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Orignal Article

Volume not number of metastases: Gamma Knife radiosurgery management of intracranial lesions from an Australian perspective

Michael A. Izard [a,b,c,*], Vaughan Moutrie [a,b], Jeffrey M. Rogers [c,d], Ken Beath [e], Michael Grace [a,b], Bianca Karle [a,b], Annie Ho [a,b], John W. Fuller [d]

[a] Department of Radiation Oncology, Macquarie University Hospital Sydney; [b] GenesisCare P/L, Alexandria; [c] Faculty of Health Sciences, University of Sydney; [d] Macquarie Neurosurgery, Macquarie University Hospital, Sydney; and [e] Department of Mathematics and Statistics, Macquarie University, Macquarie University, Australia

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ABSTRACT

Background and purpose: To assess the response of the first cohort of patients treated with Gamma Knife radiosurgery in Australia.

Materials and methods: A prospectively collected cohort of 180 patients with intracranial metastases from different primaries was treated between August 2010 and July 2017. Survival was calculated using the Kaplan–Meier's method. Cox regression was used for multivariate analysis.

Results: Currently 141 patients (78.3%) have died of their disease. The median survival for the group as a whole was 9.2 months, with observed differences resulting from the volume of tumor burden (11.4 months for volumes <3.2 cm^3 to 5.16 months for volume >9.1 cm^3). Overall 2-year survival was 20.7%.

Conclusion: Results from the first Gamma Knife radiosurgery center in Australia showed that the treatment is feasible and effective, consistent with the international experience. For patients with larger numbers of intracranial metastases, the total volume of the intracranial burden may be of more significance in predicting outcomes. While there appeared to be a difference in survival by histologic origin, this could be related to concurrent systemic immunotherapy available for certain tumors.

Brain metastases are the most common intracranial malignancy, occurring in one-quarter to one-half of patients with systemic cancer [1,2]. However the incidence of brain metastases is rising, as advances in care extend survival time and allow for the spread of cancer to the brain [3]. Efforts to further prolong survival while maintaining quality of life is therefore a primary concern in these patients.

The management of brain metastases is complex and requires tailored treatment. Mortality from brain metastases has decreased due to earlier detection and better therapy, but the median survival is measured in months [4], with a low percentage of two-year survival [5,6]. Surgical resection, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS) are the most common interventions. Surgery, with or without adjuvant WBRT, has generally been reserved for select patients with solitary lesions, while WBRT has historically been the standard treatment for patients with multiple intracranial metastases [7]. While WBRT improves tumor control at the original site of the metastasis [8], late effects of the irradiation of healthy tissue have been associated with a decline in quality of life (QoL) and cognitive function [9,10]. It is also clear that the use of WBRT fails to "inoculate" the brain and protect from subsequent metastatic deposition.

Alternatively, SRS is capable of delivering a high dose of focal radiation to the target, with minimal radiation to surrounding normal tissue [11]. Multiple SRS platforms are available, including Gamma Knife (GK) radiosurgery (Eleckta AB, Stockholm, Sweden), linear accelerator (Linac) based volumetric modulated arc therapy, TomoTherapy (Accuray Inc, Sunnyvale, CA), and CyberKnife (Accuray Inc, Sunnyvale, CA). With its greater availability, there has been a proliferation of Linac based treatment, correspondingly reflected in the clinical research literature. Subsequently many of the decision paradigms utilized in treatment planning for SRS are derived from Linac systems, which may be less pertinent in clinical decision-making in those centers with access to GK. While the Linac and GK platforms have previously been applied interchange-

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; GK, Gamma Knife; ICTV, intracranial tumor volume; SRS, stereotactic radiosurgery; QoL, quality of life; WBRT, whole-brain radiotherapy.

* Corresponding author at: Department of Radiation Oncology, Macquarie University Hospital, 3 Technology Place, Macquarie University, New South Wales 2109, Australia.

E-mail address: michael.izard@genesiscare.com (M.A. Izard).

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ably in research [12,13], they possess different delivery geometry, radiation dose distribution, and gradient slope properties [14–16], and the clinical effects of the two platforms may not be directly comparable [17]. The ability to treat more than a limited number of metastases by the GK planning process has had a significant impact on the acceptance of such patients in comparison to the difficulties that were inherent in the earlier studies using Linac based delivery. This is reflected in the literature and subsequent acceptance by the radiotherapy community in treating patients with more than "n" number of metastases, with "n" changing over time as Linac based planning systems have improved. Similarly, other studies report that with advances in computer science and treatment delivery hardware, the dosimetric parameters and target coverage are increasingly equivalent for the two platforms [18,19].

GK has typically been used only for brain metastases less than 3 cm in maximum diameter [2,20–23]. Several randomized trials have found that local control [2,23], overall survival [2], cognition [20], quality of life [20], and functional independence [13] can be optimized with GK alone in patients presenting with up to four intracranial metastases.

The efficacy of GK for treating greater numbers of metastases is unclear [24,25]. Bowden [21] reported that median survival following GK significantly declines based on the number of metastases, from 10.3 months for a solitary lesion, to 8.5 months for 2–4 metastases, and 6.1 months for five or more metastases. In contrast, the Japanese Leksell Gamma Knife Group have reported that GK is an effective treatment option for patients with five to 10 small solid (lung, breast, gastro-intestinal, renal) brain metastases [26]. Additional research has indicated GK is effective in up to 10 small metastatic brain tumors from primary breast cancer [22], or up to 14 metastases from colorectal cancer [23]. Similarly Karlsson and colleagues reported no inferiority of outcomes for patients with greater than eight metastases [27], and GK was found to preserve or improve quality of life in patients with up to six tumors [4].

In sum, a survey of the literature [25,28–35] offers compelling evidence of the efficacy for GK when used as the initial treatment for brain metastases, recognizing that further treatment (either retreatment with SRS or WBRT) will often be required. However, despite numerous published guidelines [36–38], clear standards of care according to different intra- and extra-cranial variables are lacking. In particular, it remains unclear how survival outcomes following GK treatment are affected by increasing tumor number or volume. Other factors that may influence survival following GK treatment, such as age, gender, and histology, are becoming better understood with the recursive partitioning analysis prognostic grading schemes [39], but even these are limited and fail to account for individual treatment programs and responses.

To help clarify the clinical picture, we report our experiences and outcomes at a single institution using GKS to treat a large, modern series of patients with brain metastases.

Materials and methods

Patient data (see below) was collected prospectively at the point of care and a retrospective review subsequently undertaken of patients treated with GK for brain metastases between August 2010 and July 2017. This study was approved by the Macquarie University Human Research Ethics Committee and performed in accordance with their guidelines.

Patient population

Treatment was with a committed neurosurgical and radiation oncology group with a shared management plan. A multidisciplinary team meeting assessed all patients, and a decision to treat was agreed prior to start. Eligibility criteria included: patients aged 18 years and older; with histologically confirmed malignancy; and, an ECOG Performance Status score $\geq$2. Patients with previous treatment (ie after WBRT, surgical excision, or SRS) were accepted for GK treatment. Patients with any metastasis with a maximum diameter of more than 3 cm were excluded from treatment as the GK process only recommends lesions up to 3 cm be treated with this technique [2,20–23].

GK radiosurgery

All treatment was performed using the Leksell Gamma Knife Perfexion, utilizing GammaPlan versions 9 and 10.1.1 (Elekta AB, Stockholm, Sweden) using standard GK G-frames fitted the day of treatment by the treating neurosurgeon. Planning images were from 1 mm slice axial 3T MRI images (VERIO, Siemens AG, Munich, Germany) taken with gadolinium contrast (Gadovist, Bayer AG, Thuringen, Germany). This was fused at the time of treatment with a CT image taken on the Department's planning CT scanner (Somatom Sensation Open; Siemens AG, Munich, Germany). In most cases the MRI and CT were done with frame on, but in some cases the MRI was done without a frame up to three days prior, and the image fused with the frame-fitted CT. Margins were not added to the contoured target volume. Metastases smaller than 1.5 cm in largest diameter were given a 20 Gy marginal dose, but larger lesions had a reduced margin dose of 18 or 16 Gy in line with the RTOG 9005 study [40]. All lesions were treated with a single fraction, usually dosed to the 50% isodose, although lesions 3 mm or smaller in largest diameter were treated to the 60–90% isodose line to minimize margin dose. Care was taken to avoid doses >10 Gy to structures such as the optic nerves or chiasm unless the tumor was intimately related.

Data collection

Patients were examined at presentation for the delivery of GK treatment. Data recorded at the time of presentation included age, gender, ECOG Performance Status, histologic diagnosis, and the number and volume of intracranial metastases. Ongoing review was with the referring oncologist and the GK team. If absent from the patient's medical record at the time of review, follow-up on patient mortality was collected retrospectively. Every three months MRIs were taken to assess response, and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire QLQ-C30 (version 3) with brain module QLQ-BN20 (QLQ-C30 version 3) [41] was sent to the patient by mail for completion and return. QoL questionnaires were collected as a routine process, regardless of clinical status.

The primary aim was to analyze survival rate. Survival was calculated from the date of first GK treatment until the date of death. Patients were considered to have died of neurologic causes if they had stable systemic disease and uncontrolled neurologic dysfunction.

Statistical analysis

Continuous variables were summarized by their median and range and qualitative variables by frequency. Kaplan–Meier's survival curves were calculated for the time to death, based on the following *a priori* factors: age; gender; histology; lesion number; total volume; and, presence/absence of previous treatment (e.g. surgery, WBRT). Lesion numbers per patient were divided into three categories: 1–3, 4–9, and >9. Log-rank tests were used to compare the survival curves across the different levels of each moderator. Finally, Hazard Ratios (HRs) were calculated from Cox regression analysis to identify significant predictors of survival. All analyses were completed with R version 3.3.3 [42].

Results

Patient characteristics

Between August 2010 and July 2017, 180 patients (76 male) were treated with GK (Table 1). Patients were referred from across Australasia, with the majority from New South Wales (73%) and the Australian Capital Territory (14%), but also from Queensland (6%), Victoria (3%), Western Australia and South Australia (1.7% each) and New Zealand (1 patient, 0.56%). The median age of patients was 60 years (range 21–90 years). The most common tissue histologies included non-small cell lung cancer (27%), breast carcinoma (27%), and melanoma (24%), while the site of origin in the remaining 41 cases (22%) included (but was not limited to) renal, ovarian, small cell lung cancer, and colo-rectal cancer.

Treatment

At the time of GK treatment, 86 patients (48%) were intracranial treatment naïve, while 36 patients (20%) had previously undergone intracranial surgery, 33 (18%) had previous WBRT, and 25 patients (14%) had both. 145 patients (80.6%) received a single GK session, while 27 patients (15%) had two, five patients (2.8%) had three, one patient (0.6%) had four and two patients (1.1%) had five sessions. In total, for the 180 patients there were 228 GK treatment sessions. There was a median of 5.5 and a mean of 8.5 metastases at presentation (range 1–47 lesions). The total volume of metastases ranged from <0.005 cm^3 to 5.44 cm^3, with a median of 0.57 cm^3. Data on concurrent chemotherapy or immunotherapy were not collected, and all patients continued to be treated by their referring physicians as deemed appropriate.

Table 1
Characteristics of patients treated with Gamma Knife radiosurgery for brain metastases.

Characteristic	Median (range)	*n* (%)
Number of patients		180
Number of lesions (total)		1523 (100%)
Range of metastases per patient		1–47
Median number of metastases		5.5
Mean number of metastases		8.46 (SD 8.68)
Gender ratio (male/female)		76/104
Age (years)	60 (21–90)	
<65		
>65		
Histology		
Breast carcinoma		48 (26.7%)
Non-small cell lung cancer		48 (26.7%)
Melanoma		43 (23.9%)
Renal cell carcinoma		8 (4.4%)
Ovarian		4 (2.2%)
Small cell lung cancer		4 (2.2%)
Other		25 (13.9%)
Previous brain treatment		
No		86 (47.8%)
Whole brain radiotherapy		33 (18.3%)
Neurosurgery		36 (20.0%)
Both		25 (13.9%)
Extracranial metastasis		
No		116 (64.4%)
Yes		64 (35.5%)
Baseline symptoms		115 (63.9%)
Yes		65 (36.1%)
No		115 (63.9)
Number of lesion(s) per patient	5.5 (1–47)	
1		29 (16.1%)
2–5		61 (33.9%)
6–10		43 (23.9%)
11–20		30 (16.7%)
>20		17 (9.4%)
Initial lesion volume (cm^3)	568.5 (6.1–5441.4)	
Number of Ggamma Knife sessions		
1		145 (80.5%)
2		27 (15%)
3		5 (2.8%)
4		1(0.6%)
5		2 (1.1%)

Survival outcome

The average follow-up period was 11 months (SD = 10.5 months), ranging from 0 months [5 patients (2.8%) lost to follow-up] to 5.2 years. At the time of analysis 141 patients (78.3%) had died. The median survival for the group as a whole was 9.2 months (Fig. 1). The one-year overall survival was 37.3% and the two-year overall survival was 20.7%. At the time of death 83 patients (46.1%) were known to have controlled intracranial disease, 72 patients (40%) had progressing intracranial disease, and the status in the final 25 cases (13.9%) could not be ascertained.

To manage potential acute toxicity (e.g. headache or nausea), all patients went home on a reducing dose of dexamethasone across one to two weeks depending upon the size and number of metastases. There were no reported cases of immediate post-procedure morbidity. Long-term toxicity due to suspected radionecrosis was identified in 22 cases (12.2%), including six (3.3%) with no previous intracranial treatment, six (3.33%) who had WBRT and a single GK treatment, three (1.7%) who had multiple courses of GK, three (1.7%) who had surgery prior to GK treatment, two (1.1%) who had multiple courses of GK with surgery, one (0.6%) who had WBRT and multiple GK treatments, and one (0.6%) who had WBRT, surgery, and GK treatment. Of these, 21 (95.5%) were managed conservatively with observation and steroids if needed, and one (4.5%) required intervention with surgery. That one patient had been treated with WBRT initially followed by a single GK treatment.

In univariable analysis, age had no significant effect ($p = 0.5$) on survival outcomes (Fig. 2a). There was a statistically significant difference in the survival rates between male and female patients ($p < 0.01$), seemingly related to the improved survival observed in women with intracranial metastases from breast cancer (Fig. 2b and 2c). Previous WBRT did not have a significant effect ($p = 0.09$) on survival outcomes (Fig. 2d), but there was a trend of extended survival in patients who had not had previous WBRT. There was no significant difference ($p = 0.2$) in survival when patients were compared by the number of intracranial lesions trea-

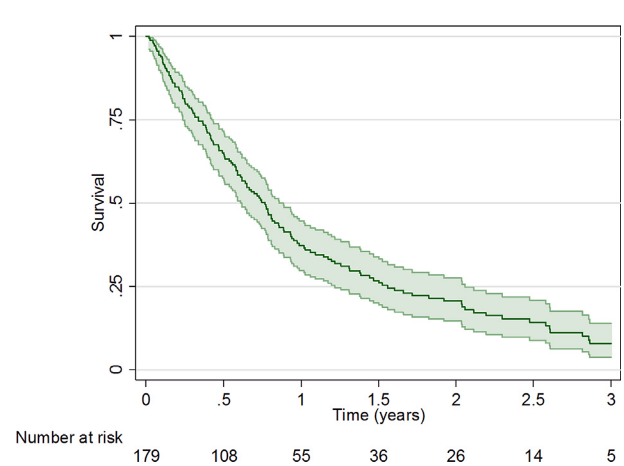

Fig. 1. Kaplan–Meier's estimates of overall survival (with 95% confidence interval) for patients with brain metastases treated with Gamma Knife radiosurgery.

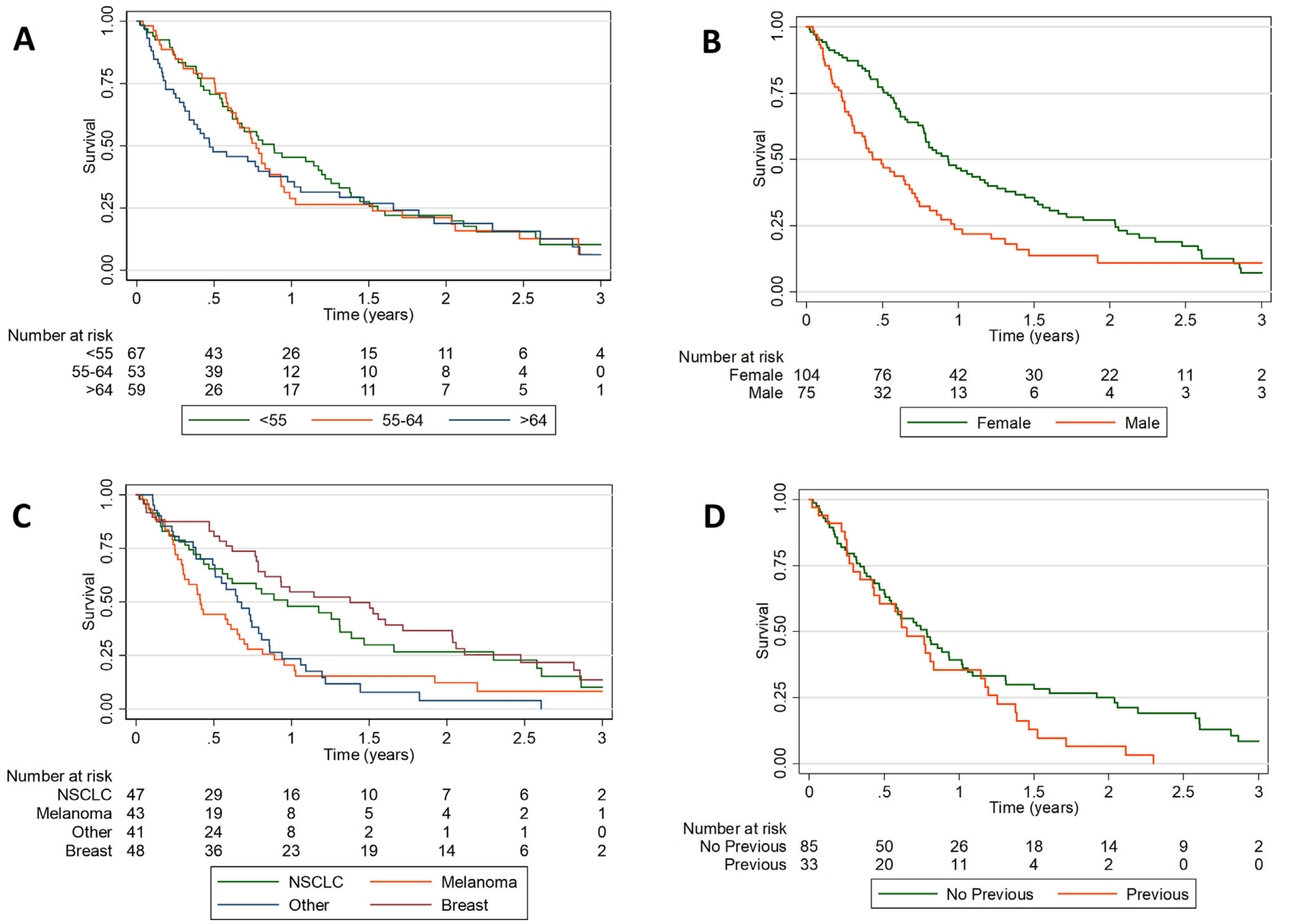

Fig. 2. Proportional survival rates as estimated with the Kaplan–Meier method. (A) By age (years), log rank test $p = 0.5$. (B) By gender, log rank test $p < 0.01$. (C) By histology, log rank test $p < 0.01$. (D) By whole-brain radiotherapy treatment history, log rank test $p = 0.09$.

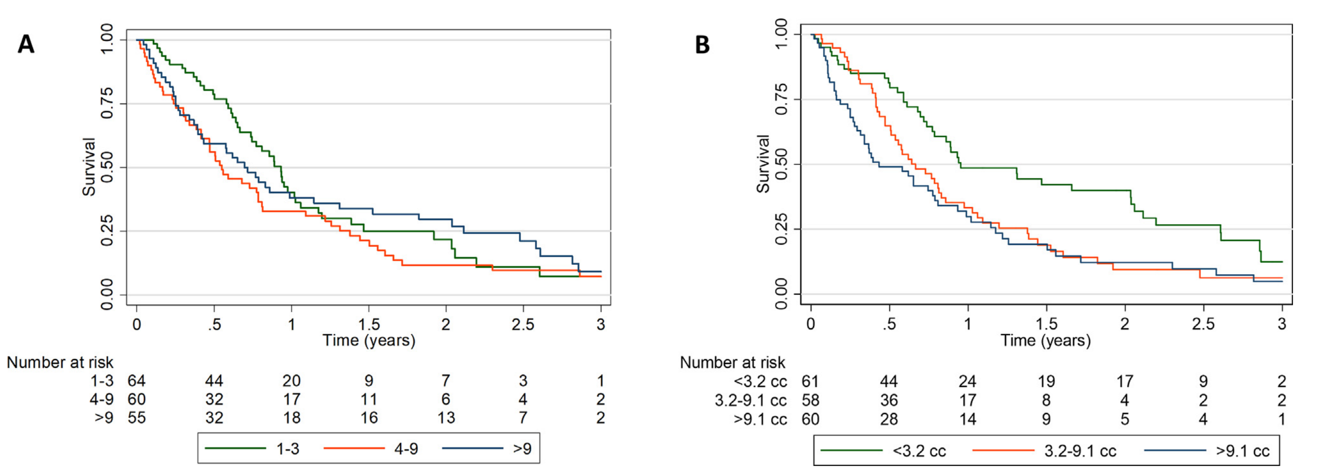

Fig. 3. Proportional survival rates as estimated with the Kaplan–Meier method. (A) By number of metastases, log rank test $p = 0.2$. (B) By total volume (cm^3) of brain lesions, log rank test $p < 0.01$.

ted (Fig. 3a), but there was a significant difference ($p < 0.01$) when the total volume of intracranial disease was compared (Fig. 3b). Specifically, patients with volumes <3.2 cm^3 experienced a median survival time of 11.4 months, while median survival time decreased to 5.2 months for patients with volumes >9.1 cm^3.

Multivariable Cox proportional regression analysis identified total tumor volume (HR 1.21, 95% CI 1.09–1.34, $p < 0.01$), age (HR 1.12, 95% CI 1.00–1.26, $p = 0.04$), and gender (HR 0.64, 95% CI 0.43–0.95, $p = 0.03$) as significant predictors of survival outcomes. The effect of gender persisted when breast cancer patients were excluded. Histology ($p = 0.09$) and the number of metastases ($p = 0.4$) were not significant multivariable predictors of survival.

Quality of life

Patients completed the EORTC QoL questionnaires QLQ-BN20 and QLQ-C30 at presentation, and at three-monthly intervals thereafter for one year. Over that year of follow-up patient's subjective ratings of health and health related quality of life were stable (Fig. 4).

Discussion

Approximately half of patients with solid tumors will develop intracranial disease and have multiple metastases at initial presentation [1,43]. Therefore, there is a need to have treatment options that are effective for multiple lesions and larger total metastatic burden. Stereotactic radiosurgery has become more favorable for the initial treatment of brain metastases, as it sharply decreases radiation toxicity to healthy tissue [44], and treatment-related side effects [4]. Furthermore, GK can often be completed in one day, negating the need to interrupt systemic treatment regimes, increasing patient convenience and allowing for rapid symptom palliation [26].

Stereotactic radiosurgery is increasingly being utilized worldwide [11,43]. Within Australia, the current GK results add to an emerging local evidence-base. Sia and colleagues [45] previously evaluated Linac-based treatment on 162 patients with limited extent intracranial disease (an average of 1.96 metastases per patient, only seven cases had more than five intracranial metastases treated). This study had a very a similar histological diagnosis (27% lung, 25% melanoma and 22% breast) and a similar median age of 60.1 years to the current study. Median survival in the previous cohort was 8.4 months, which when broken down by histologic subtype was 12.2 months for lung, 5.1 months for melanoma, and 14.7 months for breast metastases, again similar to the current results. With a mean age of 58.7, but an average number of metastases per patient of 8, the median overall survival of 9.2 months suggests that patients in the current study were appropriately selected and treated, and consistent with world standards [26,46]. These results further suggest that comparable survival results can be obtained on patients with a higher tumor number using a GK technique. While nearly half (46%) of such treated patients died with their intracranial disease controlled, the current review also identified a subset of patients (20.7%) who can survive over two years. Moreover, while having an impact on survival in the local Australian setting mirroring best international results, GK treatment was able to be administered without negatively impacting quality of life, with patient graded functioning stable over the twelve months of review following treatment.

The current findings suggest that histology has an independent impact upon survival. Patients with intracranial metastases from a breast primary had the best expectation of control, with a median survival time of 16.6 months versus 11.6 months for lung and 4.9 months for melanoma metastases. The trend was significant in univariate analysis and is consistent with local [45] and international expectations [2,13,20–23] of the impact of histology on overall survival. Age was also a significant multivariable predictor, consistent with previous reports that increasing age is a mediating factor associated with decreasing survival [21,44]. Some patients may receive both GK treatment and WBRT, and in the current study the two treatments were not considered competing modalities [11]. However, visual inspection (Fig. 2d) suggested median survival in patients with previous WBRT (7.8 months) might be reduced compared to patients with no prior treatment (9.5 months). The trend was not significant in univariate analysis ($p = 0.09$), and any difference may be explained by noting that survival was calculated from the time of GK treatment rather than from the time of diagnosis of brain metastases, which would have been earlier in cases with prior WBRT.

From our own experience, and from that shown by the JLGK0901 study [26], we argue that it is not the number of metastases specifically that limits the appropriateness of SRS treatment, but the volume of disease and thus the volume of brain irradiated. The significance of tumor quantity has previously been questioned, with multiple studies reporting that the number of brain metastases alone has negligible impact on neurological survival [20,22,44]. Bowden [21] reported a median survival of 10.3 months in patients with total tumor volume <5 cm^3, compared with a median survival of 6.4 months in patients with total tumor volume $\geq$5 cm^3. In contrast, Matsunaga [22] found that total tumor volume had no effect on overall survival, but they only included patients with a total tumor volume of <15 cm^3 in their study cohort. While Sia and colleagues [45] provided similar survival data in a cohort

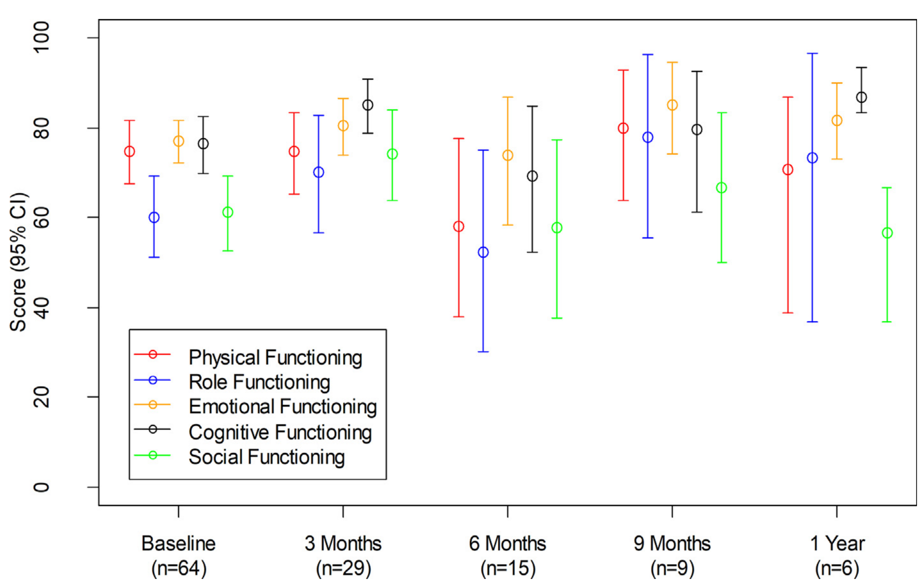

Fig. 4. Quality of life outcomes over time for patients with brain metastases treated with Gamma Knife radiosurgery.

Table 2
Comparison of total lesion volume (cm^3) relative to variations in diameter and total number.

Diameter (cm)	Radius (cm)	Volume (cm^3)	Equivalent to
0.5	0.25	0.065	
1.0	0.50	0.52	8 × 0.5 cm diameter lesions
1.5	0.75	1.77	3 × 1 cm diameter lesions
2.0	1.00	4.17	8 × 1 cm diameter lesions
3.0	1.50	14.2	28 × 1 cm diameter lesions, or 3 × 2 cm diameter lesions

with a more limited number of lesions, we suggest that the number of lesions is immaterial provided they can be treated. The effectiveness of GK treatment, despite the diversity of age, histology, and treatment history, suggests a GK technique can be impactful for many patients with brain metastases. However, a lack of statistical power prohibited further refinement of the moderating effect of total tumor volume on overall survival in each of these separate subgroups.

One significant advantage of the GK process is that with the use of a fixed frame, no margin is added to the disease outline, and subsequently the integral brain dose is substantially smaller. With the basic geometry of a sphere directly related to the cube factor in volume, a small increase in diameter will have a significant increase in volume (Table 2). This cumulative intracranial tumor volume (ICTV) was also recently demonstrated to be a significant predictor of outcomes of SRS treatment [47]. Recognition of the importance of ICTV has a dual impact. First, when planning stereotactic intracranial treatment, the emphasis should be on the total intracranial tumor volume involved rather than the number of lesions to be treated [48]. Second, as the total treatable volume involved increases, there is a proportionally significant impact of adding a margin to the target volume as is considered necessary without a fixed frame. Increased target volumes increase the volume of normal brain exposed to a sub-therapeutic but potentially toxic dose. As we have previously shown, the integral dose to brain from treating multiple metastases rises with the increase in number of lesions, but can still remain low even with multiple lesions irradiated [49].

In sum, GK treatment continues to be a valid option for the management of brain metastases [17]. Brain metastases cause significant mortality for patients with cancer, and the total volume of intracranial burden may be more prognostic of survival outcomes than tumor number or individual lesion size. Inclusion of a tumor volume index is encouraged for future studies involving patients with brain metastases, and in predicting outcomes that can be expected from stereotactic intracranial treatment.

Disclosure

This study was unsupported. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Presentations

This work was previously presented to the Royal Australasian College of Radiation Oncologists in Perth, Western Australia, in October 2017.

Conflict of interest statement

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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