Neuro-Oncology Advances

6(1), vdae047, 2024 | https://doi.org/10.1093/noajnl/vdae047 | Advance Access date 27 March 2024

Is Gamma Knife surgery, omitting adjunct whole brain radiation treatment, feasible for patients with 20 or more brain metastases?

Sherry Liu Jiani, Bengt Karlsson, Balamurugan Vellayappan, Yvonne Ang, Peng Wu, Tseng Tsai Yeo, and Vincent Nga

All author affiliations are listed at the end of the article

Corresponding Author: Bengt Karlsson, MD, PhD, National University Hospital, 5 Lower Kent Ridge Road, 119074 Singapore, Singapore (nykuttram@yahoo.se).

Abstract

Background. The importance of the number of brain metastases (BM) when deciding between whole brain radiation treatment (WBRT) and radiosurgery is controversial. We hypothesized that the number of BM is of limited importance when deciding radiation strategy, and offered Gamma Knife surgery (GKS) also for selected patients with 20 or more BM.

Methods. The outcome following single session GKS for 75 consecutive patients harboring 20 or more (20+) BM was analyzed. Data was collected both retro- and prospectively.

Results. The median survival time was 9 months. Two grade 3 complications occurred, 1 resolved and 1 did not. Sex and clinical condition at the time of GKS (ECOG value) were the only parameters significantly related to survival time. Eighteen patients developed leptomeningeal dissemination with or without distant recurrences (DR), and another 32 patients developed DR a total of 73 times. DR was managed with GKS 24 times, with WBRT 3 times and with systemic treatment or best supportive care 46 times. The median time to developing DR was unrelated to the number of BM, but significantly longer for patients older than 65 years, as well as for patients with NSCLC.

Conclusions. GKS is a reasonable treatment option for selected patients with 20 or more BM. It is better to decide the optimal management of post-GKS intracranial disease progression once it occurs rather than trying to prevent it by using adjunct WBRT.

Key Points

- Median survival of patients with ≥20 brain metastases treated with GKS was 9 months.
- Distal recurrences can mostly be managed adequately with repeat GKS or systemic treatment.
- Omitting whole brain radiation treatment makes it available should future leptomeningeal dissemination develop or should the intracerebral tumor burden no longer be treatable with GKS.

It took more than 20 years between the introduction of Gamma Knife surgery (GKS) and the first published report of using this technique to treat brain metastases (BM).[1] The number of patients with BM treated with GKS increased rapidly as the treatment results exceeded expectations, and the first series of patients treated with GKS for a single BM was reported only 2 years later.[2] As GKS was developed by neurosurgeons, it was natural that only patients with single brain metastasis were initially considered for GKS. The observed high tumor control rate made it logical to extend GKS

Importance of the Study

The study supports the hypothesis that the value of the number of brain metastases (BM) is insignificant when deciding between whole brain radiation treatment (WBRT) and GKS for patients with 20 + BM. The integral brain radiation dose was <3 Gy for 63/75 patients, explaining the low radiation-induced complication rate seen. Furthermore, omitting adjunct WBRT was beneficiary for most of the patients. The clinical condition at the time of GKS was strongly related to the survival time.

to patients with oligometastases, and a large study based on 160 patients with 235 BM was reported another 2 years later, confirming that patients with more than 1 BM could benefit from GKS as well,[3] allowing us to conclude already in 1994 that GKS, omitting whole brain radiation therapy (WBRT), is the treatment of choice for oligometastatic disease to the brain.[4]

The development from treating only patients with single BM to those with oligo BM was relatively uncontroversial, with many setting an upper limit of 3 or 4 BM to be deemed suitable for GKS. There were several rationales for this limitation. The more lesions, the higher the radiation load to the brain. The more the lesions, the higher the risk of leaving micrometastases untreated. The more lesions, the more aggressive the intracerebral disease and thus a shorter expected survival time, minimizing the benefit of GKS were some of the arguments used. The relevance of these arguments will be addressed below.

In 2002, a study was presented arguing for treating patients with more than 10 BM with GKS.[5] The auditorium, including the senior author of this publication (BK), was skeptical, taking the median survival time of only 4 months as an argument not to use GKS for numerous BM. The fear of radiation-induced toxicity when treating numerous BM was subsequently addressed by Yamamoto et al.[6] suggesting that the cumulative radiation dose when treating numerous BM was significantly lower than a whole brain dose of 8 Gy, which was deemed to be safe.[7] Furthermore, a recent study supports the assumption that the cumulative radiation dose is not a limiting factor when treating numerous BM.[8]

The arguments above, suggesting that the more the BM the lesser the benefit of GKS, have proven to be inaccurate. A study published in 2009, based on close to 2000 patients, showed that the number of BM had no impact on the survival time for patients with multiple BM.[9] This has later been corroborated in a Japanese study, the JLGK0901 study, hereafter the JLGK study,[10] showing a median survival of 11 months for the 531 patients with 2–4 BM as well as for the 208 patients with 5–10 BM.

Patchell et al. showed in 1990 a significant survival and quality of life benefit if a BM was removed prior to WBRT as compared to being treated with WBRT alone.[11] As radiosurgery was deemed to be a surgical intervention, it was natural to use the same concept following radiosurgery. This is reflected in the first randomized studies comparing radiosurgery + WBRT to WBRT alone,[12,13] as well as a subsequent ASTRO evidence-based review of the role of radiosurgery for BM.[14] These guidelines concluded that radiosurgery and adjunct WBRT were feasible for patients with oligo-BM.

The Karolinska group, being pioneers in using GKS to treat BM, used another strategy. Their philosophy was that adjunct WBRT may decrease, but not eliminate, the risk for distant recurrences (DR). Instead of adjunct WBRT, they monitored the patients with serial imaging, and recommended the optimal management for DR (repeat GKS, microsurgery or WBRT) should they surface. This philosophy minimizes the number of patients suffering from WBRT-induced neurocognitive impairment,[15] the value of which increases with the longer survival times modern systemic treatments result in. This is reflected in a recent guideline, stating that radiosurgery, omitting WBRT, is indicated also for patients with more than 4 BM as long as the tumor volume does not exceed 7 cm.[3,16]

Adhering to the above, we have neither implemented a strict upper limit for the number of BM or an absolute upper limit for the total BM volume for patients to be considered for GKS. We have now collected our results for all patients with 20 or more (20+) BM treated with GKS in a single session, and we have now sufficient data to allow us to assess the feasibility of this concept.

Materials and Methods

Seventy-five consecutive patients treated with single session GKS in Singapore for 20 + BM from 2016 to September 2023, without evidence of leptomeningeal tumor dissemination (LMD) at the time of GKS, were eligible for and included in the study. Follow-up information was available for all patients. Patients either agreed to contribute with their data, or, when applicable, a consent waiver was obtained as per the Institutional Regulatory Board (DSRB 2022/00177). The patient population is described in Table 1.

Three contrast-enhanced MR pulse sequences (MP RAGE, axial, and coronal T1) with 2 mm slice thickness was included in the stereotactic MR protocol. The lesion must be visible on images from at least 2 pulse sequences to be defined as a BM, allowing us to differentiate a BM with <2 mm diameter from an artifact or a blood vessel. All visible lesions were treated. The majority of the tumors, 83%, had a volume of ≤0.1 cm^3. The prescription dose varied from 10 to 25 Gy, depending on the tumor location, prior radiation, total tumor volume and the 3-dimensional tumor distribution. Patients with long treatment times were offered to divide the treatment into multiple sessions, but none of them opted to do so. The follow-up was defined as being complete when the latest follow-up information was

Table 1. Patient and Treatment Parameters. Complete Follow-Up Denotes the Last Information After December 1, 2023, for the Surviving Patients

Category	*N*	Category	*N*	Σ
Male	24	Female	51	75
Age ≤ 65 years	54	Age > 65 years	21	75
NSCLS	53	Other primary	22	75
20–30 BM	36	>30 BM	39	75
Tumor volume ≤ 7 cc	44	Tumor volume > 7 cc	31	75
Alive	19	Dead	56	75
Extracranial death	35	Intracranial death	10	45
Complete follow-up	72	incomplete follow-up	3	75
ECOG = 0	49	ECOG > 0	26	75
Synchronous BM	24	Metachronous BM	51	75
WBRT before GKS	8	WBRT after GKS	14	22
GKS prior to study GKS	13	GKS after study GKS	12	25
Diagnostic MRI: <20 BM	43	Diagnostic MRI: ≥ 20 BM	26	69
Average brain dose < 3 Gy	63	Average brain dose ≥ 3 Gy	12	75
Treatment time < 6 h	27	Treatment time ≥ 6 h	48	75

dated after December 1, 2023, or when the date of death was known. The primary outcome was survival time, and secondary outcomes were neurocognitive impairment, development of LMD, development of DR and, if so, whether they were managed with radiation treatment (GKS or WBRT) or not. The local tumor response was not analyzed, as it was assumed that it was unrelated to the number of lesions treated. The treatment data is described in Table 1.

The patients were followed with regular MR examinations and clinical visits every 3 months as long as it was deemed meaningful or as long as the patients stayed in Singapore. The follow-up times were as follows: median 9 months and mean 13 months. The follow-up images were, when available, coregistered with the stereotactic images from the day of GKS to define whether DR or LMD had developed or not. We relied on the radiology reports if the follow-up images were unavailable. The number of DR was registered as well as evidence of LMD. Freedom from DR was defined as the time between GKS and the time for the first imaging diagnosing DR or the latest follow-up, whichever comes first. A finding of DR was disregarded if it occurred simultaneously with the diagnosis of LMD, as all WBRT naive patients with LMD were recommended WBRT independent of the intracerebral tumor control. Development of white matter changes (WMC) was assessed on the latest follow-up scan if > 6 months had elapsed between GKS and the latest MR imaging.

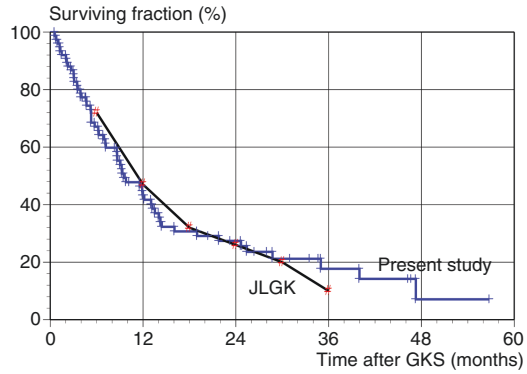

Figure 1. Survival time following GKS. JLGK refers to data from Ref. 10.

The Kaplan–Meier method was used for calculating survival time and freedom from DR and LMD. The Log rank (Mantel–Cox) proportional hazard method was used to correlate different patient, treatment and tumor parameters with survival time. The χ^2 test was used for nominal data and the Mann-Whitney test for continuous and nominal data. A relation was deemed to be statistically significant if $P < .05$. Two decimals were used when reporting the *P*-values. The deidentified data collected in the study will be available upon reasonable request.

Results

Survival Time

The survival time is illustrated in Figure 1. As seen, the median survival time was 9 months. Two-third of the patients lived more than 6 months, almost half of them more than 1 year, a quarter more than 2 years and around a fifth more than 3 years following GKS. As seen in Figure 1, the survival times in our patient population are similar to that of the survival time for patients with 5–10 BM in the JLGK study10. Sex and clinical condition at the time of GKS and ECOG value (0 or >0) were the only parameters significantly related to survival time (Table 2).

Cause of Death

The cause of death was extracranial for 35 patients, intracranial for 10 and unknown for 11 patients. LMD had developed in 5 of the 10 patients who succumbed due to intracranial disease. The course of death in the remaining 5 patients was unrelated to intracranial tumor progression (hemorrhage and seizure) in 3 and due to progressive intracerebral disease in 2.

Leptomeningeal Tumor Dissemination

Eighteen patients developed LMD after GKS. Four were diagnosed within 3 months, seven within 6 months, 13 within 1 year and all within 3 years following GKS. Two

Table 2. Relation Between Median Survival Time and Different Patient- and Tumor Parameters. Synchronous Presentation of BM is Defined as <3 Months Between Diagnosis of BM and Diagnosis of Primary Cancer

Category	MST	Category	MST	*P*
ECOG > 0	5	ECOG = 0	14	<.01
Male	5	Female	12	.04
20-30 BM	9	>30 BM	12	.06
Metachronous BM	9	Synchronous BM	14	.09
Extracranial death	6	Intracranial death	9	.15
Non-NSCLC primary	7	NSCLC primary	12	.46
Age ≤ 65 years	9	Age > 65 years	13	.52
>7 cc tumor volume	9	≤7 cc tumor volume	13	.75

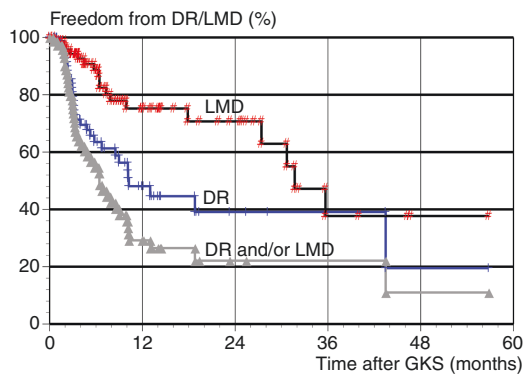

Figure 2. The time between GKS and freedom from distant recurrences (DR), leptomeningeal dissemination (LMD) as well as intracranial tumor progression.

of the patients received WBRT before GKS, 11 after GKS, while 5 did not receive any additional radiation treatment. The incidence of LMD was more common in younger patients, $P = .04$, but unrelated to primary disease (NSCLC or not), $P = .62$, the number of BM, $P = .21$ and tumor volume, $P = .06$. The timing of the development of LMD can be seen in Figure 2.

Freedom From and Management of DR

Thirty-two patients developed DR without evidence of LMD. DR was diagnosed for the first time within 3 months for 13 patients, within 6 months for 23 patients, and within a year for 29 patients. The remaining 3 patients developed DR between 1 and 4 years after GKS (Figure 2). DR was diagnosed 73 times; once for 14 patients, twice for 7 patients, 3 times for 5 patients, 4 times for 2 patients, 5 times for 2 patients and 6 times for 2 patients. DR was managed with GKS 24 times, with WBRT 3 times (3. 8 and 13 months following GKS, respectively), and with systemic treatment or best supportive care 46 times. There was a significantly longer time between GKS and the development of DR for older patients and patients with NSCLC (Table 3). The management of DR is illustrated in Figure 3.

Table 3. Relation Between Median Time to First Distant Recurrence (MTDR) and Different Patient and Tumor Parameters. NR Denotes that the Median Time Has Not Yet Reached

Category	MTDR (mos)	Category	MTDR (mos)	*P*
Age ≤ 65 years	9	Age > 65 years	NR	.02
Non-NSCLC primary	6	NSCLC primary	19	.02
Metachronous BM	9	Synchronous BM	43	.07
≤7 cc tumor volume	7	>7 cc tumor volume	19	.19
Female	10	Male	NR	.41
Extracranial death	9	Intracranial death	9	.48
20–30 BM	9	>30 BM	13	.77
ECOG > 0	9	ECOG = 0	10	.97

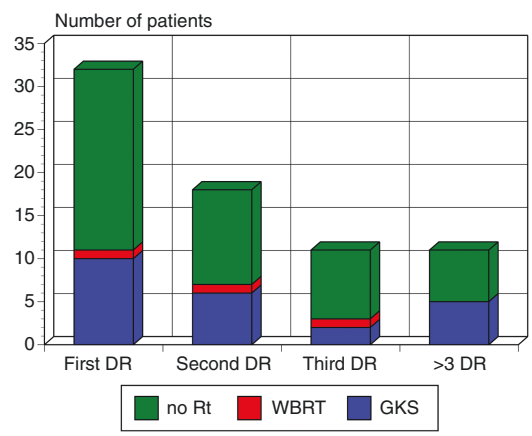

Figure 3. Management of distant recurrences (DR).

Radiation-Induced Complications

Besides local radionecrosis, no significant radiation-induced complication occurred in all but 2 patients, who developed RTOG toxicity grade 3. The average brain dose for the 2 patients mentioned above was 2.7 and 3.6 Gy, respectively, as compared to a median dose of 2.0 Gy for the total patient population. One of them developed symptoms from extensive edema 1 month post-GKS, resulting in a midline shift of 7 mm. The edema resulted in dysphasia, dysgraphia, right-sided weakness, and drowsiness. The patient was admitted and initially treated with high doses of intravenous dexamethasone. She improved, and was discharged with slow steroid weaning over 2 months, and completely recovered another 2 months later.

The second patient developed generalized weakness leading to functional decline 9 months following GKS due

to extensive edema resulting in a 2 mm midline shift. The patient was admitted, treated with oral dexamethasone, and discharged 3 days later in a clinically unchanged condition, and the patient was clinically stable at the latest follow-up another month later.

Neurocognitive Status

Changes in the patient's neurocognitive status following GKS were subjectively assessed by the patient and their relatives, and thus minor changes in the neurocognitive status were likely undetected. A neurocognitive deterioration was documented in 14 patients, of whom 9 had been treated with WBRT. This represents an incidence of 9/19 following WBRT + GKS as compared to 5/56 following GKS only ($P < .01$). Thus, the likelihood of subjective neurocognitive impairment is higher following WBRT than following GKS in patients with 20 + BM.

White Matter Changes

White matter changes (WMC) were assessed on the latest MR imaging in all the 37 patients in whom the latest MR imaging was done ≥6 (mean 19 and median 13) months following GKS. WMC was graded according to Fazekas et al.[17] Twelve patients were graded as grade 0, 15 as grade 1, 6 as grade 2, and 4 as grade 3. There was no significant relation between mild (grade 0 vs. > 0) or pronounced (grade < 3 vs. 3) WMC and the integral radiation dose, $P = .85$ and .75, respectively. Six of the patients received WBRT ≥ 3 months prior to the latest MR examination, and 2 of them developed WMC grade 3. This can be compared to the other 31 patients, of whom 2 developed WMC grade 3 ($P = .15$).

Discussion

Survival Time

As seen in Figure 1, the survival time in our patient population is similar to the survival time for patients with 5–10 BM in the JLGK study. An important difference can, however, be observed. The fraction of surviving patients in our series was, as compared to the JLGK series, 5% lower at 6 months, 4% lower at 1 year, and 1% lower at 18 months following GKS. Thereafter, the surviving fraction is larger in our series: 1% at 2 years and 8% at 3 years. The patients in our series were treated around 10 years later than those in the JLGK series, and the larger fraction of long-time survivors in our series probably reflect better systemic treatments in later years.[18] It can be assumed that intracerebral tumor burden is less important for survival time than a response to systemic treatment. All 5 patients that survived >3 years suffered from NSCLC, and all but 1 of them were Epidermal Growth Factor Receptor positive, which supports this assumption.

Death due to intracranial disease does not necessarily translate to death due to uncontrolled intracerebral disease. Out of 10 patients who succumbed to intracranial disease, 5 was diagnosed with LMD, 2 suffered from an intracerebral hemorrhage, and 1 succumbed due to status epilepticus. Thus, the likelihood of succumbing due to uncontrolled intracerebral disease was low in our patient population.

Omitting Adjunct WBRT—Burden or Asset?

Does the benefit of avoiding the risk of neurocognitive impairment following WBRT as well as having the treatment option available in the future exceed the disadvantage of leaving potential micrometastases untreated? LMD was diagnosed within 3 months following GKS in 4 patients, of whom 1 received WBRT before GKS. It can be argued that LMD was present at the time of GKS in these patients, and thus, in retrospect, GKS should have been replaced with WBRT in 3 of them.

This is balanced by the fact that WBRT was available for the 14 patients in whom LMD was diagnosed more than 3 months following GKS, of whom 10 was treated with WBRT, as well as for the 2 patients in whom the intracerebral disease progression was deemed to be beyond being manageable with GKS. In balance, 3 patients may have benefited from adjunct WBRT, while twelve patients benefited from omitting it. In addition, the majority of patients avoided the risk for neurocognitive impairment that adjunct WBRT would have resulted in. Thus, omitting adjunct WBRT was, on average, beneficial for the patients.

White Matter Changes

WMC was seen in 27/38 patients, which is higher than the 19% found by Marcrom et al.[19] and similar to the 60% found by Cohen-Inbar et al.[20] This can be compared to data following WBRT. Fujii et al analyzed 20 patients treated with WBRT and followed for >6 months.[21] Eight of them were diagnosed with minor WMC and the remaining 12 with significant WMC. This is compatible with the findings of Monaco III et al., reporting that 36/37 patients had WMC following WBRT.[22] If GKS would have significantly contributed to the development of WMC, it would have been expected that the higher the integral dose delivered at the time of GKS, the higher the incidence of WMC. This was not the case. The average brain dose delivered during GKS was 2.4 Gy for the patients without WMC as compared to 2.3 Gy for those with, suggesting that the risk of GKS causing WMC is low.

Our Results Compared to Other Studies

The published experience for patients with up to 10 BM treated with GKS is extensive. As a consequence, treating patients harboring ≤ 10 BM with GKS is relatively uncontroversial today. The results following GKS for patients with 10–20 BM have also been analyzed, but we found only 1 publication reporting the results following GKS for patients with 20 + BM from different primary tumor locations.[23] The number of patients included in the study by Wei et al. was, serendipitously, the same as in our study, 75. According to Table 2 in their study,[23] they observed the development of DR in 51 patients and LMD in 16 patients, as compared to 32

and 18, respectively, in our study. The numbers are not directly comparable, as we did not register potential DR once LMD was diagnosed. They treated 49 patients with repeated GKS as compared to 12 in our study. The number of DR and repeated GKS differed significantly between the studies, with $P < .01$ for both. The median survival in their study was 6 months, shorter than the 9 months found in our study. Other differences were a number of tumors, total tumor volume, treatment time, and the amount of intracerebral energy delivered. The median values in our study were 31, 6.3 cm^3, 420 min and 2.3 J (assuming an average brain weight of 1.2 kg) as compared to 24, 3.7 cm^3, 160 min and 5.5 J in theirs. The differences above imply different patient selection criteria and different treatment techniques. In spite of the differences, both studies conclude that GKS is a reasonable treatment option for selected patients with 20 + BM, giving further support for our conclusion.

Limitations

It can be assumed that patients with 20 + BM with poor prognosis or in poor clinical condition, the number of patients being unknown, were not referred to us to be considered for GKS. If so, our results reflect a subgroup of patients with 20 + BM and being in good clinical condition. The contribution of systemic treatments to intracerebral tumor control, which probably has been significant in a number of patients, is not analyzed in this study. The lack of objective neurocognitive testing pre- and post-GKS is another limitation.

Conclusions

The median survival time in this study is long enough and the risk for radiation-induced complications is low enough to justify GKS for selected patients with 20 + BM. It is advantageous to omit adjunct WBRT and instead use WBRT when clinically indicated. Ten patients received WBRT or repeat GKS for DR within 1 year following the study GKS treatment and the intracranial disease was controlled without additional radiation treatment 1 year following GKS in a third of the patients. It is thus possible to control the intracerebral disease in the majority of patients with 20 + BM with upfront GKS, followed by repeat GKS, WBRT, or systemic treatment when indicated. The fact that all patients tolerated the long treatment times in our study may not be representative of a general patient population, and thus splitting up the treatment into several sessions may be preferred in some centers.[24]

Keywords

brain metastases | Gamma Knife surgery

Funding

There is no external funding for this study.

Conflict of interest statement

None of the authors have declared any conflict of interest.

Authorship statement

S.L.J.: formal analysis, visualization, manuscript writing. B.K.: conceptualization, data curation, investigation, methodology, supervision, draft writing. Y.A., B.V., P.W., T.T.Y., V.N.: manuscript editing.

Affiliations

Department of Surgery, Division of Neurosurgery, National University Hospital, Singapore, Singapore (S.L.J., B.K., T.T.Y., V.N.); Department of Radiation Oncology, National University Hospital, Singapore, Singapore (B.V.); Department of Medical Oncology, National University Hospital, Singapore, Singapore (Y.A.); Department of Radiology, National University Hospital, Singapore, Singapore (P.W.)

References

1. Lindquist C. Gamma Knife surgery for recurrent solitary metastasis of a cerebral hypernefroma: case report. *Neurosurgery.* 1989;25(5):802–804.
2. Kihlström L, Karlsson B, Lindquist C, Norén G, Rähn T. Gamma Knife surgery for cerebral metastasis. *Acta Neurochir Suppl (Wien).* 1991;52(suppl(1)):87–89.
3. Kihlström L, Karlsson B, Lindquist C. Gamma Knife surgery for cerebral metastases. Implications for survival based on 16 years experience. *Stereotact Funct Neurosurg.* 1993;61(Suppl 1):45–50.
4. Karlsson B, Kihlström L, Lindquist C. Medical controversy: is Gamma Knife surgery the treatment of choice for cerebral metastases? *Trends Exp Clin Med.* 1994;4(4):396–402.
5. Amendola BE, Wolf A, Coy S, Amendola MA. Radiosurgery as palliation for brain metastases: a retrospective review of 72 patients harboring multiple lesions at presentation. *J Neurosurg.* 2002;97(Suppl 5):511–514.
6. Yamamoto M, Ide M, Nishio S, Urakawa Y. Gamma Knife radiosurgery for numerous brain metastases: is this a safe treatment? *Int J Radiat Oncol Biol Phys.* 2002;53(5):1279–1283.
7. Brewster AE, Hopwood P, Stout R, Burt PA, Thatcher N. Single fraction prophylactic cranial irradiation for small cell carcinoma of the lung. *Radiother Oncol.* 1995;34(2):132–136.
8. Becker SJ, Lipson EJ, Jozsef G, et al. How many brain metastases can be treated with stereotactic radiosurgery before the radiation dose delivered to normal brain tissue rivals that associated with standard whole brain radiotherapy? *J Appl Clin Med Phys.* 2023;24(3):e13856.
9. Karlsson B, Hanssens P, Wolff R, et al. Thirty years experience of Gamma Knife surgery for metastases to the brain. *J Neurosurg.* 2009;111(3):449–457.

10. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol.* 2014;15(4):387–395.
11. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990;322(8):494–500.
12. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys.* 1999;45(2):427–434.
13. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet.* 2004;363(9422):1665–1672.
14. Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys.* 2005;63(1):37–46.
15. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* 2009;10(11):1037–1044.
16. Graber JJ, Cobbs CS, Olson JJ. Congress of neurological surgeons systematic review and evidence-based guidelines on the use of stereotactic radiosurgery in the treatment of adults with metastatic brain tumors. *Neurosurgery.* 2019;84(3):E168–E170.
17. Fazekas F, Chawluk JHB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Roentgenol.* 1987;149(2):351–356.
18. Karlsson B, Yamamoto M, Hanssens P, et al. Does modern management of malignant extracranial disease prolong survival in patients with ≥3 brain metastases? *World Neurosurg.* 2016;92:279–283.
19. Marcrom SR, Foreman PM, Colvin TB, et al. Focal management of large brain metastases and risk of leptomeningeal disease. *Adv Radiat Oncol.* 2019;5(1):34–42.
20. Cohen-Inbar O, Melmer P, Lee C, et al. Leukoencephalopathy in long term brain metastases survivors treated with radiosurgery. *J Neurooncol.* 2015;126(2):289–298.
21. Fujii O, Tsujino K, Soejima T, et al. White matter changes on magnetic resonance imaging following whole-brain radiotherapy for brain metastases. *Radiat Med.* 2006;24(5):345–350.
22. MonacoEA3rd, Faraji AH, Berkowitz O, et al. Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer. *Cancer.* 2013;119(1):226–232.
23. Wei Z, Luy DD, Jose S, et al. Single-session gamma knife radiosurgery for patients with 20 or more brain metastases. *Neurosurgery.* 2023;93(4):857–866.
24. Kim M, Cho KR, Choi JW, et al. Two-staged gamma knife radiosurgery for treatment of numerous (>10) brain metastases. *Clin Neurol Neurosurg.* 2020;195(105847):105847.