ORIGINAL ARTICLE - BRAIN TUMORS

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The influence of histology on the response of brain metastases to gamma knife radiosurgery: a propensity score-matched study

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Abstract

Background In terms of response to fractionated radiotherapy, metastatic brain tumors of certain origins are considered radioresistant.

Objective To determine the influence of "radioresistant" histology on outcomes of brain metastases treated with radiosurgery.

Methods Between 2001 and 2017, 121 patients with brain metastases from renal cell carcinoma (RCC) and 2151 from non-small cell lung cancer (NSCLC) were reviewed. Eighty-seven pairs were derived using propensity score matching. Local progression-free survival (PFS), progression patterns, distant PFS, and overall survival were investigated.

Results The median follow-up period was 13.7 months (range, 1.6–78.4 months). A total of 536 lesions were treated using gamma knife radiosurgery (GKS), with a median dose of 20 Gy (range, 12–28 Gy). The actuarial local PFS rates in the RCC group were 91% and 89% at 6 and 12 months, respectively, and did not differ from the NSCLC group (97% and 83% at 6 and 12 months, respectively). Continuous progression, without response to GKS, was noted in seven of the eight progressed RCCs. However, six of the seven progressed NSCLCs showed transient shrinkage before progression. The median distant PFS was 9.3 months (95% CI, 6.3–12.2) in the RCC group and 8.0 months (95% CI, 5.5–10.4) in the NSCLC group. The median overall survival was 16.1 months (95% CI, 11.3–20.8) and 14.9 months (95% CI, 11.9–17.8) in RCC and NSCLC groups, respectively.

Conclusion Histological differences had no effect on local control in the single high-dose range used for radiosurgery. However, changes in tumor volume during progression varied across tumor histology.

Keywords Brain metastasis · Propensity score matching · Radioresistant · Radiosurgery

Abbreviations

WBRT	Whole brain radiotherapy
RCC	Renal cell carcinoma
MRI	Magnetic resonance imaging
SRS	Stereotactic radiosurgery
NSCLC	Non-small cell lung cancer
GKS	Gamma knife radiosurgery
PSM	Propensity score matching
KPS	Karnofski performance score
SMD	Standardized mean difference
LMS	Leptomeningeal seeding
PFS	Progression-free survival
OS	Overall survival

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Introduction

Fractionated whole brain radiotherapy (WBRT) has been a standard treatment for brain metastases [17]. The prognosis of patients with brain metastases is generally poor, with a median survival of only 3 to 4 months following a conventional WBRT regimen (30 Gy in 10 fractions) [16]. Metastatic brain tumors from melanoma, sarcoma, and renal cell carcinoma (RCC) are generally categorized as radioresistant because they are refractory to conventional fractionated radiotherapy [5]. The notion of radioresistance in metastatic brain tumor may not be useful because it assumes that all radiotherapies are equal [8].

Technical advances in both high-resolution magnetic resonance imaging (MRI) and the delivery platforms of stereotactic radiosurgery (SRS) have allowed SRS to be used in the management of brain metastases [14]. Across a variety of primary tumor origins, the tumor control rate of SRS is promising and reproducible [14]. Brain metastases from lung cancer are the most common, and local control rates after SRS range between 80 and 98%, with better outcomes when minimum doses of 18 Gy are applied [6, 15, 17, 23, 29]. Several authors have reported a local control rate of 88% after SRS in patients with radioresistant brain metastases, while others have found no difference in tumor control between radioresistant and non-radioresistant tumors [1, 2, 18, 28]. Regardless, clinicians may consider increasing SRS doses to treat radioresistant brain metastases [14].

The present study aimed to determine the influence of radioresistant histology on the outcomes of brain metastases treated using a single high-dose irradiation. Because metastatic brain tumors are highly heterogeneous, we designed a propensity score–matched case–control study to minimize potential imbalances in confounders.

Methods

Patient selection and propensity score matching

Between December 2001 and October 2017, 121 patients with brain metastases from RCC and 2151 with brain metastases from non-small cell lung cancer (NSCLC) who underwent gamma knife radiosurgery (GKS) were reviewed. Among the latter, only lung adenocarcinoma cases were enrolled to enhance the homogeneity of the tumors. Patients were excluded if they were unavailable to undergo at least one MRI or underwent fractionated GKS. Ultimately, 118 patients with RCC and 1402 with NSCLC who had brain metastases were subjected to case-control matching (Fig. 1).

The propensity score matching (PSM) method was adopted to minimize the bias arising from heterogeneity among patients with brain metastasis. A multivariate logistic regression model was built based on the following covariates: age, sex, Karnofski Performance Score (KPS; dichotomized at 70), total tumor volume, radiation dose, and previous or adjuvant WBRT. Total tumor volume was divided into four ranges; 1–500, 501–4000, 4001–13,500, and > 13,500 mm³. Using the 1:1 nearest matching algorithm (caliper < 0.001), each patient with RCC metastasis was matched with a patient with NSCLC metastasis. Finally, a total of 87 pairs were derived, and the balance between the RCC and NSCLC groups for each variable was assessed using standardized mean difference (SMD) as follows: an SMD of less than 0.1 indicated a negligible difference; a value between 0.1 and 0.3 indicated a small difference; a value between 0.3 and 0.5 indicated a

moderate difference; and a value above 0.5 indicated a considerable difference [22].

All patients were treated with GKS (Leksell Gamma Knife model B, C, Perfexion, or Icon; Elekta AB, Stockholm, Sweden). In general, dose was selected based on the recommendations from the SRS dose escalation trial RTOG 90-05, and modified according to the situation of each individual patient [24]. In particular, tumor size, adjacent vital structures, and previous history of WBRT were considered when prescribing dose. Follow-up MRI and clinical evaluations were typically obtained at 3-month intervals or when clinically necessary. Salvage treatments, including GKS, tumor resection, and WBRT, were actively performed to prolong survival time according to the patient's situation. The clinical and radiological data of patients were retrospectively collected.

Primary and secondary outcomes

The primary endpoint was local control without progression. Local progression was defined as a combination of a 20% increase in volume of the GKS-treated lesions and one of the following criteria: (1) histological confirmation of tumor progression after surgical resection; or (2) increased cerebral blood volume of the lesion noted in subsequent MRI if surgery was not indicated. In progressed lesions, tumor volumes from the time of GKS to the last MRI were serially measured using the GKS planning software (Gamma Plan®; Elekta AB, Stockholm, Sweden). Within this volumetric analysis, patterns of local progression were categorized as either (1) continuous progression without any response to GKS or (2) progression after transient shrinkage. Relationship between pre-GKS factors and local progression was also investigated.

The secondary endpoints were distant (intracranial) progression, radiation-induced complication, and overall survival. Distant progression was defined as the appearance of new parenchymal lesions and/or leptomeningeal seeding (LMS). Radiation-induced complication was defined as an increase in tumor volume not caused by tumor recurrence, and was confirmed retrospectively, by thorough medical charts and MRI reviews, and/or by histological confirmation through surgery. The dates of death were collated from the data provided by the "Ministry of the Interior and Safety" for academic purposes only. If a patient died, or if surgical resection was performed due to radiation-induced complication, data were censored in the primary outcome analysis.

Statistical analysis

All statistical analyses were performed using SPSS software (version 24.0, IBM Corp., NY, USA) and R software (R Project for Statistical Computing), and a two-sided p value of 0.05 was used as the threshold of significance in

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┌─────────────────────────┐        ┌─────────────────────────┐
│  Brain metastases from  │        │ Brain metastases from   │
│  RCC (n=121)            │        │ lung cancer (n=2151)    │
└───────────┬─────────────┘        └───────────┬─────────────┘
            │                                  │
            │                      ┌────────────▼──────┐      ┌─────────────────────────┐
            │                      │ adenocarcinoma?   ├─────▶│ SCLC (n=209)            │
            │                      └────────────┬──────┘      │ NSCLC other than        │
            │                                   │             │ adenocarcinoma (n=365)  │
            │                                   │             └─────────────────────────┘
            │                      ┌────────────▼──────────────┐
            │                      │ Brain metastases from lung │
            │                      │ adenocarcinoma (n=1577)   │
            │                      └────────────┬──────────────┘
┌───────────────────┐     │                     │         ┌───────────────────┐
│ Inadequate data   │◀────┤                     ├────────▶│ Inadequate data   │
│ quality (n=3)     │     │                     │         │ quality (n=175)   │
└───────────────────┘     │                     │         └───────────────────┘
            ┌─────────────▼───────┐   ┌─────────▼───────────┐
            │ Included patients   │   │ Included patients   │
            │ with RCC (n=118)    │   │ with NSCLC (n=1402) │
            └─────────────┬───────┘   └─────────┬───────────┘
                          └───────────┬─────────┘
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                          │ Matched 87 pairs     │
                          │ (n=174)              │
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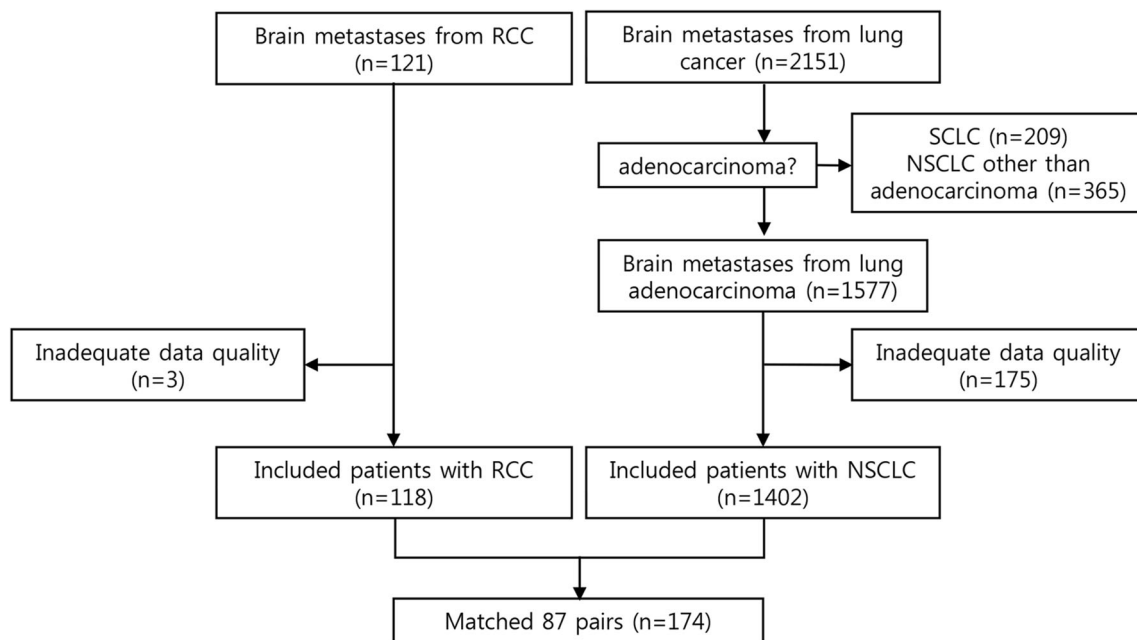
Fig. 1 Patient selection flow chart. RCC, renal cell carcinoma; SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer

all tests. Categorical data were presented as the number of patients with percentages, parametric continuous variables as mean with standard deviation, and non-parametric data as median with range. The Mann–Whitney U test and Fisher's exact test were used to analyze normally distributed categorical and non-parametric continuous variables, respectively. After PSM, matched pairs were compared using the Wilcoxon signed-rank test, McNemar test, and generalized estimating equation. The Kaplan–Meier method was applied to analyze local and distant progression-free survival (PFS), as well as overall survival (OS), with the two groups being compared using the stratified log-rank test. The stratified Cox proportional hazards model was used for univariate and multivariate analyses. The Spearman correlation coefficients were derived to reveal the dose–volume relationship in locally controlled and progressed lesions, and compared each other using Z test.

Results

Of the 174 patients (87 pairs), 122 (70%) were male and 52 (29%) were female. The median age at the time of GKS was 58 years (range, 32–84 years), and the median follow-up period was 13.7 months (range, 1.6–78.4 months). A total of 536 lesions (217 from RCC and 319 from NSCLC) were treated using GKS, with a median dose of 20 Gy (range, 12–28 Gy) at the median 50% (range, 45%–85%) isodose line. The median value of coverage, the target volume within the prescription isodose line, was 98% (range, 95–100%).

Patient characteristics before and after propensity score matching

The clinical demographics of the patients before and after matching are shown in Table 1. Before matching, the RCC group showed significant male pre-dominance ($P < 0.001$) and had undergone more tumor resections before GKS ($P < 0.001$). The mean total tumor volume was had a smaller trend in the RCC group ($P = 0.087$), and the mean radiation dose in the RCC group was larger than in the NSCLC group, without significance ($P = 0.076$). After PSM, no significant differences were found in any matched variables and all SMD values were improved. Negligible differences between matched groups were noted in age, KPS, total tumor volume, radiation dose, and history of WBRT. Small differences were noted in sex and history of tumor resection.

Local progression

The crude local tumor control rates were 90% and 92% in the RCC and NSCLC groups, respectively. In the RCC group, eight patients (9%) experienced local progression, while three of them underwent surgical resection, and five were subjected to repeat GKS. The actuarial local PFS was 91% and 89% at 6 and 12 months, respectively. In the NSCLC group, seven patients (8%) experienced local progression, while five underwent tumor resection and two were subjected to repeat GKS. The actuarial local PFS was 97% and 83% at 6 and 12 months, respectively. There was no significant difference in actuarial local PFS between the two groups (Fig. 2a).

Table 1 Patient characteristics before and after propensity score matching (all categorical variables are presented as a number of items with percentage; all mean values are presented with standard deviation)

Characteristics	Before matching				After matching			
	RCC	NSCLC	P value	SMD	RCC	NSCLC	P value	SMD
No. of patients	118	1402	N/A	N/A	87	87	N/A	N/A
Mean age (years)	58.6 (10.6)	59.1 (10.9)	0.432	0.048	58.7 (10.1)	58.4 (9.7)	0.318	0.027
Female	26 (22)	655 (46)	< 0.001	0.538	21 (24)	30 (34)	0.064	0.229
KPS > 70	64 (54)	756 (53)	1.000	0.006	50 (57)	50 (57)	1.000	< 0.001
Mean total tumor volume (cm^3)	5.1 (5.4)	6.2 (7.5)	0.087	0.161	5.1 (5.4)	5.4 (6.5)	0.832	0.033
Total tumor volume			0.975	0.270			1.000	< 0.001
< 0.5 cm^3	9 (7)	193 (13)			7 (8)	7 (8)		
< 4.0 cm^3	59 (50)	541 (38)			44 (50)	44 (50)		
< 13.5 cm^3	37 (31)	505 (36)			28 (32)	28 (32)		
≥ 13.5 cm^3	13 (11)	163 (11)			8 (9)	8 (9)		
Mean radiation dose, Gy	20.5 (3.7)	19.7 (4.0)	0.076	0.204	20.5 (3.7)	20.3 (3.4)	0.488	0.075
Previous WBRT	14 (11)	230 (16)	0.240	0.131	10 (11)	10 (11)	1.000	< 0.001
Previous craniotomy	17 (14)	65 (4)	< 0.001	0.383	14 (16)	6 (6)	0.077	0.291

KPS, Karnofsky performance score; *RCC*, renal cell carcinoma; *NSCLC*, non-small cell lung cancer; *SMD*, standardized mean difference; *N/A*, not applicable; *WBRT*, whole brain radiation therapy

Patterns of local progression and progression-related factors

The RCC and NSCLC groups showed different aspects in terms of the timing of progression (Fig. 3). In the RCC group, seven of the eight locally progressed lesions (87%) showed continuous progression, without any response to GKS. Only one RCC metastasis showed a transient shrinkage after GKS. Among the seven patients who showed no response, five underwent neurosurgical intervention after the first follow-up MRI. In contrast, six of the seven locally progressed NSCLC cases (85%) showed tumor progression after obvious tumor shrinkage. Representative cases are shown in Fig. 4. In the stratified Cox proportional hazards model, none of the pre-GKS factors were related to local progression. In the dose–

volume scatter plot, cases of local progression showed similar distribution to locally controlled cases, regardless of primary origins (Fig. 5). Local progression developed at dose ranges between 16 and 25 Gy. The Spearman correlation coefficients were − 0.685 ($P < 0.001$) and − 0.676 ($P = 0.006$) among locally controlled ($n = 159$) and locally progressed ($n = 15$) lesions, respectively. These two correlation coefficients did not differ significantly from each other.

Distant progression, radiation-induced complication, and overall survival

Distant progression was found in 51 patients with RCC (58%) and in 53 with NSCLC (60%). The median estimated distal PFS after GKS was 9.3 months (95% CI, 6.3–12.2) in the
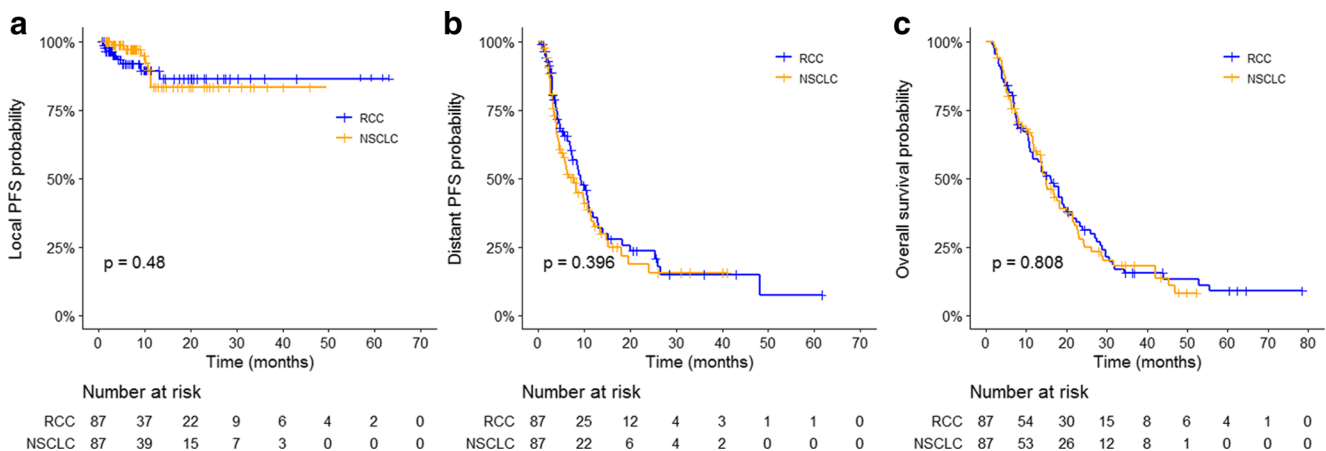

Fig. 2 Kaplan–Meier Curves of **a** local progression-free survival (PFS), **b** distant PFS, and **c** overall survival in RCC and NSCLC groups

Fig. 3 Volumetric analysis of lesions with local progression in the **a** RCC group and **b** NSCLC group. Patterns are categorized into continuous progression without any response to GKS (blue) and transient response to GKS before progression (orange). The dominant pattern in each group is indicated by solid line
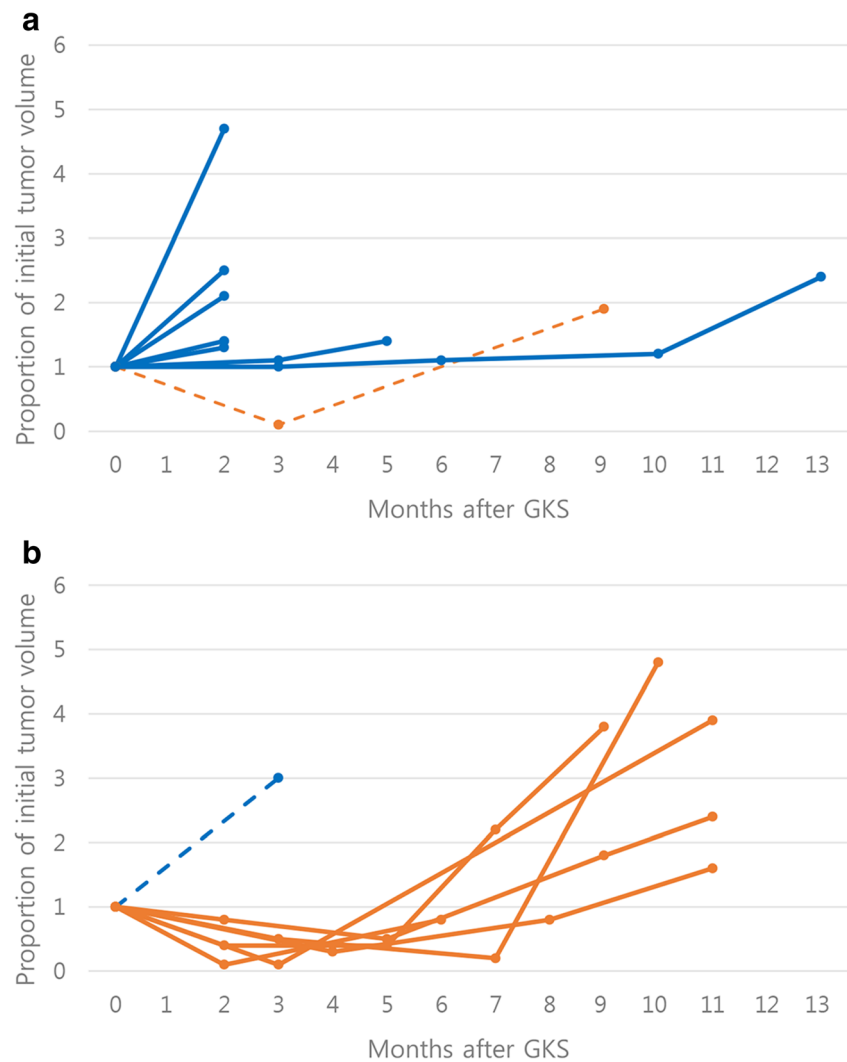
RCC group and 8.0 months (95% CI, 5.5–10.4) in the NSCLC group (Fig. 2b). LMS was more prevalent in the NSCLC group than in the RCC group (11 patients [12%] vs. 3 patients [3%], $P = 0.048$). LMS was diagnosed at the first follow-up MRI in one patient in the RCC group and 6 patients in the NSCLC group.

Radiation-induced complication developed in four patients in the RCC group (4%) and six in the NSCLC group (6%), and no significant difference was noted between two groups in this regard. Radiation-induced complication occurred at doses between 20 and 23 Gy. None of the pre-GKS factors, including dose, total tumor volume, and history of WBRT, was predictive of complication development.

In the RCC group, the median estimated OS after GKS was 16.1 months (95% CI; 11.3–20.8), and 10 patients (11%) died of active intracranial progression. Thirty-seven patients (42%) died of extracranial progression and/or treatment-related complications, and the other 40 (46%) had undefined cause of death. In the NSCLC group, the median estimated OS from the time of GKS was 14.9 months (95% CI, 11.9–17.8); this

was not significantly different from the RCC group (Fig. 2c). Twelve patients (13%) died of intracranial progression, 46 (52%) from extracranial disease, and the other 29 (33%) of unknown causes.

Discussion

Metastatic brain tumors are the most common intracranial tumor and they vary widely in their characteristics, making them difficult to compare in terms of histology [4, 27]. PSM is widely used in observational studies to reduce selection bias [7]. In the present study, well-matched groups derived using PSM were investigated to compare the effects of GKS on brain metastases from different origins.

The results indicated that GKS conferred equivalent local tumor control rates (over 90%) in radioresistant and non-radioresistant brain metastases. In previous studies, the reported local control rates of SRS have varied depending on primary origins: 90–94% in breast cancer, 81–98% in lung
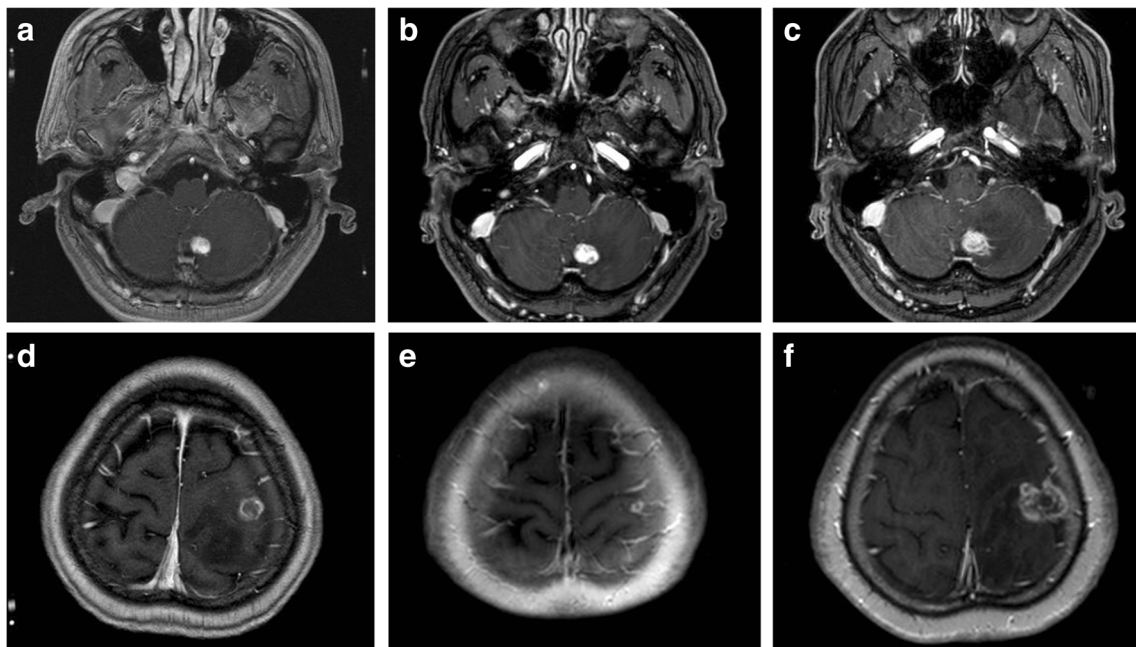
Fig. 4 Illustrative cases. **a** A 55-year-old male with a single brain metastasis from RCC underwent GKS (25 Gy). **b** Two months later, the tumor volume increased to 1.5-fold. **c** At 5 months after GKS, the tumor continuously increased in volume without any response to GKS, and caused headache. The lesion was resected by microsurgery and the metastatic RCC was histologically diagnosed. **d** A 70-year-old female presented with right side weakness. She had two brain metastases from NSCLC and underwent GKS (25 Gy). **e** The lesions were significantly decreased after 2 months of GKS. **f** However, at 9 months after GKS, one lesion progressed considerably and was surgically removed. Metastatic NSCLC was histologically confirmed

Fig. 5 Dose–volume scatter plot. The Y axis (total tumor volume) is expressed as a square value. The solid line indicates a linear correlation between radiation dose and total tumor volume in locally controlled RCC and NSCLC metastases, and the dashed line indicates a correlation in locally progressed RCC and NSCLC metastases. There was no significant difference between the distribution of locally progressed and controlled lesions
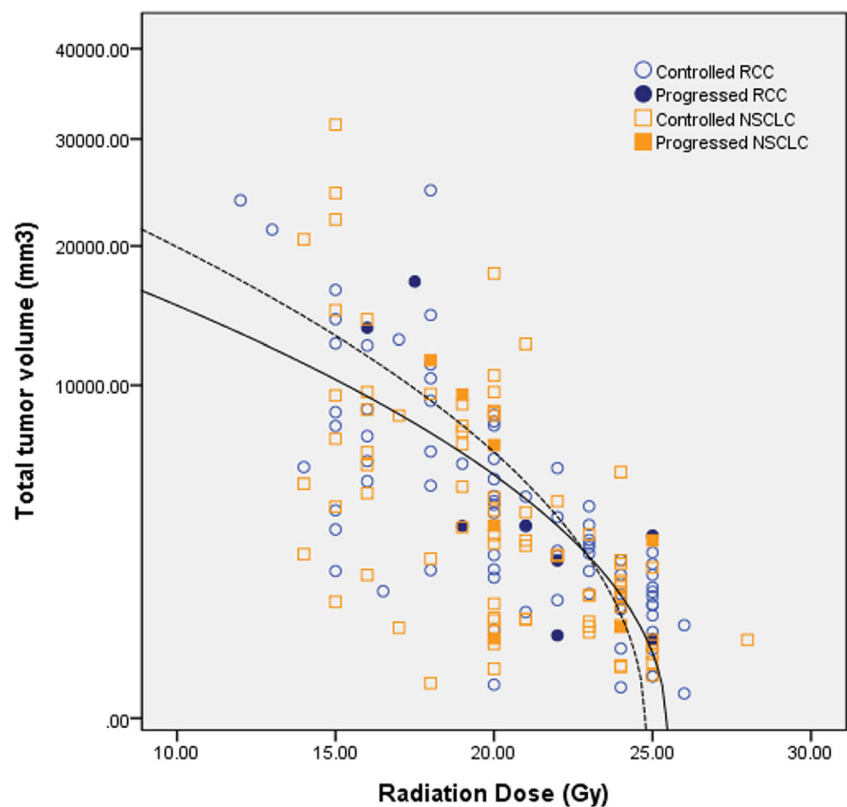
cancer, 73–90% in melanoma, and 83–96% in RCC [1, 2, 6, 9, 11, 13, 14, 17, 19, 23]. Because most studies included brain metastases from single or heterogenous originating sites, radioresistant metastases have not been properly compared with non-radioresistant. Though no difference in tumor control rates is obviously expected, we confirm the assumption that GKS has similar effects regardless of tumor histology.

Some authors have reported that radiation dose influences local tumor control, suggesting that higher doses result in better outcomes [20, 25]. Theoretically, increased radiation doses may result in greater tumor control rate but lead to greater radiation toxicity [24]. However, a complete mechanistic explanation in terms of a high single-dose radiation is still in debate [3, 12, 26]. Based on experience from their own center, Kondziolka et al. advocated that marginal doses above 20 Gy to treat brain metastases are unnecessary. [14] It is assumed that the undefined effects of high single-dose irradiation on tumor vasculature and additional biological pathways may affect tumor regression. In the present study, the relationship between local progression and predisposing factors such as radiation dose, total tumor volume, and WBRT was unclear. Even low doses below 15 Gy showed effective tumor control. The dose range prescribed in this study (between 12 and 28 Gy) suppressed over 90% of local progression regardless of histology. These results should be interpreted with caution. This study had statistical limitations indicating a meaningful relationship because the incidence of local progression was low and the sample size was small.

On the other hand, each tumor histology responds to high single-dose radiation differently. In the present study, most locally progressed NSCLCs showed a transient shrinkage after GKS, followed by progression, while most locally progressed RCCs never shrank after GKS. These findings partly corroborate a recent report suggesting that volumetric responses after GKS depend in part on tumor cell origin. In that analysis, the NSCLC group was categorized into non-responders, mixed responders, and sustained responders while the radioresistant group (melanoma) was divided into non-responders and sustained responders [10]. The same study also reported that brain metastases from breast cancer regressed more quickly and extensively than that from other origins [13, 14]. Therefore, histological differences are crucial in determining radiosurgical response. In practice, early neurosurgical intervention may be warranted if radioresistant tumors such as melanoma and RCC show no response to radiosurgery.

Most patients with brain metastases die of extracranial disease, regardless of primary origin site. Therefore, local tumor control using SRS should be emphasized because it is minimally invasive and effective treatment for all kinds of brain metastases. To date, SRS has been ineffective in preventing newly developed intracranial metastasis, and distant progression rates are uniformly high as our results [6, 25]. However, prophylactic intracranial radiation is not recommended, because the traditional concept of sub-clinical spread of micrometastasis was proven to be incorrect since the introduction of high-resolution MRI [14]. Instead, salvage SRS is a reasonable option when the number and size of newly developed lesions are acceptable. Because of active intracranial salvage treatment, OS after GKS was substantially longer in our cohort than in historical data [2, 9, 17, 21].

This study had some limitations. Firstly, although we used PSM to reduce the effects of heterogeneity and non-randomization, this was not a randomized controlled trial. Furthermore, confounding factors, such as concurrent chemotherapy and genetic variation related to radiosensitivity could not be balanced in this study. We also found no definitive pre-GKS factors related to local progression and radiation-induced complication. Multivariate analysis using a large number of cases, or a randomized controlled study, may be necessary to determine this relationship in detail.

Conclusion

So-called "radioresistant" RCC brain metastases were comparable to NSCLC brain metastases in local tumor control by GKS. The difference in the radiosensitivity to conventional fractionated radiotherapy between these histologies did not have a significant influence on local tumor control by a single high-dose irradiation. However, temporal course of progression after GKS varied across histology.

Compliance with ethical standards

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

Ethical statements All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review boards (No. 2017-10-067); For this type of study, formal consent is not required.

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