatment at Karolinska.

Gamma Knife surgery was repeated in 415 patients (22%): 296 patients received 2 treatments, 80 patients received 3 treatments, 21 received 4, 17 received 5, and 1 patient received treatment 7 times, for a total of 2448 GKS procedures. The average number of GKS treatments was 1.32 per patient. There were 593 repeat GKS procedures performed in a total of 1914 patient years, amounting to 0.31 retreatments per patient year. Survival time was defined as the time between treatment and death in the patients who died, and the time between treatment and date of last available information in the other patients.

The age distribution was 19–90 years (median and mean 60 years). The primary tumors were as follows: lung cancer in 892 patients (48%), breast cancer in 223 (12%), renal cell carcinoma in 183 (10%), malignant melanoma in 169 (9%), and gastrointestinal cancer in 163 patients (9%). Other primary tumor locations were found in 110 (6%), and in 115 patients (6%) the primary tumor location was unknown. Patients with gastrointestinal cancer were on average 63 years old at treatment, with a mean number of 1.9 brain tumors per person. The average age and number of lesions in patients with renal cell carcinoma was 64 years and 2.3 lesions, 61 years and 2.5 lesions in patients with lung cancer, 56 years and 2.9 lesions in patients with malignant melanomas, and 54 years and 3.0 lesions in patients with breast cancer. Almost half of the patients, 860 (46%), had 1 brain lesion at the time of the first GKS; 411 (22%) had 2 lesions; 351 (19%) had 3–4 lesions; 183 (10%) had 5–8 lesions; and 50 (3%) had > 8 lesions, for a total of 4598 treated lesions. Information about whether there had been WBRT treatment prior to GKS was unavailable in 640 patients. The indication for GKS was local or distant tumor recurrence in the 231 patients who had undergone prior WBRT.

Statistical Analysis

Kaplan-Meier survival statistics were used to analyze survival. A difference in survival between 2 nominal parameters was analyzed with the log-rank test. The Mann-Whitney U-test was used to compare nominal and continuous data, and the Fisher exact test was used for nominal data. Differences were considered statistically significant for probability values < 0.01.

Results

Primary Tumor Control, Number of Brain Metastases, and Survival

The relationships between survival, number of brain lesions, and primary tumor control are shown in Fig. 1.
The median survival time was significantly longer for the 465 patients with controlled primary disease than the 458 patients with uncontrolled primary disease (9.8 vs 5.2 months, p < 0.0001). The median survival time was 8.6 months both for the 244 patients with multiple lesions and controlled primary disease as well as for the 52 patients with > 4 metastases and controlled primary disease, both significantly longer than the 5.4-month survival for the 164 patients with a single lesion and uncontrolled primary disease, (p < 0.0001 and 0.0015, respectively).

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The relationship between primary tumor control and number of brain metastases was also analyzed. The mean number of metastases in patients with controlled primary disease was 2.4, compared to 3.2 in patients with uncontrolled primary disease (p < 0.0001).

Number of Metastases and Survival

The median survival was 7.5 months in patients with a single lesion compared to 6.1 months in patients with multiple lesions (p < 0.0001). The significance disappeared when groups with controlled and uncontrolled primary disease were analyzed separately. A median survival of 12.1 months for single lesions and 8.6 months for multiple lesions was found in patients with controlled primary disease (p = 0.012). For patients with uncontrolled primary disease, the numbers were 5.4 and 5.1 months, again a nonsignificant difference (p = 0.62) There were no significant differences in median survival time between the groups of patients with 2, 3–4, 5–8, and > 8 metastases (Fig. 2).

A significant difference in survival time was found when patients with 1–2 metastases were compared to those with > 2 metastases (7.3 vs 5.8 months, p = 0.0001). However, there were no significant differences when patients were grouped according to other numbers of lesions (≤ 3 vs > 3 lesions or ≤ 4 vs > 4 lesions, for example).

Primary Tumor Location, Survival, and Primary Tumor Control

The relationship between primary tumor location, tumor control rate, and survival is shown in Table 1. Information is given for each primary tumor location as well as for controlled and uncontrolled primary disease. Patients with breast cancer and controlled primary disease had the longest median survival time, 15.1 months, while patients with gastrointestinal cancer and uncontrolled primary disease had the shortest, 3.2 months.

Patient Age, Number of Metastases, and Survival

Figure 3 illustrates the relationship between the age of the patient, the median survival time, and the number of metastases to the brain. The median survival of patients ≥ 60 years of age was 5.3 months, compared to 8.3 months in younger patients (p < 0.0001). There was also a significant relationship between age and successful
primary disease control. The mean age was 58.9 years in patients with controlled primary disease versus 60.8 years in patients with uncontrolled primary disease (p = 0.0081).

Previous WBRT

The median survival was 7.4 months in patients who had undergone WBRT before GKS, which did not significantly differ from the 7.0 months in patients who had not (p = 0.43). Fifty-seven of the 231 patients (25%) in whom WBRT preceded GKS underwent repeated GKS, compared to 22% (212 of 984) of those who had not undergone any previous radiation treatment before the first GKS. This difference was not statistically significant (p = 0.31).

Small Cell Versus Non–Small Cell Lung Cancer

There was a significantly higher fraction of patients with small cell lung cancer who had undergone previous WBRT as compared to patients with non–small cell lung cancer (Table 2). There were, however, no significant differences in median survival, number of brain metastases, and need for repeated GKS between the 2 groups of patients.

Longer Survival in the More Recently Treated Patients

The median survival period was 6.3 months in the 437 patients treated between 1975 and 1995, 6.1 months for the 430 patients treated between 1996 and 2001, and 7.0 months for the 988 patients treated in 2002 and later. For patients with single metastases, the numbers were as follows: 6.5 months for the 251 patients treated between 1975 and 1995, 7.7 months for the 206 patients treated between 1996 and 2001, and 8.0 months for the 403 patients treated in 2002 and later.

Number of GKS Treatments and Number of Metastases

There was no statistically significant relationship between the number of brain metastases at the first treatment and the total number of GKS treatments. Patients with 1 metastasis received 1.31 treatments on average, patients with 2 lesions received 1.37 treatments, patients with 3–4 lesions received 1.32, patients with 5–8 lesions received 1.32, patients with 9–16 lesions received 1.43, and patients with more than 16 lesions received 1.51 treatments.

<table>
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<th>Characteristic</th>
<th>No. of Patients W/ SCLC</th>
<th>No. of Patients W/ NSCLC</th>
<th>p Value</th>
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<td>251</td>
<td>0.40</td>
</tr>
<tr>
<td>median age at 1st GKS</td>
<td>66.7</td>
<td>63.5</td>
<td>0.14</td>
</tr>
<tr>
<td>median survival (mos) at 1st GKS</td>
<td>5.8</td>
<td>5.6</td>
<td>0.27</td>
</tr>
<tr>
<td>underwent repeated GKS</td>
<td>11%</td>
<td>21%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* NSCLC = non–small cell lung cancer; SCLC = small cell lung cancer.
received 1.31, and those with > 8 metastases underwent an average of 1.08 GKS treatments.

Long-Term Survivors

There were long-term survivors among patients with metastases to the brain. The percentages of patients with 1, 2, 3, and 5 years’ median survival time after the first GKS treatment are shown in Table 3. Survival data are given for the whole patient population, for patients with single and multiple metastases to the brain, and for those with controlled versus uncontrolled primary disease. Survival in patients with breast cancer was also analyzed separately. There was a 15% 2-year survival rate in the whole patient population, and a 9% 5-year survival rate in patients with controlled primary disease. Historical data concerning outcomes after WBRT alone are given for comparison.

Discussion

Survival, Primary Tumor, and Patient Age

The impact of age is analyzed using univariate survival analysis in most studies, which requires that the continuous parameter age has to be redefined as a 2-group parameter (younger or older than an arbitrarily defined break point). Aoyama et al., Nam et al., and Saito et al. all used 65 years as the break point and found no influence of age on survival. In contrast, Noordijk and colleagues and Andrews et al. found a significant relationship between age and survival when 60 years of age was used as the break point.

Lagerwaard et al. had the advantage of a large patient population (1292 patients), which they divided into 3 groups as follows: patients ≤ 60 years of age, patients 60–69 years of age, and patients > 70 years. They found a median survival of 3.9, 3.3, and 2.6 months, respectively, compared to 8.3, 5.6, and 4.6 months found in the present study. Thus, it seems likely that survival is unrelated to age in patients up to ~ 60 years, after which the median survival time decreases in a linear fashion by ~ 1 month for every 10 years of age. This decrease in survival does not seem to be explained by different patterns of care.

Survival and Number of Brain Lesions

As mentioned above, a strong relationship was found between the number of brain lesions and survival, as well as between the number of brain metastases and primary tumor control. Thus, the parameters of controlled primary disease and number of metastases to the brain are covariates; that is, patients with uncontrolled primary disease are more likely to harbor a larger number of brain lesions than patients in whom the primary tumor is controlled. So which is the more important of the two? The findings illustrated in Fig. 1 suggest that primary tumor control is more important for survival time than the number of brain lesions. A firm conclusion cannot be drawn from this data, however, because primary tumor status was only known in 923 patients, which is less than half of the total patient cohort. Certainly, significant relationships may be undetected if too few patients are analyzed, as has been pointed out by Patchell et al. in their criticism of the conclusions drawn by Aoyama and colleagues in their study of 132 patients. The same criticism applies to the work of Andrews et al., who analyzed 131 cases of multiple metastases to the brain. The study failed to show a prolonged survival for patients with 2–3 brain metastases receiving radiosurgery and WBRT compared to WBRT alone. However, based on our findings, it is likely that a prolonged survival after radiosurgery would have been found should more patients have been analyzed, especially if patients with controlled extracerebral disease would have been included. We therefore believe that it is more appropriate to use primary tumor control as a limiting parameter for GKS than the number of brain metastases, but a prospective randomized study is probably necessary before any definite conclusions can be drawn.
Using Number of Metastases to Define the Upper Limit of Radiosurgery

The benefits of using GKS in patients with a single metastasis to the brain is now well-established. Most authors agree that GKS should also be considered in patients with 2–3 brain metastases, but that minimal benefit can be expected if the number of brain lesions exceeds 3 or 4. This dogma is so well-established that the mere fact that a radiosurgical study is limited to patients with ≤ 4 brain metastases has been taken as evidence that patients with > 4 brain metastases should instead receive WBRT. In an editorial commenting on the work of Aoyama et al.,3 Raizer23 concluded that “patients with more than 4 metastases should continue to be treated with WBRT.”

The present study and others challenge this philosophy.1,4 We have found long-term survivors among patients with > 4 cerebral metastases who underwent GKS. Of patients with > 4 metastases, 48 (21%) survived or are still alive ≥ 1 year after treatment. The 10% survival time was 27 months and the 5% was 43 months. One patient remains alive after having undergone GKS for 8 cerebral lesions in early 1994, and an additional lesion in late 1994. As seen in Fig. 4, there have been no significant white matter changes in this patient in the 11 years since the 2 GKS treatments for a total of 9 metastases.

Dogmatic Versus Pragmatic Use of WBRT

All patients included in the present study underwent GKS for all visible lesions and underwent imaging follow-up every 3 months thereafter; prophylactic WBRT was not used. A major drawback to this management choice is that micrometastases are potentially left untreated. However, we have not seen any significant clinical disadvantage to MR surveillance and subsequent appropriate management of new lesions (WBRT, GKS, or no treatment) should they develop.10 Still, many authors advocate prophylactic WBRT to treat potential micrometastases with the rationale of avoiding a situation in which micrometastases develop into multiple new visible lesions that can no longer be treated with either radiosurgery or WBRT. In reality, the risk of this occurring seems minimal because we have not encountered it as a clinical problem.

Why do so many advocate prophylactic WBRT if there are no significant disadvantages to omitting it? One could argue that WBRT: 1) controls potential micrometastases, and 2) that these micrometastases represent a bigger threat to the patient than the migration of new tumor cells into the brain. If this were true then the likelihood of a patient needing a second GKS would be lower, the number of lesions fewer, and the time between the first and second treatment would be longer in patients who had previously undergone WBRT compared to those who had not; this was not the case, however. We earlier concluded that the incidence of repeated GKS treatments was the same in patients who received WBRT and those who did not. The mean number of lesions was 3.5 in the patients who had received WBRT compared to 2.5 in those who did not (p = 0.0002). There was no significant difference in time between the first and second treatment between the groups, 7.3 months with WBRT versus 8.6 months without it (p = 0.19). Selection bias might have influenced the numbers above, but it is still reasonable to conclude that if a disadvantage to omitting WBRT exists, it is very limited.

When WBRT is given prophylactically, some patients benefit from it, some do not, and some experience side effects. The challenge is not only to define which patients will benefit, but also to determine the optimal timing of the treatment, as it can be given once only. We do not understand the general perception that WBRT must be given immediately or not at all. For example, in Slotman and colleagues’26 study, patients with small cell lung carcinomas without evidence of metastases to the brain were randomized to either initial WBRT or no treatment at all. The results were that symptomatic brain metastases developed in 24 of the 143 patients who received WBRT and in 59 of the 143 patients who were untreated. If WBRT controls micrometastases, then it follows that the new tumor cells must have migrated to the brain after WBRT in the 24 patients in whom the treatment failed. Thus, 35 (24%) of 143 patients benefitted from prophylactic WBRT, 84 (59%) received unnecessary treatment, and 24 patients (17%) in whom new tumor cells migrated to...
Gamma Knife surgery for metastases to the brain

the brain were disadvantaged by the prophylactic WBRT, as the treatment was no longer an option when symptoms arose. The results would have been better, the number of treated patients fewer, and side effects avoided in patients in whom the treatment was not indicated if instead of prophylactic WBRT the patients had undergone frequent MR imaging surveillance until there was evidence of metastatic lesions.

An argument seldom mentioned is the increased toxicity of combining WBRT with radiosurgery. This increased risk prompts many to decrease the radiosurgical dose when both treatment modalities are given. The magnitude of the increased toxicity is difficult to assess in patients with brain metastases because of the typically short survival time and the fact that tumor recurrences and radiation-induced complications have the same appearance on MR images as on CT scans. We can approximate the magnitude of the increased risk by examining the case of 14 patients with arteriovenous malformations who underwent GKS after radiation therapy. Complications developed in 4 patients, and radiation-induced edema developed in another 3, which should be compared with the calculated cumulative risk for complications, 0.81, based on our arterious malformation risk estimation. We can therefore conclude that the radiation toxicity is increased if GKS is combined with WBRT.

Micrometastases and GKS

Fifty-two percent of our patients (112 of 215) who underwent observation for ≥2 years received GKS a second time, and in the great majority of cases this was due to distant recurrences. We can assume that most of these lesions would have appeared within the first 6 months to a year after the first GKS if micrometastases had been the most significant source, and later if new hematogenous seeding was more common. Fifteen patients were treated within 6 months, 57 within 1 year, and 55 underwent retreatment 1 year after the first surgery, suggesting that new hematogenous seeding is a larger threat for long-term survivors than micrometastases.

This finding is illustrated graphically in Fig. 5, with the patients grouped based on observation time. It can be seen that the fraction of patients who need a second GKS treatment increases with time to ~50% at 2 years, and then stabilizes thereafter. The graph also shows the percentage of retreatments within 6 months of the first GKS and the percentage of risk time constituted by the first 6 months after the first GKS. These 2 values are similar in each group, suggesting that the development of new tumors is evenly distributed in time. A boost of new tumors within the first 6 months, which would have been the expected result from untreated micrometastases should they have existed, could not be seen. Therefore, survival time

![Fig. 5. Bar graph of the patient population grouped according to observation time in months (x axis). The percentages of patients treated with a second GKS is given for each group. The percentage of retreatments occurring within the first 6 months after GKS is illustrated. For comparison, the percentage of time at risk that the first 6 months constitutes (for example, 50% if time at risk is 1 year and 25% if time at risk is 2 years) is also illustrated. Note that repeated treatments are evenly distributed in time.](image)
is a more important factor for distant recurrences than the potential presence of micrometastases, and new hematogenous seeding is the main risk factor for developing new lesions for long-term survivors.

**Different Radiosurgery Techniques**

The local tumor control rate after radiosurgery is dependent on the radiation dose given to the tumor, and thus independent of the equipment used. The decisive factor for complications is the total dose delivered, which increases with increasing number and volume of tumors. It is therefore important to keep the dose to the extratumoral tissue low, especially when multiple tumors are treated. The radiation dose between lesions can be significant in linear accelerator radiosurgery of multiple cerebral lesions, especially if the lesions are eccentrically located. A cumulative dose of 40 Gy to the extratumoral tissue has been reported when multiple lesions are treated despite the fact that the maximum prescribed tumoral dose was 22 Gy. Thus, there is an upper limit to how many lesions can be safely treated with linear accelerator radiosurgery. The situation is different for GKS. Due to the multiplanar radiation distribution from 201 sources, the extratumoral dose is lower than the dose to the target volume, allowing more metastases to be treated before the integral dose to the brain is too high. It has been shown that the integral dose is acceptable even if > 10 lesions are treated.

**Long-Term Survivors**

We observed that 48 (2.6%) of 1855 patients survived for > 5 years, and 25 patients survived for > 10 years after GKS. Other authors have reported observed long-term survivors among patients with brain metastases as well. Chao et al. reported long-term survival in 32 (2.5%) of 1288 patients, and Lutterbach and colleagues noted 12 (1.3%) of their 916 patients survived ≥ 5 years after surgery, WBRT, or radiosurgery of brain metastases. We found that the patients who received treatment most recently had longer survival periods, presumably because of more efficient systemic treatments. This improvement is likely to continue, and it is therefore likely that the 9% 5-year survival rate in patients with controlled primary disease and the 4% 5-year survival rate in patients with multiple metastases will increase in the future. One consequence of this is that long-term toxicity after treatment of metastases to the brain will become even more important in the future. It has been shown that GKS does not cause any long-term intellectual sequelae, while the opposite is true of WBRT. In Fig. 4 no white matter changes can be seen in a patient 11 years after GKS for 9 metastases. This finding implies that the value of repeated GKS for brain metastases will increase with time, and that WBRT should be used more for patients with documented brain disease not suitable for GKS than as a prophylactic treatment.

**Conclusions**

Patient age and primary tumor control status are the decisive factors for survival in patients with metastatic cancer to the brain. The number of brain metastases should not be used as a criterion to judge who will benefit from GKS and who will not. There are long-term survivors found among patients with multiple brain metastases. Micrometastases is a limited clinical problem that does not justify a prophylactic treatment. Instead, regular follow-up imaging after GKS and management of potential new lesions with the optimal treatments as they are discovered (WBRT, GKS, or no treatment) should be recommended.

**Disclosure**

Drs. Karlsson and Lindquist serve as consultants to Elekta Instrument AB.

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Accepted October 6, 2008.
Please include this information when citing this paper: published online February 6, 2009; DOI: 10.3171/2008.10.JNS08214.
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