

## Clinical Article

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# Gamma Knife Surgery for Brain Metastasis from Renal Cell Carcinoma : Relationship Between Radiological Characteristics and Initial Tumor Response

**Objective :** The authors have speculated that metastatic brain lesions from renal cell carcinoma (RCC) show diverse radiological patterns and tumor responses after Gamma knife surgery (GKS), and have hypothesized that these can be predicted from tumor radiological characteristics. The goal of the current study was to identify the radiological characteristics of RCC brain metastases and the predictors of initial radiosurgical response after GKS.

**Methods :** A retrospective analysis was performed on 48 lesions in 18 patients with RCC brain metastasis treated by GKS. The radiological characteristics of these lesions in magnetic resonance images (MRI) were classified into 3 categories according to enhancement patterns in T1-weighted images and signal intensity characteristics in T2-weighted images. Responses to GKS were analyzed according to these categories, and in addition, other potential predictive factors were also evaluated.

**Results :** MRI findings in the three categories were diverse, though numbers of the lesion were comparable. At 2-month MRI follow-ups after GKS, response rate was 54% and the local tumor control rate 83%. T2 signal intensity was found to be the principal predictive factor of response to GKS, namely negative predictive factor. Other variables such as age, sex, tumor volume, dose, duration from initial diagnosis to GKS, and previous systemic therapies failed to show significant relationships with treatment response by multivariate analysis.

**Conclusion :** Careful evaluation of the radiological characteristics of brain metastases from RCC is important prior to GKS because MRI heterogeneity has predictive value in terms of determining initial tumor response.

**KEY WORDS :** Renal cell carcinoma · Brain metastasis · Gamma knife surgery · Tumor control · Radiological characteristics.

## INTRODUCTION

Renal cell carcinoma (RCC) constitutes 80-90% of all primary kidney tumors and 2% of all cancers<sup>8,16,19</sup>. Moreover, the overall incidence of RCC is increasing possibly due to the higher discovery rates of recently introduced imaging modalities<sup>5,16</sup>. In addition, the chance of encountering metastatic brain tumors from RCC is also increasing due to advances made in the treatment of primary disease<sup>16,18</sup>. The brain metastasis occurs in around 10% of RCC patients<sup>8,14,18,19</sup>. Brain metastases from renal cell carcinoma make up about 6% of all the brain metastatic lesions<sup>2</sup>. Patients who develop brain metastasis from RCC are likely to have a poorer prognosis because of its radio-resistant nature<sup>3,4,8,18,19</sup>. Treatment options for brain metastasis from RCC include surgery, radiosurgery, chemotherapy, immunotherapy and conservative treatment with steroid<sup>16,19</sup>, and of these, radiosurgery, especially Gamma Knife surgery (GKS), has been reported to provide effective local tumor control in the selected patients contraindicated for surgery<sup>8,13,16,18</sup>. However, it has also been reported that tumor response to GKS varies considerably<sup>14,18</sup>.

Another peculiar feature of RCCs is that they are likely to develop intratumoral hemorrhage, and metastatic lesions from RCC share this characteristic<sup>13</sup>. However, this peculiarity may provide a characteristic radiological pattern that might be discernable in magnetic resonance images (MRI). Several reports have concluded that the radiological characteristics of these tumors are related to tumor response after GKS<sup>6,7,15,17</sup>. Therefore, the authors hypothesized that the responses of metastatic brain lesions from RCC to GKS can be predicted using their radiological characteristics. To investigate this possibility, the

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authors retrospectively analyzed 48 individual metastatic lesions in 18 RCC patients.

## MATERIALS AND METHODS

### Study population

Between June 1998 and January 2006, 25 brain metastasis patients, whose primary lesion had been previously confirmed as RCC histologically, were treated by GKS. Of these, 7 patients were excluded due to a lack of radiological follow-up data. The medical records and radiological data of the remaining 18 patients were reviewed. A total of 48 lesions in 18 patients were available for analysis. There were 14 men and 4 women of median age 55 (range 39 to 77 years), and their median KPS was 80 (range 60 to 100).

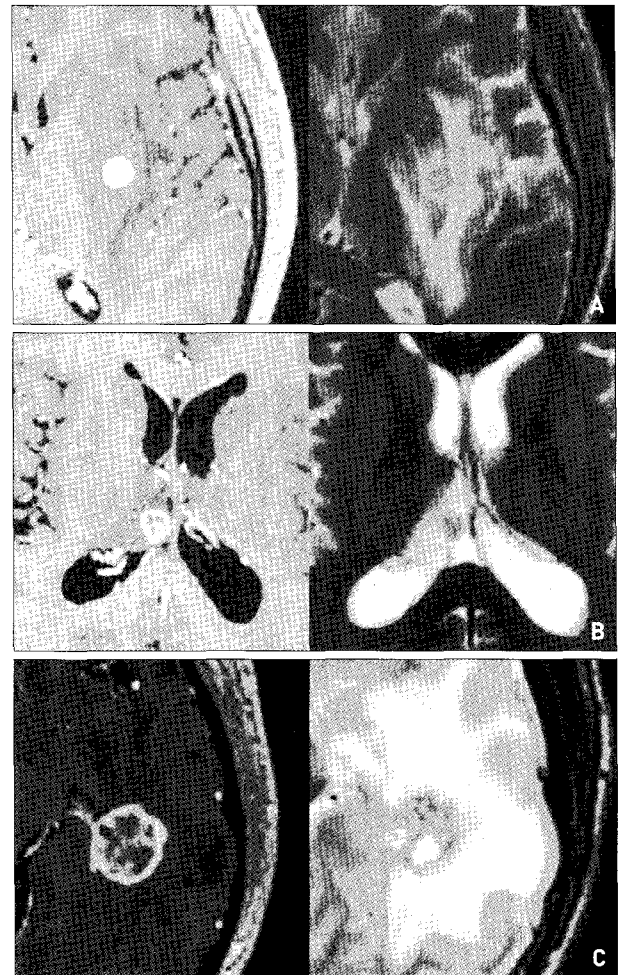
Six patients revealed brain metastasis as an initial manifestation of RCC. Six (33%) patients of the 18 showed no evidence of primary lesion recurrence or metastasis other than to the brain. One patient had a history of conventional radiotherapy for brain metastases, which failed to control the lesions. Twelve patients had undergone either chemotherapy or immunotherapy before GKS. However, no other treatment modalities were applied during the follow-up period after GKS in this series.

### Classification of lesions according to their radiological characteristics

Ten patients had a solitary lesion, 3 double lesions, and 5 multiple lesions. The radiological characteristics of these lesions in MRI were evaluated pre-GKS and were classified into 3 categories according to T1-weighted enhancement patterns and T2-weighted signal intensity characteristics. These were: 1) T1 homogeneous enhancement-T2 homogenous signal intensity lesion (T1HmT2Hm); 2) T1 heterogeneous enhancement-T2 homogenous signal intensity lesion (T1HtT2Hm); and 3) T1 heterogeneous enhancement-T2 heterogeneous signal intensity lesion (T1HtT2Ht) (Fig. 1). No lesions showed T1-weighted homogeneous enhancement and T2-weighted heterogeneous signal intensity (T1HmT2Ht). Responses to GKS were analyzed according to these three groups.

### Radiosurgical techniques and evaluation of treatment response

Gamma Knife surgery was performed using a Leksell Gamma knife Model B2 unit (Elekta Instruments, Norcross, GA, USA). Leksell Gamma Plan (Elekta AB, Stockholm, Sweden) was used for treatment planning. For target localization, MRI was obtained using a GE Horizon Signa 1.5 Tesla unit. A three-dimensional spoiled gradient echo pulse



**Fig. 1.** Classification of lesions according to magnetic resonance radiological characteristics. A : T1HmT2Hm : T1 homogeneous enhancement and T2 homogeneous signal intensity, B : T1HtT2Hm : T1 heterogeneous enhancement and T2 homogeneous signal intensity, C : T1HtT2Ht : T1 heterogeneous enhancement and T2 heterogeneous signal intensity.

sequence and fast spin echo T2-weighted sequence were used to produce T1 images of 1.0 mm and T2 images of 1.5 mm slice thickness. A median radiation dose of 20 Gy at a 50% isodose line was delivered to a median target tumor volume of 3.59 cm<sup>3</sup> (0.014 - 31.6).

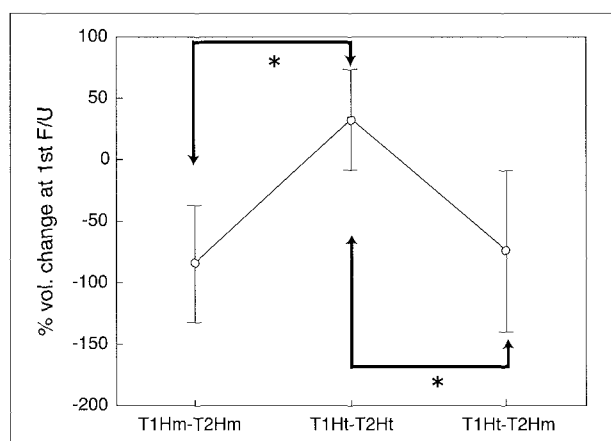
Contrast-enhanced MRI at 2 months after GKS was used to evaluate initial radiosurgical response. Tumor volumes were measured in MR images using Osiris software (version 4.0, UIN/HUCUG, Geneva, Switzerland). Tumor volumes were computed by specifying an object in a series of regions of interest (ROIs) over a set of multiplanar images and then summing ROI areas in each plane. The error associated with repeat measurements of tumor volume in one MR scan was within  $\pm 2\%$ .

The response was evaluated in two ways. First, tumor volume changes after treatment were calculated by subtracting

baseline tumor volume from tumor volume at 2 months after GKS. Second, response to treatment was scored as complete response (CR, complete disappearance), partial response (PR,  $\geq 50\%$  reduction in the product of the three orthogonal diameters as compared with measurements taken on the day of GKS), stable disease (SD,  $< 50\%$  reduction or  $< 25\%$  increase), and progressive disease (PD,  $\geq 25\%$  increase). Response rates (CR + PR%) of lesions and initial tumor control rates (CR + PR + SD%) were measured.

**Statistical analysis**

Initially, a linear regression model was used to identify potential predictors of treatment response. Simple linear



**Fig. 2.** Responses of brain metastasis from renal cell carcinoma to gamma knife surgery according to radiological characteristics. Noticeably, lower responses are observed when tumors are heterogeneous on T2 weighted images. Asterisks depict statistically significant differences between two groups.

**Table 1.** Numbers of lesions and magnetic resonance image patterns

| T1 enhancement-T2 signal intensity     | Number of lesions |
|--|-------------------|
| homogeneous-homogeneous (T1HmT2Hm)     | 17 ( 35%)         |
| heterogeneous-homogeneous (T1HtT2Hm)   | 8 ( 17%)          |
| heterogeneous-heterogeneous (T1HtT2Ht) | 23 ( 48%)         |
| Total                                  | 48 (100%)         |

**Table 2.** Reported radiosurgical responses of brain metastasis from renal cell carcinoma

| Authors, Year  | Number of Patients | Dose (GY) (50% isodose line) | Total Number of lesions | Tumor Control Rate (%) |
|----------------|--------------------|------------------------------|-------------------------|------------------------|
| Mori, 1998     | 35                 | 17                           | 52                      | 90                     |
| Amendola, 2000 | 22                 | 18                           | 38                      | 91                     |
| Payne, 2000    | 21                 | 20                           | 36                      | 100                    |
| Wowra, 2002    | 75                 | 21                           | 350                     | 95                     |
| Hoshi, 2002    | 42                 | 25                           | 113                     | 93                     |
| Brown, 2002    | 23                 | 18                           | 61                      | 88                     |
| Sheehan, 2003  | 69                 | 16                           | 146                     | 96                     |
| Muacevic, 2004 | 85                 | 21                           | 376                     | 94                     |
| Chang, 2005    | 77                 | 18                           | 99                      | 81                     |
| Shuto, 2006    | 69                 | 21.8                         | 314                     | 83                     |
| Present study  | 18                 | 20                           | 48                      | 83                     |

regressions were performed repetitively for each identified predictor to determine their effects. Multiple linear regression then used to determine if associations held after adjustment for the other factors. Statistical significance was accepted for p values of less than 0.05.

After screening each potential factor using the multiple regression model, we focused on the predictive power of radiologic characteristics. To determine the effect of this factor appropriately, analysis of covariance (ANCOVA) was adopted. Covariates used in this analysis were age, sex, tumor volume evaluated pre-GKS, dose of radiation applied, duration from initial diagnosis to GKS, and pre-GKS adjuvant therapy.

The Tukey HSD test was used for post hoc analysis, and the analysis was conducted using SPSS 12.0 for Windows (SPSS, Inc., Chicago, IL).

**RESULTS**

The distributions of the lesions according to MRI pattern classifications are shown in Table 1. Observed radiological patterns were diverse but the three classifications had comparable numbers of lesions.

At 2-month follow-up MRI, mean lesion volume showed a 22% reduction. Eleven lesions (23%) totally disappeared and 27 lesions (56%) showed measurable volume reduction. However, 10 lesions (21%) increased in volume with a maximum 391% increase from baseline. These results correspond to CR in 11 patients (23%), PR in 15 (31%), SD in 14 (23%) and PD in 8 (17%). The response rate of lesions 2 months post-GKS was 54% and the local tumor control rate was 83%.

Tumor responses were noticeably different in the radiological groups (Fig. 2). The T1HtT2Ht group (mean volume change %=27.2) showed poor response, whereas the T1HmT2Hm group (mean volume change %=-78.2) and the T1HtT2Hm group (mean volume change %=-68.0) responded well. Moreover, this result was statistically significant by univariate ( $p=0.001$ ) and by multivariate analysis ( $p=0.003$ ). Post hoc multiple comparisons also revealed significant differences between T1HmT2Hm and T1HtT2Ht ( $p=0.002$ ), and between T1HtT2Hm and T1HtT2Ht ( $p=0.03$ ). These findings indicate that T2 signal intensity is the principal predictive factor of treatment response to GKS in cases of RCC metastasis.

Other variables such as age ( $p=0.30$ ), sex ( $p=0.20$ ), tumor volume ( $p=0.43$ ), dose ( $p=0.89$ ), duration from initial diagnosis to GKS ( $p=0.90$ ), and previous systemic therapies (chemotherapy ( $p=0.32$ ) or immunotherapy ( $p=0.24$ )) failed to show a significant relationship with treatment response by multivariate analysis.

## DISCUSSION

The tumor control rate for brain metastasis from RCC by GKS is reported to range from 81% to 100% (Table 2)<sup>1,3,4,10,12-14,16,18,19</sup>. These previous reports were based on the evaluation made at 7-16 months after GKS. Since the current study evaluated the images 2 months after the GKS, the tumor control rate would be the initial tumor control rate. However, the initial tumor response rate (83%) found in the present series falls within this range for comparable radiosurgical treatment parameters. Several studies have sought to determine the prognostic factors that influence the local control of RCC brain metastasis by GKS<sup>3,16,18</sup>. Sheehan et al.<sup>16</sup> concluded that age, pre-GKS functional status, time from initial cancer diagnosis to brain metastasis, and dose delivered to tumor were statistically significant prognostic factors. Shuto et al.<sup>18</sup> found that tumor volume and peripheral dose delivered to tumor were the important predictors of local tumor control after GKS. In the present study, we examined these previously mentioned predictive factors, but failed to find any significance.

As was originally hypothesized, we were able to confirm that metastatic brain lesions from RCC have diverse radiological patterns, and that these radiological characteristics predict initial tumor response to GKS. In the current study, T2 heterogeneity was found to be a negative predictive factor of response. The previous studies which evaluated the pre-GKS T1 enhancement pattern, reported that heterogeneous enhancement pattern in T1-weighted images was a negative predictive factor for GKS response which could be because radiologically heterogeneous lesions contain more necrotic and hemorrhage areas with hypoxic tumor cells that are known to be correlated with radioresistance<sup>6,7,15,17</sup>. In addition to the body of literature ascertaining the importance of the enhancement pattern of the pre-GKS T1-weighted images, our results suggest that heterogeneous signal intensity in T2-weighted images also play an important role for the GKS response of the RCC brain metastases. It could be suggested that response should be poor after GKS if a lesion has a heterogeneous pattern by both T1-weighted enhanced and T2-weighted MRI. The importance of radiological characteristics as a predictive factor of response to radiosurgery for brain metastasis has been evaluated previously<sup>6,7,15,17</sup>.

Goodman et al. reported that heterogeneous tumor enhancement pattern might be a negative predictive factor for brain metastasis from breast cancer, lung cancer, melanoma, kidney cancer, and other<sup>6</sup>. Peterson et al. found that a homogeneous tumor enhancement pattern at baseline is correlated with local tumor control<sup>15</sup>. Shiau et al. also found that a homogeneous enhancement pattern is an important indicator of protracted freedom from progression<sup>17</sup>. For RCC brain metastasis, heterogeneity in T1-weighted images is predominantly due to intratumoral hemorrhage with an overall incidence of up to 46%<sup>13</sup>. Therefore, based on the above it appears likely that intratumoral hemorrhage is related with a poor response to GKS. Similarly, evidence of hemorrhage has been reported to predict local tumor control failure after GKS in those with melanoma brain metastasis<sup>11</sup>.

With regard to the heterogeneous signal intensity on T2-weighted images, it is considered to reflect the hemorrhagic tendency of the tumor. This is because T2 hypointensity in brain metastatic lesions is attributed to the presence of blood, iron, calcium or mucin<sup>9</sup>. Considering the underlying mechanism of the heterogeneous signal intensity described above, and our finding suggesting the importance of the T2 radiological characteristics as a predictive factor for the GKS response, the lesions with heterogeneous signal intensity that show poorer response to GKS might be explained by the presence of the radioresistant hemorrhagic or necrotic component of the tumor.

In the present study, we cannot affirm that initial radiological tumor response and radiological characteristics are directly correlated with clinical outcome due to limitations in study design. However, these preliminary observations provide good reason to conduct further studies on a larger scale in RCC brain metastasis patients. Furthermore, the application of adjuvant methods, such as, fractionation, the use of radiosensitizers, or hypoxic cell sensitizers, that are designed to improve GKS response in radiologically heterogeneous lesions should be further considered.

## CONCLUSION

Careful evaluation of the radiological characteristics of brain metastases from RCC is important prior to GKS because MRI heterogeneity has predictive value in terms of determining initial tumor response.

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