

REVIEW ARTICLE

Stereotactic radiosurgery for the treatment of brain metastases: impact of cerebral disease burden on survival

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Abstract

Stereotactic radiosurgery (SRS) for brain metastases has been carried out at the Leeds Gamma Knife Centre since March 2009. The aim of this study was to examine the outcomes and toxicity in our initial cohort of patients. The medical records of patients with brain metastases referred to the Leeds Gamma Knife Centre between March 2009 and July 2010 were retrospectively reviewed. Data on survival, primary tumour, Karnofsky performance status, time from diagnosis to identification of brain metastases, previous treatment for brain metastases and results of staging prior to SRS were recorded. Patients were followed up with regular magnetic resonance imaging of the brain for a minimum of 6 months and data on toxicity and oral steroid dose were recorded. Statistical analysis was carried out using SPSS v14.0. Survival curves were compared using the Log Rank test. Fifty eight patients (19 male) had a median survival of 50.4 weeks (95% CI, 32.6–68.2 weeks). Lung (36%) and breast (27%) were the most common primary tumours. Patients with a total volume of metastases treated $< 5000 \text{ mm}^3$ ($p = 0.007$) or between 5000 mm^3 and 10000 mm^3 ($p = 0.01$) had significantly improved survival compared with patients with a total treated volume $> 10000 \text{ mm}^3$. In addition, largest treated lesion $< 5000 \text{ mm}^3$ was a positive prognostic factor. Patients with a single metastasis did not survive significantly longer than those with multiple metastases. Steroid dose dropped significantly after SRS ($p < 0.01$) and was the same or less in 91% of patients. There were only three cases of grade 3 toxicity. Our study reports survival comparable with other series on radiosurgery and demonstrates a significant decrease in steroid dose following treatment. It also shows that the size of the largest treated metastasis and total volume of metastatic disease seemed a better predictor of outcome than number of metastases treated.

Keywords: brain metastasis; gamma knife; radiosurgery; intracranial metastasis

Introduction

Brain metastases are a significant cause of mortality and morbidity in patients with solid tumours. Between 20% and 40% of patients with metastatic cancer will have brain metastases

at autopsy,¹ however, the incidence varies depending on the primary site of the tumour. The management of patients with brain metastases will depend on many factors including: the number, site and size of metastases as well as the patient's performance status (PS) and the extent, prognosis and treatability of any extra cranial disease. Some of these factors are used in prognostic scoring systems such as the recursive partitioning analysis (RPA) classification, which assess a patient's PS, age and the extent of extracranial disease.^{2,3} Interestingly, the RPA does not consider intracranial disease although the score index for radiosurgery (SIR) does include the number of lesions and size of the largest single metastasis in addition to age, Karnofsky performance status (KPS) and the extent of systemic disease.⁴

Corticosteroids can be used to improve the symptoms of brain metastases by reducing cerebral oedema but without further treatment, the effect rapidly reduces as the tumour burden increases. Patients frequently experience unpleasant steroid-induced side effects, such as agitation, wakefulness, weight gain, proximal myopathy, bruising, and symptomatic glucose intolerance. These side effects are usually dose dependent.⁵

Whole brain radiotherapy (WBRT) has been used for many years to treat patients with brain metastases despite a lack of randomised data comparing it to best supportive care. This is currently the subject of the national Quality of Life after Treatment of Brain Metastases (QUARTZ) trial in patients with lung cancer.^{6,7}

Surgical resection of brain metastases may benefit some patients, particularly those with a solitary metastasis causing raised intracranial pressure, where decompression produces rapid symptom relief. In these cases, surgery followed by WBRT has been shown to significantly prolong survival and functional independence compared to WBRT alone.⁸

Stereotactic radiosurgery (SRS) has emerged as a treatment for brain metastases in the last 20 years. SRS precisely delivers a single high dose of radiation to a small target while sparing surrounding tissue. It is generally considered suitable for metastases $< 3 \text{ cm}$ in size that are radiographically discrete. SRS can control multiple brain metastases without

the neurological side effects of WBRT or the need for invasive surgery.⁹ Uncontrolled studies have shown local control rates of around 85% at 1 year.^{10,11} One study demonstrated a median survival of 11 months following radiosurgery for solitary brain metastases with significantly better outcomes for patients with breast cancer.⁹

A randomised controlled trial by Andrews et al. of WBRT versus WBRT and SRS in patients with up to three brain metastases demonstrated that WBRT and SRS improved survival in patients with a solitary metastasis. Moreover, patients who received SRS had a significant decrease in steroid dose and improved performance status at 6 months.¹²

Most of the major randomised trials evaluating SRS in brain metastases have selected patients with up to 3 metastases. Consequently, the commissioners of SRS services in the United Kingdom tend to restrict funding to this patient group. Some areas have even more restrictive criteria. While this is relatively convenient, it ignores other important prognostic factors that may be highly favourable in a particular patient. There continues to be controversy about the importance of the number of metastases compared to the volume of disease as prognostic factors. As larger metastases are harder to control than smaller ones, it is plausible that SRS may be more effective at treating two or three metastases of an equivalent total volume to one large metastasis.

This is a retrospective audit of the first 58 patients with brain metastases to be treated with SRS at the Leeds Gamma Knife Centre. The aim of this study was to determine the level of acute toxicity in patients undergoing SRS. We also assessed various prognostic factors including the impact of cerebral disease load on survival.

Methods

The medical records of all patients with brain metastases referred to the Leeds Gamma Knife Centre between March 2009 and July 2010 were retrospectively reviewed. Patients with brain metastases were referred for consideration of SRS if they had a KPS ≥ 70 and a prognosis of greater than 6 months as defined by their tumour site specific team. Patients were also required to have three or fewer brain metastases, each < 3 cm in diameter. Patients with more than three brain metastases were occasionally considered, if they were exceptionally fit with no extra-cranial disease. Those who had previously undergone WBRT for brain metastases were considered for SRS, if they had a good KPS and their disease was otherwise well controlled.

Information on KPS, primary tumour, dates of initial diagnosis and diagnosis of brain metastases, previous treatment for brain metastases, oral steroid dose at time of SRS, results of magnetic resonance imaging (MRI) of the brain and a staging computed tomography (CT) scan to assess for the presence of extra-cranial disease prior to SRS were recorded.

Patients were followed up after 8 weeks and then every 3 months thereafter until January 2011 with MRI brain. Most patients were followed up at the Leeds Gamma Knife centre; when this was not the case, follow up MRI data were obtained from the referring centre. Median follow-up was 55 weeks. Data on treatment toxicity and oral steroid dose were

prospectively collected at the first follow-up appointment. Toxicity questionnaires were not used to assess patients until August 2009, so only 39 questionnaires were available.

Radiosurgical technique

On the day of radiosurgery, patients were cannulated and given 1 mg oral lorazepam as a sedative. A Leksell stereotactic G frame was fitted under local anaesthetic by the treating clinical oncologist. T1 weighted MRI with gadolinium contrast enhancement, with 1.5 mm slices of whole brain, was carried out. The images were reviewed by a consultant oncologist and radiologist to determine the number of metastases. The Leksell GammaPlan PFX™ treatment planning system was used to outline individual lesions and determine their volume. No margins were added. Shots were placed to achieve at least 98% coverage of the targets with the prescription isodose. Leksell Gamma Knife Perfexion™ was used for treatment. Doses of 18–24 Gy were delivered to the prescription isodose (16–20 Gy if prior whole brain radiotherapy). Prophylactic anti-epileptics were not prescribed. Patients on steroids prior to treatment were given a reducing course to follow over the next few weeks. Patients not requiring steroids prior to treatment received a bolus dose of dexamethasone on the day only.

Statistics

Survival analysis was performed using SPSS v 14.0. Kaplan-Meier survival curves were plotted, with survival being defined as time from first Gamma Knife treatment to death. Curves were compared using the Log-Rank test. Steroid dose before and after SRS were compared using a two-sided t-test.

Results

A total of 152 brain metastases were treated in 58 patients with SRS at the Leeds Gamma Knife Centre between March 2009 and July 2010. The demographics of these patients are shown in Table I. One patient had a KPS of 60 at the time of initial assessment for SRS following surgery for his primary

Table I. Characteristics of the 58 patients who underwent SRS for brain metastases.

| | |
|------------------|-------------|
| Age | |
| Median | 62 years |
| Range | 30–83 years |
| Sex | |
| Male | 19 (33%) |
| Female | 39 (67%) |
| KPS | |
| 100 | 19 (33%) |
| 90 | 19 (33%) |
| 80 | 10 (17%) |
| 70 | 6 (10%) |
| 60 | 1 (2%) |
| Not recorded | 3 (5%) |
| Primary tumour | |
| Lung | 21 (36%) |
| Breast | 16 (28%) |
| Melanoma | 7 (12%) |
| Renal | 5 (8%) |
| Ovarian | 5 (8%) |
| Gastrointestinal | 4 (7%) |
| Unknown primary | 1 (2%) |

KPS, Karnofsky performance status

tumour, however, 3 weeks later he was re-assessed and his KPS had improved to 70.

Median survival was 50.4 weeks after SRS (95% CI, 32.6–68.2 weeks). Median survival varied between primary tumour site (Table II) although there was no significant difference in survival between groups.

Patients who had < 5000 mm³ of brain metastases treated with SRS survived significantly longer than those in whom the total volume treated was more than 10 000 mm³ ($p = 0.007$). Patients with a total treated volume between 5000 mm³ and 10 000 mm³ also had significantly improved survival compared to those with a treated volume > 10 000 mm³ ($p = 0.01$) (Fig. 1). Patients whose largest treated metastasis was < 5000 mm³ had improved survival compared to patients whose largest treated metastasis was over 10 000 mm³ ($p = 0.001$) (Fig. 2). Patients with a single metastasis did not survive significantly longer than those with multiple metastases (Fig. 3).

The median time from initial diagnosis to the diagnosis of brain metastases was 56 weeks (range 0–470 weeks). Fig. 4 shows that there was a trend towards improved survival in patients who developed brain metastases more than 1 year after the initial diagnosis of cancer compared to those who had brain metastases within 1 year of initial diagnosis, although this was not statistically significant ($p = 0.07$).

Twenty-nine patients (50%) had extra-cranial disease at the time of SRS. There was no significant difference in survival in patients with or without extra-cranial disease at the time of SRS.

Seven patients (12%) had WBRT prior to SRS. These patients had an average survival of 54.2 weeks from their salvage SRS (95% CI, 41.6–66.8 weeks). There was a trend towards improved survival in these patients compared to those who did not have previous WBRT however, this was not significant ($p = 0.09$). These were a highly selected group of patients who had long survival following WBRT. During the relatively short follow up in this study, nine patients (16%) had WBRT following SRS and five patients had more than one SRS treatment. Average time to further radiotherapy for brain metastases was 17 weeks.

Sixteen patients (28%) had new brain metastases visible on MRI at first follow-up and 8 (14%) patients had new brain metastases at their second MRI.

Thirty-nine side effects questionnaires were completed. Three patients filled out 2 questionnaires as they had more than one SRS treatment. The results are shown in Table III. The toxicities experienced by patients who had undergone SRS for brain metastases were generally very mild with only three patients experiencing grade 3 toxicity.

Table II. The median survival of patients with brain metastases by the site of the primary tumour. There was no statistically significant difference in survival depending on the primary tumour site.

| Primary tumour | Median survival (weeks) |
|------------------|-------------------------|
| Lung | 32.0 |
| Breast | 59.5 |
| Melanoma | 27.0 |
| Ovarian | 39.7 |
| Renal | 43.7 |
| Gastrointestinal | 20.1 |
| Unknown | 28.1 |

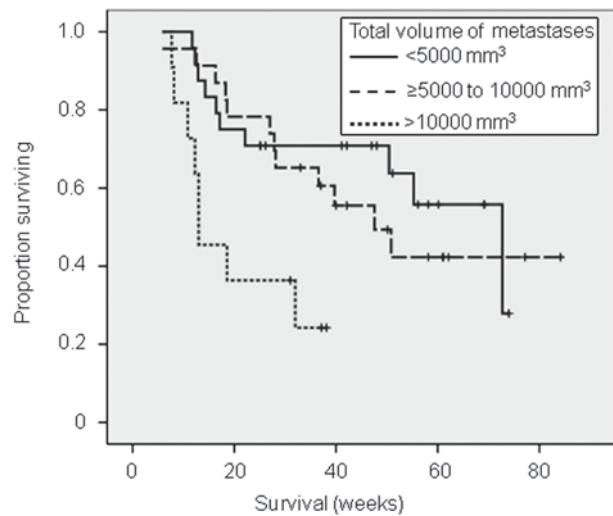


Fig. 1. Kaplan-Meier graph comparing survival by the total volume of brain metastases treated with radiosurgery. Patients with a total treated volume of metastases < 5000 mm³ ($p = 0.007$) or ≥ 5000 to 10 000 mm³ ($p = 0.01$) had improved survival compared to patients with a total treated volume > 10 000 mm³.

Data on oral steroid dose was available for 50 patients (86%) at their first follow-up appointment. Oral steroid dose was significantly decreased at first follow-up ($p = 0.007$) and 44 patients (76%) were on the same or a reduced dose compared to before SRS.

Discussion

Brain metastases are a common cause of morbidity and mortality in patients with solid tumours. There are different treatment options depending on the number, size and location of brain metastases and on the general condition of the patient. Stereotactic radiosurgery is increasingly used to treat brain metastases as it avoids many of the side effects of whole brain radiotherapy or the need for invasive surgery.^{9,11,13}

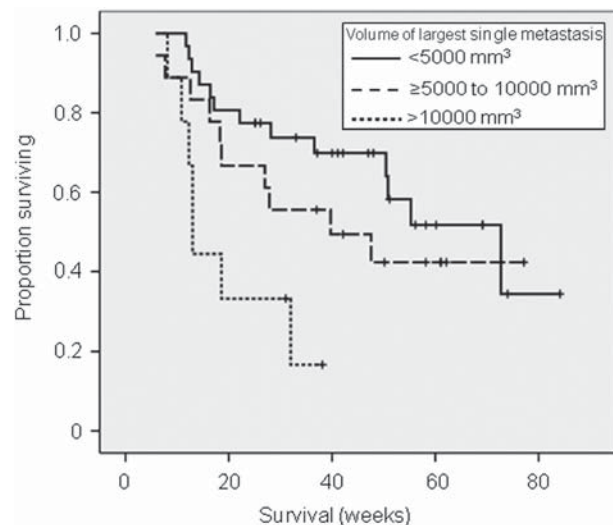


Fig. 2. Kaplan-Meier graph of survival by the size of the largest single metastasis treated with radiosurgery. A largest treated metastasis < 5000 mm³ compared to > 10 000 mm³ conferred a survival advantage ($p = 0.01$). Largest treated metastasis 5000–10 000 mm³ was not significant compared to < 5000 mm³ ($p = 0.3$) or > 10 000 mm³ ($p = 0.07$).

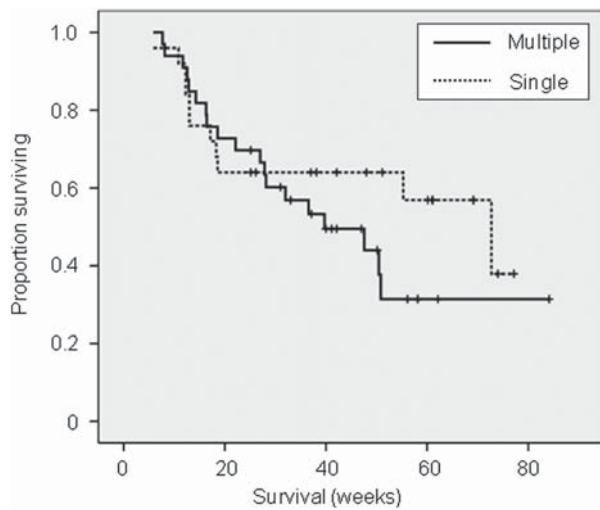


Fig. 3. Kaplan-Meier graph of survival following radiosurgery in patients with single compared with multiple metastases. There was no significant difference in survival ($p = 0.7$).

This study looked at the outcomes of the first 58 patients treated at the Leeds Gamma Knife Centre between March 2009 and July 2010. Our study is limited by the small number of patients and short median follow-up of a year. Five patients did not have repeat MRI brain as they did not wish to attend for follow-up in Leeds. It was not possible to collect data about patients' neurological symptoms at the time of death as very few were in-patients in Leeds; most were cared for in a hospice or at home. We were however able to collect accurate volumetric data on all lesions treated with SRS and prospective data on the acute toxicities encountered by patients following treatment.

Median survival was 50.4 weeks which is comparable with other series of SRS for brain metastases.^{11,14,15} This suggests that the tumour site specific and neurosurgical multidisciplinary teams selected appropriate patients for SRS. Overall survival varied depending on the primary tumour, with patients with breast cancer having the best outcomes as has

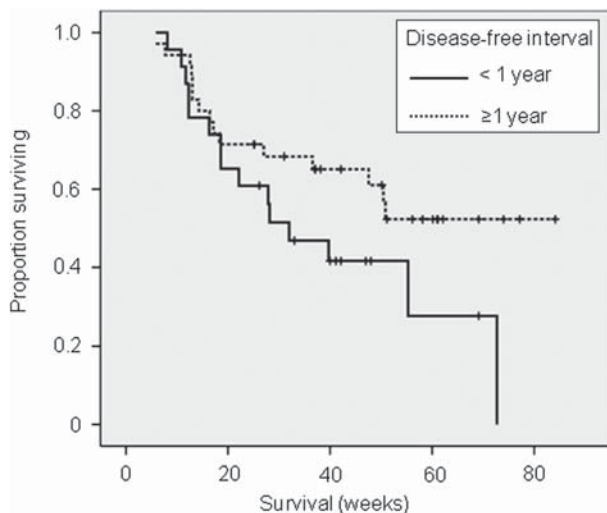


Fig. 4. Kaplan-Meier graph of survival by disease free interval. There was a trend towards improved survival in patients with ≥ 1 year between initial diagnosis and the diagnosis of brain metastases ($p = 0.07$).

been seen in other series.^{10,11} In this series, Karnofsky performance status and the presence or absence of extracranial disease at the time of SRS were not found to significantly affect survival. This finding may be due to the small numbers and the fact that patients were carefully selected prior to SRS; all patients had a KPS ≥ 70 by the time they were treated making KPS less discriminating.

Our study did not show any significant difference in overall survival in patients with single as opposed to multiple metastases but we did find that patients with a total treated volume $< 5000 \text{ mm}^3$ or between 5000 mm^3 and 10000 mm^3 had significantly improved survival compared with patients with a total treated volume over 10000 mm^3 . Other groups have demonstrated similar results. A large retrospective study of patients with breast cancer undergoing SRS showed that the number of brain metastases did not influence survival, whereas a total treated volume $< 3 \text{ cm}^3$ was significantly associated with improved survival in univariate and multivariate analysis.¹⁶ Not only does the total volume of metastases treated appear to be a predictor of survival, but our study also shows that the size of the largest treated metastasis is also important. Patients with a largest treated lesion $< 5000 \text{ mm}^3$ had significantly improved survival compared to patients whose largest treated metastasis was over 10000 mm^3 . A retrospective study into prognostic indicators for radiosurgery in brain metastases found that patients with a single metastasis had significantly better overall survival than those with two or more metastases.⁴ This paper also assessed survival in relation to the volume of the largest brain lesion and found that patients with a largest metastasis of 5 cm^3 , or between 5 cm^3 and 13 cm^3 had significantly improved survival compared to patients with a largest metastasis over 13 cm^3 . This is therefore used in the SIR score.⁴

Why might the volume of individual metastases and the total volume of brain lesions be more important prognostic indicators than the number of metastases? This may be because larger lesions are harder to control with radiation, since the total safe dose is lower. Furthermore, larger metastases may also have a more aggressive biology. For instance, they may represent a group with higher than average growth rates and a more infiltrative growth pattern, making SRS less effective without a bigger margin. The total volume of disease may also be important because, as volume increases, pressure effects and associated neurological dysfunction will also

Table III. The incidence of side effects reported by patients who underwent SRS for brain metastases at their first follow-up appointment. Grade 1 represents mild toxicity, grade 2 moderate, grade 3 severe and grade 4 represents life threatening side effects.

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|----------------------|----------|---------|---------|---------|
| Fatigue | 14 (35%) | 1 (2%) | 1 (2%) | 0 |
| Skin soreness | 3 (7%) | 0 | 0 | 0 |
| Hair loss | 12 (30%) | 0 | 0 | 0 |
| Anorexia | 3 (7%) | 0 | 0 | 0 |
| Taste change | 4 (10%) | 0 | 0 | 0 |
| Weakness | 0 | 0 | 1 (2%) | 0 |
| Sensory change | 0 | 1 (2%) | 0 | 0 |
| Cognitive impairment | 1 (2%) | 0 | 0 | 0 |
| Headache | 3 (7%) | 0 | 0 | 0 |
| Dizziness | 3 (7%) | 1 (2%) | 0 | 0 |
| Memory | 2 (5%) | 0 | 0 | 0 |
| Seizure | 0 | 4 (10%) | 1 (2%) | 0 |

increase. This would frequently correlate with a deterioration in performance status and increase the risk of neurological death.

In this study, there was a rapid rate of intracranial relapse. Thirty-six per cent of patients had new brain metastases by the time of their second follow-up MRI. This rapid rate of intracranial relapse has also been shown in two randomized controlled trials. In the study by Aoyama et al., the SRS alone arm had a 12-month tumour recurrence rate of 76.4%.¹⁷ The relapse rate was 31% at treated sites and 48% at new sites at 2 years in another study by Kocher et al.¹⁸

As WBRT is generally more toxic than SRS and has known detrimental cognitive effects,^{19,20} there has been a trend to holding it in reserve for use in those patients who fail intra-cranially after SRS. Two randomised trials have evaluated the effect of this policy and shown that while immediate WBRT reduces rates of intracranial relapse, it does not affect overall survival.^{17,18} Furthermore, only a minority of patients ever require WBRT using this strategy. A recent meta-analysis has also endorsed this approach.²¹ The advantage of SRS compared to WBRT is that it is thought to have fewer side effects.^{19,20} This study demonstrates the low toxicity of SRS. The most common side effects were grade 1 fatigue and grade 1 hair loss. This represents only patchy hair loss or thinning, which was not usually evident to others and affected only a small area. The patients who reported seizures or weakness had these symptoms prior to SRS and it is therefore hard to know whether the treatment itself caused the symptoms.

Patients are also spared side effects from steroids that can affect quality of life following treatment of brain metastases.⁵ We found that oral steroid dose was significantly reduced following SRS. Fourteen patients who were not on steroids prior to SRS remained steroid free.

This study adds to the increasing body of knowledge on radiosurgery and its side effects. Patients with one large metastasis had a worse outcome than those with several smaller ones and this may be an interesting area of research for the future. It will clearly be important to update our results when we have a larger cohort of patients and longer follow-up.

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Declaration of interest: PH and CL are employed by Leeds Teaching Hospitals NHS Trust, but work in collaboration with Nova Healthcare to provide treatment for brain metastases patients at the Leeds Gamma Knife Centre. The authors alone are responsible for the content and writing of the paper.

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