


Fractionated stereotactic radiotherapy for metastatic brain tumors that recurred after gamma knife radiosurgery results in acceptable toxicity and favorable local control

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Abstract

Background To treat local recurrence of brain metastases after gamma knife radiosurgery (GKS), we have used fractionated stereotactic radiotherapy (SRT). The purpose of this study was to evaluate the efficacy and toxicity of SRT in these patients.

Methods Fifty locally recurrent metastatic brain tumors in 47 patients were treated with SRT. The median prescribed dose of GKS was 20 Gy at the periphery. The median interval between the GKS (the last session in cases in which multiple GKS procedures were performed) and recurrence was 7.5 (range 1–33) months. Several dose-fractionation protocols were used for SRT, depending on the size and location of the tumor and previous GKS dose. The median prescribed dose of the SRT at the isocenter was 30 Gy with a median of ten fractions.

Results Among the 50 lesions treated with SRT, 26 did not recur locally before the patient's death or the last follow-up examination, and 24 recurred locally. The median follow-up period for the surviving patients was 24 months after

the first GKS procedure, and the overall survival rate was 80% at 1 year and 57% at 2 years. The median time to local re-recurrence after the SRT (16 months) was significantly longer than the median interval between the last GKS and recurrence (7.5 months; $P < 0.001$). Only two patients developed \geq grade 2 radiation necrosis.

Conclusions Stereotactic radiotherapy appeared to be an effective treatment for recurrent metastatic brain tumors and yielded relatively good local control. The associated adverse events were generally acceptable.

Keywords Stereotactic radiotherapy · Metastatic brain tumor · Re-radiation

Introduction

Gamma knife radiosurgery (GKS) is an established primary treatment for solitary or oligometastatic brain tumors [1–4], allowing multiple metastatic brain tumors to be treated in a single session. However, local recurrence of the tumor(s) after GKS is not uncommon, and the management of local recurrence after GKS poses a problem due to the normal tissue tolerance limits of the brain to radiation [5]. A second GKS is occasionally employed for short-term palliation, and although whole-brain radiotherapy may be indicated, especially when recurrent tumors are multiple, attending physicians often fear late adverse effects, such as dementia and brain atrophy [6, 7]. Consequently, the attending physicians may be hesitant to initiate whole-brain radiation therapy when there is no other tumor besides local recurrence. On the other hand, the recently published results from a phase III randomized trial [Japan Clinical Oncology Group (JCOG) 0504] demonstrate that there were no significant differences in the 1-year Mini-Mental

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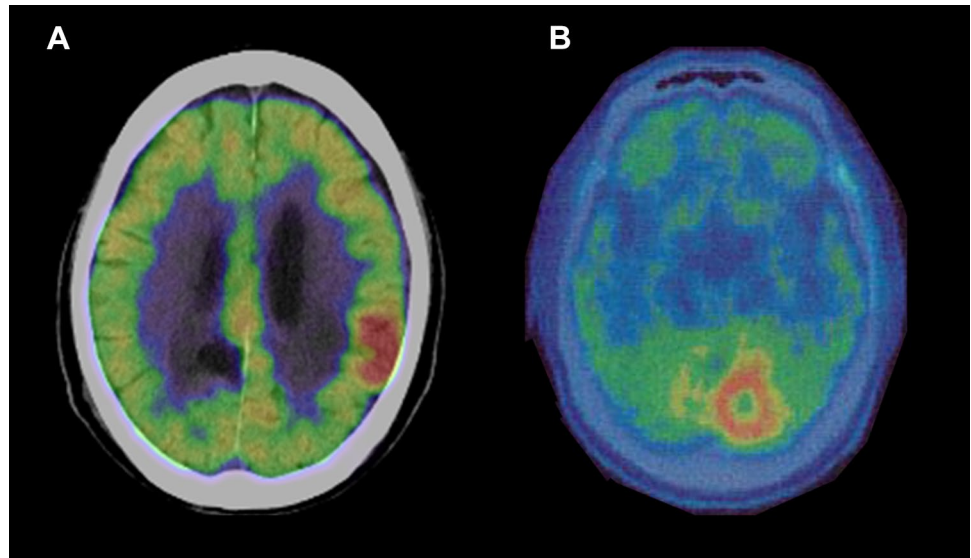
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Fig. 1 Representative images of ^{18}F -fluorodeoxyglucose-positron emission tomography (PET) (a) and ^{11}C -methionine-PET (b) suggesting local recurrence



State Examination (MMSE) scores and performance status (PS) between postoperative patients treated by stereotactic radiosurgery and those treated by whole-brain radiotherapy and that intracranial control rates were higher in the whole-brain-treated group [8]. Thus, although the optimal salvage therapy for recurrent tumors after initial radiosurgical treatment may remain open to discussion, we postulated that fractionated stereotactic radiotherapy (SRT) might be an option for metastatic brain tumors that recur after a single high-dose GKS.

Our institution treats more than 500 patients with brain metastases using GKS each year, and we encounter local recurrence after GKS relatively frequently. Since the installation of a modern linear accelerator at our institution in 2008, we have used SRT rather than GKS to treat patients who fulfill the criteria outlined in the [Materials and methods](#). We chose to use SRT as a second-line treatment because we considered that it would cause fewer and less severe toxicities and have a greater biological effect than single-fraction GKS and because such tumors are often large and/or located in close proximity to critical structures. The purpose of this study was to evaluate the efficacy and toxicity of SRT for locally recurrent brain metastases that had previously been treated with GKS.

Materials and methods

Patient characteristics

This retrospective study was approved by the institutional review board of Fujieda Heisei Memorial Hospital (No. 26-1). Informed consent had been obtained from all patients prior to initiation of SRT. From October 2008 to

December 2013, 1238 patients were treated with GKS for brain metastases at our institution. Although about 30% of the patients were not followed, local recurrence of brain metastases was identified in 156 patients. Among these, 27 were not re-irradiated, and 82 were treated with a second GKS for local recurrence. The remaining 47 patients with a total of 50 recurrent metastatic brain tumors that had developed after the GKS were treated with SRT, and it is this patient cohort that is the focus of present study. The choice of GKS or SRT for re-irradiation was mainly at the discretion of the attending neurosurgeons, but tumors existing near critical structures, such as the brain stem and optic apparatus, and larger tumors were more likely be treated with SRT. There appeared to be no difference in the patient characteristics, such as age, gender, and PS, between the GKS- and SRT-treated patients, but patients with extensive extracranial metastases tended to be treated with GKS.

Of the 47 patients, 20 were male and 27 were female. At the time of the SRT, the median age of the patient cohort was 61 (range 40–85) years. Tumor diameter ranged from 14 to 63 (median 32) mm. Tumor recurrence was first suspected based on the patients' magnetic resonance imaging (MRI) findings [9, 10]. Since functional imaging techniques, such as positron emission tomography (PET), are considered to be useful diagnostic tools for distinguishing metastatic lesions from necrosis [11], we used ^{18}F -fluorodeoxyglucose (FDG)-PET or ^{11}C -methionine-PET (methionine-PET) to diagnose local recurrence in all suspected cases, with positive findings observed on all of the images. Figure 1 shows typical images of FDG-PET and methionine-PET; apparent uptake of the isotopes was observed in the contrast-enhanced regions on MRI. Of the 50 tumors which were imaged, 13 had been treated twice with GKS, and one had been treated 3 times with GKS. None of the

Table 1 Patients and tumor characteristics

Characteristics	All patients	SRT group ^a	GK–SRT group ^b	<i>P</i>
Number of patients	47	34	13	–
Number of tumors	50	36	14	–
Age (years)	61 (40–85)	65 (42–85)	54 (40–79)	0.14
Gender male/female	20/27	17/17	3/10	0.09
KPS (≥ 70 / < 70)	39/8	31/3	8/5	0.02
RPA (I/II/III)	9/30/8	6/25/3	3/5/5	<0.001
Primary tumor site (lung/breast/colon/other)	20/13/7/7	16/6/6/6	4/7/1/1	<0.001
Number of tumors $\frac{1}{2}$	44/3	32/2	12/1	0.82
Number of GKS procedures before SRT ($\frac{1}{2}$ /3)	36/13/1	36/0/0	0/13/1	

Values in table are presented as a number with the exception of age which is presented as the median with the range in parenthesis

KPS Karnofsky performance status, RPA recursive partitioning analysis

^a Patients primarily treated with stereotactic radiotherapy (SRT) for local recurrence

^b Patients who first underwent gamma knife radiosurgery (GKS) for local recurrence and subsequently received SRT

Table 2 Parameters and follow-up periods for the gamma knife radiosurgery and stereotactic radiotherapy

Parameters and follow-up	GKS ^a	SRT
Total dose (Gy)	20 (4–42)	30 (20–36)
Fraction	1 Fr: 43 2 Fr: 7	10 (6–12)
BED10 (Gy) ^b	60 (5.6–130.2)	39 (25–47.25)
PTV (cm ³)	10.4 (0.4–72.5)	28.8 (7.1–103)
Follow-up (months)	8 (1–33)	10 (1–40)

Values in table are reported as the median with the range in parenthesis, with the exception of Fraction for GKS, where the values are numbers

BED Biological effective dose, PTV planning target volume

^a Last session in cases involving multiple GKS procedures

^b This parameter has been reported to be incorrect when used for single-fraction irradiation [14, 15] (see text)

patients had received whole-brain radiotherapy before the SRT. The characteristics of the patients and tumors are summarized in Table 1.

Gamma knife treatment

Gamma knife surgery has been described previously [12, 13]. Briefly, each patient underwent a contrast-enhanced MRI examination for treatment planning (SIGNA EXCITE XL 1.5 T scanner; GE Healthcare, Milwaukee, WI) and a Leksell frame attached to the head under local anesthesia. The treatment planning was performed using Leksell GammaPlan (Elekta AB, Stockholm, Sweden). The planning target volume (PTV) was defined as the contrast-enhanced tumor region plus a 1-mm margin. The GKS was performed with a Leksell gamma knife unit (Model C; Elekta AB). The median prescribed dose was 20 Gy at the

periphery (the 50% isodose line). Of the 50 tumors, seven were subjected to two GKS sessions, which were performed 2 months apart. The median PTV was 10.3 (range 0.4–72.5) cm³, and the median interval between the GKS (the last session in the cases involving multiple GKS procedures) and recurrence was 7.5 (range 1–33) months.

Stereotactic radiotherapy method

The SRT was performed with a linear accelerator (Synergy S, Elekta AB) equipped with 4-mm multileaf collimators. The treatment planning was carried out using the Pinnacle³ Treatment Planning System (Philips NV, Amsterdam, The Netherlands). The PTV was defined as the gross tumor volume plus 2-mm margins in the lateral and anteroposterior directions and a 3-mm margin in the craniocaudal direction. Several dose-fractionation protocols were used for the SRT, depending on the size and location of the tumor and previous GKS dose. The median prescribed dose for SRT at the isocenter was 30 (range 20–36) Gy, and a median of ten fractions were administered (range 6–12). The median D95 (dose that covers 95% of the PTV) was 94.2% (range 71.0–97.5%) of the isocenter dose. The median V90 (PTV volume that received $\geq 90\%$ of the prescribed dose) was 98.6% (range 69.1–100%). The median PTV for the SRT was 28.8 (range 7.1–103) cm³, which was significantly larger than the median PTV for the GKS (median 10.4 cm³; range 0.4–72.5; $P < 0.0001$). Detailed information about the GKS and SRT is summarized in Table 2. Biological effective doses (BED) for $\alpha/\beta = 10$ Gy (BED10) are shown for convenience. However, it has been reported that the standard BED10 values for single-fraction treatment are incorrect [14] and very recently suggested that the BED10 values for GKS would reflect the true biological effects

of the procedure more accurately if they were reduced by $\geq 20\%$ [15].

Evaluation

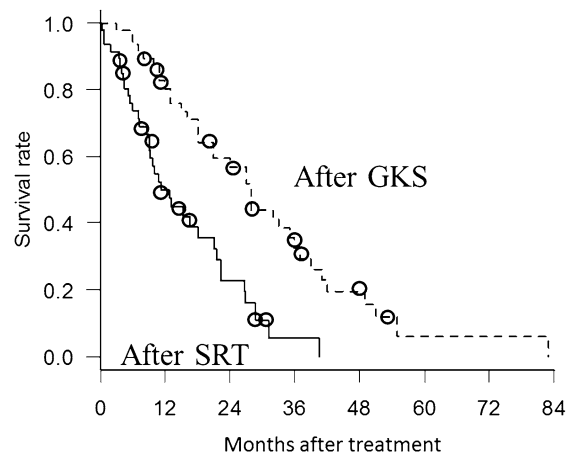
All of the patients were scheduled to undergo contrast-enhanced MRI or computed tomography before the SRT and every 2–4 months after the SRT, although regular follow-up was occasionally not possible in patients with poor health. Local re-recurrence was suspected when enlargement of the contrast enhancement of the irradiated region ($>20\%$ in the longest diameter compared with that before SRT) was detected on MRI or CT images. Shrinkage of the tumors was observed in most cases after the initial GKS. Slight enlargement of the shrunken contrast-enhanced mass was followed for a short period to time because radiation-induced changes are more likely to develop due to repeat irradiation, and when the contrast-enhanced mass became larger than the initial size, further imaging evaluation was performed. Suspected re-recurrent lesions were identified using the same MRI criteria as were used to detect the initial recurrent lesions [11]. Re-recurrence was definitively diagnosed based on strong uptake of radioactivity on FDG- or methionine-PET (standardized uptake value: >5) or the findings of surgery or biopsy. Time to local re-recurrence was evaluated based on the imaging follow-up. Toxicities were evaluated using the Common Terminology Criteria for Adverse Events Version 4.0 (National Institutes of Health/National Cancer Institute, Bethesda, MD).

Statistical analysis

Differences in patient or tumor characteristics between the groups were examined using the Chi-square test or *t* test. Overall survival was calculated from the start of the first GKS and also from the start of SRT using the Kaplan–Meier method. The log-rank test was used to compare survival curves. The time to local recurrence was calculated from the last GKS or SRT. Fine and Gray's competing risks regression model was used to estimate and compare cumulating incidences of local recurrence, thereby considering patient death as a competing risk. All statistical analyses were carried out using R version 2.13.0 for Windows (The R Foundation for Statistical Computing, Vienna, Austria). *P* values of <0.05 were defined as significant.

Results

Of the 47 patients included in this retrospective analysis, 12 were alive and 35 were dead at the time of the study. In total, 14 patients died of systemic disease, 15 patients died due to the progression of brain lesions, two patients



No. at risk	
After GKS	47 35 22 11 5 1 1
After SRT	47 19 7 1

Fig. 2 Overall survival curves for all patients obtained after the first stereotactic radiotherapy (SRT) and gamma knife surgery (GKS)

died of other diseases, and the cause of death was unclear in four patients. Among the 15 patients who died of brain lesions, nine died as a result of re-recurrence after the SRT, three died of other new brain metastases, and three patients died of both causes. After the first GKS, the median follow-up period for all patients was 24 (range 3–83) months, and the median survival time was 27 months. The overall survival rates after the first GKS were 80% at 1 year and 57% at 2 years (Fig. 2). After the SRT, the median follow-up period for all patients was 10 (range 1–40) months, the median survival time was 12 months, and the 1-year overall survival rate was 50%. The 36 tumors in 34 patients were primarily salvaged by SRT. In this group, the median survival time was 27 months after the first GKS, and the median survival time was 13 months after the SRT. The other 14 tumors in 13 patients had been first treated by GKS for local recurrence. This group of patients had a median survival time of 35.5 months after the initial GKS and 11 months after the SRT. There were no differences between these two groups.

The median imaging follow-up period using MRI or CT after the SRT was 7 months for all patients (range 1–28 months). Of the 50 lesions that were treated with SRT, 26 did not recur prior to the patient's death or the last follow-up examination, and the remaining 24 recurred. Local re-recurrence was confirmed by surgery or biopsy in seven patients. The cumulative incidence of local recurrence after SRT was 15% at 6 months and 37% at 1 year, and the median time to local recurrence was 16 months. On the other hand, the local recurrence rate after the last GKS was 44% at 6 months and 78% at 1 year, and the median time to local recurrence was 7.5 months. The median

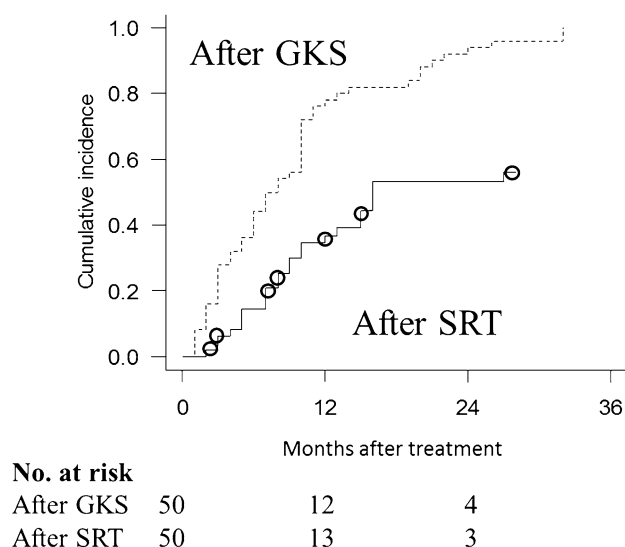


Fig. 3 Cumulative incidences of local recurrence after GKS and SRT. GKS indicates the last session of GKS in the cases in which multiple GKS procedures were performed. The median time to local re-recurrence after SRT was significantly longer than the median interval between the last GKS and recurrence ($P < 0.001$)

time to re-recurrence after the SRT (16 months) was significantly longer than the median interval between the last GKS and recurrence ($P < 0.001$) (Fig. 3). In the group primarily salvaged by SRT, the median time to local re-recurrence was 6.5 months after GKS and 16 months after SRT. In the group primarily salvaged by GKS, the median time to local re-recurrence was 10 months after the last GKS and 14 months after SRT. There were no differences between the two groups.

Performance status scores were maintained or became higher than the pretreatment values until recurrence or last follow-up in 21 of the 47 patients (45%). Symptomatic radiation-induced edema was noted in 24 patients (49%) at 1–12 (median 4) months after the SRT. Corticosteroids were used temporarily by 22 patients and for >4 months by 2 patients; four patients died during the period of corticosteroid administration. Eight patients developed grade ≥ 2 radiation necrosis at 3–17 (median 5) months, and two patients underwent surgery for necrosis. These patients had no apparent risk factor with respect to the tumor size and radiation dose for developing brain necrosis. One patient undergoing surgery for necrosis was administered corticosteroid therapy for >4 months.

Discussion

Re-irradiation of central nervous system (CNS) tumors has long been considered to be contraindicated based on the belief that normal brain tissue would likely not be able to

recover from the tissue damage caused by the radiation. More recently, however, it has been shown that re-irradiation of previously irradiated regions does not necessarily result in an excessive risk of late radiation damage, leading to re-irradiation protocols being used with increasing frequency [16]. Nevertheless, radiation oncologists remain reluctant to re-irradiate the CNS using conventional radiotherapy techniques. Localized irradiation, to the contrary, appears to be an acceptable alternative as it seems to exhibit an acceptable toxicity profile. One approach to localized irradiation is intraoperative radiotherapy. Shibamoto et al. [17] obtained durable remission after tumor resection and intraoperative radiation in patients with ependyoma, anaplastic ependyoma, or anaplastic oligodendroglioma. Stereotactic radiosurgery and SRT are increasingly being used as treatments for recurrent CNS tumors [16]. The accumulation of clinical data is expected to prove the safety and efficacy of such approaches.

A second GKS is occasionally performed to treat locally recurrent brain metastases after the initial GKS. The median survival time of patients undergoing a second GKS has been reported to range from 15 to 22.4 months from the first GKS [18–20]. The median overall survival time after the first GKS of the patients in our study was 27 months, which compares favorably with that reported in previous studies in which second GKS was performed for locally recurrent brain metastases. We divided our patients into two groups, one treated primarily by SRT for local recurrence and the other treated first by GKS and then by SRT, and we found no differences between the two groups in terms of prognosis after SRT. This result may suggest the usefulness of SRT even after repeat GKS for local recurrence. The relatively favorable survival outcomes in our patients may partly derive from our exclusion of patients with extensive extracranial metastases. Of the 35 patients who died in our study, 15 (42%) died due to uncontrolled brain metastases. Although this rate is similar to that previously reported by Penny et al. [11], the frequency of neurogenic death after first-line GKS was reported to be 6–10% in a recent large prospective study [21]. This difference indicates that our patients may have been selected for secondary treatment for local recurrence after GKS because their extracranial metastases were not extensive. Nevertheless, the favorable survival outcomes obtained in our study were derived, at least in part, from the use of SRT for re-treatment.

Although this study focused on second-line treatment for tumor recurrence, the median time to local re-recurrence after the SRT (16 months) was significantly longer than the median interval between the last GKS and recurrence (7.5 months). The 1-year local recurrence rate was 37% whereas it was 78% after the GKS. Since the second-line treatment yielded better results than the first-line treatment, one may question whether the diagnosis of local recurrence

was correct (none of the recurrent masses were subjected to biopsy examinations before the SRT). We carefully followed all of the patients in this study, and a review of their follow-up data suggested that the diagnosis of recurrence was correct in all cases. Namely, contrast-enhanced masses shrunk in response to the SRT in the majority of cases, and the shrunken masses remained stable or enlarged thereafter. One of the possible reasons for the longer interval to local re-recurrence may be our policy of diagnosing re-recurrence. As stated in the [Materials and methods](#), we did not diagnose re-recurrence even when the contrast-enhanced image of the shrunken mass showed enlargement because it was difficult to distinguish between re-recurrence and radiation-induced changes. We performed a further evaluation only after the contrast-enhanced image became larger than the size of pre-SRT mass. Because of this, the time to local re-recurrence might have been elongated by a few months.

Several authors have obtained encouraging clinical results when using SRT for the treatment of large brain tumors [22]. Investigators have recently also used fractionated GKS to treat large brain metastases [23, 24]. In our study, the median PTV for the SRT was 28.8 cm³, which was significantly larger than the median PTV for the GKS (10.4 cm³), and we used SRT. Large tumors may contain more hypoxic cells, which are resistant to radiation [25, 26]; consequently, the reoxygenation of such cells may be important during the treatment of recurrent metastatic brain tumors [27, 28]. SRT has radiobiological advantages over GKS because the reoxygenation of hypoxic tumor cells and the redistribution of the cell cycle to a more sensitive phase are expected to occur between fractions in SRT [29]. Since the backgrounds of the patients in our study who underwent SRT for local recurrence did not seem to differ from those of the patients undergoing GKS for local recurrence, the radiobiological aspect may be important in explaining the better outcome in our study. Thus, the re-treatment of recurrent tumors with SRT was effective and yielded relatively good local control. GKS may be suitable to treat small local recurrences owing to the high conformity of such recurrences, and SRT should be considered especially for cases involving large locally recurrent lesions.

The results of this study suggest the potential usefulness of fractionated radiotherapy for recurrent brain metastases. Since the doses we used are similar to those employed in whole-brain radiotherapy, the relative merits of SRT compared with whole-brain radiation remain controversial and should be investigated in future studies. It is possible that whole-brain radiotherapy may achieve comparable results. In a Chubu Radiation Oncology Group study, brain atrophy developed after whole-brain radiation in up to 30% of patients, but it was not necessarily accompanied by a decline in the MMSE score, and dementia after whole-brain radiotherapy unaccompanied by tumor recurrence

was infrequent [7]. Coupled with the findings obtained in the JCOG 0504 study [8], the neurocognitive decline after whole-brain radiation may develop after 2 years. So, the possibility of developing clinically significant decline in cognitive function is considered to be small in the re-irradiation setting compared with the initial treatment because of the relatively short expected survival period. The risk of cognitive dysfunction may not be a major problem in most of the current cohort of patients with poor life expectancy. On the other hand, incidences of grade 2–4 adverse events were higher in the whole-brain-treated group than in the radiosurgery group in the JCOG 0504 study [8], whereas intracranial disease control was better with whole-brain radiotherapy, and a new brain lesion was the cause of death in six of 15 patients who died of brain lesions. To summarize, each approach has both merits and demerits.

The adverse events experienced by the patients in our study were generally acceptable. Symptomatic radiation-induced edema was noted in 24 patients, but in most cases it was controllable with corticosteroids. GKS for large brain metastases (maximum diameter ≥ 3 cm) can lead to severe neurotoxicity, and it is recommended that the marginal dose should be reduced [2, 30]. However, SRT allows the delivery of a higher radiation dose and causes fewer adverse events than GKS [6].

Conclusion

The results of our study suggest the potential usefulness of salvage SRT in the treatment of locally recurrent brain metastases after GKS. However, the question of whether the salvage SRT approach is superior to the whole-brain radiotherapy approach remains open to discussion. At present, both approaches may be possible options, and further studies are necessary.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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