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# Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma

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## OBJECTIVES

To analyse the safety and efficacy of simultaneous standard anti-angiogenic therapy and stereotactic radiosurgery (SRS) in patients with spinal and cerebral metastases from renal cell carcinoma.

## PATIENTS AND METHODS

In all, 106 patients with spinal ($n$ = 55) or cerebral ($n$ = 51) metastatic lesions and an Eastern Cooperative Oncology Group status of 0 or 1 were treated with sorafenib or sunitinib and simultaneous SRS. The primary endpoint was local control. Secondary endpoints were toxicity and overall survival.

## RESULTS

Median follow up was 14.7 months (range 1–42 months). Forty-five patients were treated with sunitinb and 61 patients with sorafenib. Two patients had asymptomatic tumour haemorrhage after SRS. No skin toxicity, neurotoxicity or myelopathy occurred after SRS, and SRS did not alter the adverse effects of anti-angiogenic therapy. Local tumour control 15 months after SRS was 98% (95% confidence interval 89–99%). The median pain score before SRS was 5 (range 1–8) and was lowered to 0 (range 0–2, $P < 0.01$) after SRS. There were no treatment-related deaths or late complications after SRS. Overall survival was 17.4 months in patients with spinal lesions and 11.1 month in patients with cerebral lesions ($P$ = 0.038).

## CONCLUSIONS

Simultaneous systemic anti-angiogenic therapy and SRS for selected patients with renal cell carcinoma who have spinal and cerebral metastases is safe and effective. Single-fraction delivery allows for efficacious integration of focal radiation treatment into oncological treatment concepts without additional toxicity. Further studies are needed to determine the limits of SRS for renal cell carcinoma metastases outside the brain and spine.

## KEYWORDS

renal cell cancer, cyberknife, sunitinib, sorafenib, stereotactic, robotic surgery, spinal tumours, cerebral metastasis

## INTRODUCTION

Approximately 30% of patients with RCC have synchronous metastases, and about 40% will develop metachronous metastatic spread [1]. Anti-angiogenic treatment based on sunitinib, sorafenib and temsirolimus can double progression-free survival while prolonging overall survival [2–5] so it is regarded as standard therapy in patients with metastases who do not have further surgical treatment choices. Nevertheless, the outcomes of anti-angiogenic treatment in patients with cerebral metastases are limited and spinal lesions can result in pain, altered function or instability.

The role of conventional radiotherapy in metastatic RCC remains controversial. Local control of the tumour is rare, rendering radiotherapy a palliative treatment for selected patients [6]. Consequently radiotherapy is considered to have only minimal effects in controlling RCC metastases [7]. Stereotactic radiosurgery (SRS) is well established as an effective therapeutic method in patients with brain metastases from renal cancer [8–10], and knowledge is accumulating that spinal lesions can be treated effectively with spinal SRS [11–20]. In the SRS series published to date, metastatic lesions from RCC have been included but little is known about the combination of anti-angiogenic therapy and SRS in terms of toxicity and local tumour control in patients with advanced disease. The present consecutive case series evaluated the toxicity and effectiveness of a combined systemic (angiogenic inhibitors) and local (SRS) treatment of patients with metastatic RCC.

## PATIENTS AND METHODS

A consecutive series of 106 patients with spinal ($n$ = 55) or cerebral ($n$ = 51) metastatic lesions from RCC underwent SRS using the CyberKnife System (Accuray Incorporated, Sunnyvale, CA, USA) from August 2005 to

May 2009. All treatments were performed in an outpatient setting.

All patients included had histological confirmation of RCC. Metastatic disease had to be proven by CT scans according to the Response Evaluation Criteria in Solid Tumors (RECIST) without a surgical treatment choice. All patients had to have progressive disease as seen in imaging over at least 1 month. Patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and a Karnofsky performance status of at least 60. Only patients with an estimated life expectancy of 3 months or more were selected. All patients had to sign informed consent before SRS. Patients had to be on anti-angiogenic therapy for metastatic RCC. Spinal lesions were included if they were clinically relevant in the sense of causing pain, infiltrating the neuroforamina, or when instability appeared imminent.

Patients were excluded if there was evidence of acute spinal instability or if lesions compressed the spinal cord and caused neurological deficits. Patients were treated for metastatic lesions of the brain when there were no more than five lesions and there was no chance for surgical removal. Patients with surgically removable lesions were not included.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, Version 3.0.

The primary endpoint was local control. Lesions with at least 6 months of radiographic follow up were considered assessable for local control. Secondary endpoints were toxicity and overall survival.

The SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The endpoints of the study were local tumour control, local pain control and rate of adverse effects of SRS. These outcome parameters were estimated using the Kaplan–Meier method and a log-rank test. Multivariate and univariate analyses were performed with the Cox proportional hazard model.

All patients were treated systemically with anti-angiogenic therapy based on sorafenib or sunitinib for metastastic RCC. Treatment was chosen for the individual underlying situation before entry into this protocol. Therapy with sorafenib was given orally at 400 mg twice daily, suntinib was administered orally at 50 mg daily for 4 weeks with a subsequent 2-week wash-out phase. Dose was not withheld or delayed while patients were simultaneously treated with SRS. Adverse effects were graded according to the National Cancer Institute Common Toxicity Criteria 3.0 and were considered unrelated to SRS if they appeared before or later than 6 weeks after SRS therapy. Local adverse effects at the site of the SRS treatment were regarded as related to SRS no matter how much after SRS was the time of appearance.

The SRS treatment procedure has been described in detail recently [15,20–22]. The CyberKnife and the skeletal structure tracking software (XSIGHT, Accuray Inc.), were used for spinal radiosurgery in all patients. Previous studies have shown the feasibility and submillimetre accuracy of this fiducial-free, frameless method [15,20,21,23,24]. Planning and delivery of treatment were performed as outpatient procedures. The planning CT was acquired with the patient in the supine position without any support. Gadolinium-enhanced MRI scans were used in addition to a dedicated thin-cut (1-mm slice thickness) CT investigation for treatment planning and follow-up examinations of all patients. The planning target volume was the gross tumour volume. The patient's head was positioned during treatment using a custom-fitted face mask and patient movements of up to 10 mm in translation and 1 degree in rotation (3 degrees for yaw movements) were automatically corrected using the updated information of the image guidance system [Lit]. The treatment volumes were prescribed to a median isodose of 70% (range 50–85%). The median number of beams during treatment was 112 for cranial lesions and 127 for spinal tumours (range 27–328). These parameters where chosen on the basis of suggested dose levels in the literature and according to our personal experience over the years.

All treatments were performed in a single fraction. The procedure time was between 1 and 3 h. For treatment delivery the patients were placed on the CyberKnife treatment couch reproducing their individual position during pretreatment CT scanning. If required, patients were given analgesics or mild sedation. The interval between the first interview of the patients and the radiosurgical procedure did not exceed 10 days.

First clinical follow up occurred 1 week after treatment to assess the patient status with particular emphasis on the pain level and adverse effects after SRS. Further clinical evaluation and CT and/or MRI imaging studies were done every 12 weeks according to a preplanned tumour restaging schedule for systemic therapy. Any tumour growth or recurrence of a treated tumour during follow up with imaging was classified as treatment failure. Distant recurrences were disregarded for calculation of local tumour control.

## RESULTS

Median time from initial diagnosis to metastatic spread was 0.6 years (range 0–3.5 years). Follow up information was verified in all patients. Median follow up was 14.7 months (range 1–42 months). Local tumour control of 240 treated metastases 15 months after SRS was 98% (95% CI 89–99%). As previously reported, the statistical model failed to identify factors predictive of local tumour control [23]. Median overall survival was 15.2 months after SRS. Median time from initial diagnosis of RCC until SRS was 3.1 year. Patients and treatment characteristics are given in Table 1.

Forty-five patients were treated with oral sunitinib (50 mg daily, 4 weeks on, 2 weeks off) and 61 patients were treated with oral sorafenib (400 mg twice daily).

Systemic therapy caused adverse effects, as previously published [25]. Grade three adverse effects comprised hypertension, rash, mucositis, diarrhoea, thrombocytopenia, anaemia, hand–foot syndrome, myocardial infarction and thrombosis. They were not seen during SRS and were classified as unrelated to SRS because they did not appear within 6 weeks of SRS. All adverse effects were not related to SRS but to the underlying systemic treatment. In none of our patients did SRS influence the adverse effects of anti-angiogenic therapy and in no patient was it necessary to modify the dose of the systemic therapy. It should also be noted that patients were treated with SRS during the treatment phase of the 4-week-on/2-week-off regimen of sunitnib treatment, and throughout the intake of sorafenib. Two patients had grade two complications after SRS; a tumour haemorrhage occurred, but no further

*TABLE 1 Patients and treatment characteristics*

| | All | Spinal lesions | Cerebral lesions | *P* value |
|---|---|---|---|---|
| Median age, years (range) | 63.6 (21.6–85.8) | 62.3 (21.6–85.8) | 64.2 (30.5–83.5) | 0.89 |
| Median follow up, months (range) | 14.7 (1–42) | 33.4 (1–31) | 16.3 (2–49) | 0.51 |
| Median lesions treated per patient and session, *n* (range) | 1.20 (1–2) | 1.9 (1–5) | 2.6 (1–5) | 0.71 |
| Median treatments per patient, *n* (range) | 1.04 (1–2) | 1.3 (1–10) | 1.05 (1–2) | 0.91 |
| Median treatment-free interval*, months (range) | 61.9 (0.4–351.9) | 60.7 (0.4–351.9) | 63.6 (0.5–228.2) | 0.88 |
| KPS† > 70 | | 46 | 38 | 0.74 |
| KPS† < 70 | | 7 | 13 | 0.87 |
| Mean volume, $cm^3$ (range) | | 30.1 (0.5–152.8) | 1.7 (0.1–26.6) | <0.001 |
| Overall survival, months | 15.2 | 17.4 | 11.1 | 0.038 |

**Disease-free interval: time between diagnosis of primary tumour and stereotactic radiosurgery; †Karnofsky performance status.*

*TABLE 2 Stereotactic radiosurgery-related adverse effects (within 6 weeks of treatment)**

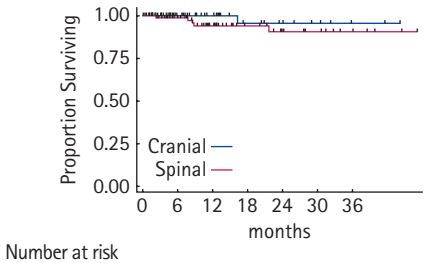
| Adverse effect | *n*, grade |
|---|---|
| Tumour haemorrhage | 2 (grade II) |
| Convulsions | 3 (grade II) |
| Abdominal pain | 1 (grade I) |

**No late complications related to stereotactic radiosurgery seen.*

*TABLE 3 Clinically relevant adverse effects during systemic therapy, not within 6 weeks of stereotactic radiosurgery treatment*

| Grade III/IV | % of patients |
|---|---|
| Hypertension | 4 |
| Rash | 1 |
| Mucositis | 1 |
| Diarrhoea | 1 |
| Thrombocytopenia | 2 |
| Anaemia | 11 |
| Hand–foot syndrome | 1 |
| Myocardial infarction | 2 |
| Thrombosis | 1 |

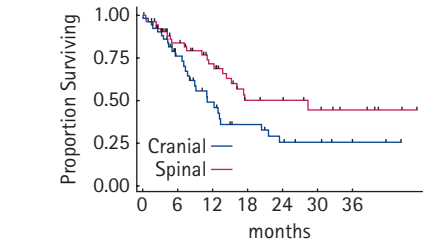
*FIG. 1. Local tumour control of lesions treated with stereotactic radiosurgery by treatment arms; P < 0.5.*




Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cranial | 135 | 72 | 36 | 21 | 10 | 5 | 2 |
| Spinal | 105 | 73 | 47 | 31 | 20 | 16 | 7 |

*FIG. 2. Overall survival by treatment arms; P = 0.038 (log-rank).*




Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cranial | 51 | 26 | 15 | 10 | 7 | 5 | 2 |
| Spinal | 55 | 38 | 27 | 14 | 12 | 8 | 5 |

treatment was needed. Convulsions occurred within the first 3 weeks of treatment in three cases undergoing cranial SRS but these were controlled by systemic cortisone treatment. No added skin toxicities or influence on the adverse effects of systemic anti-angiogenic therapy were seen. One patient experienced abdominal pain after SRS. There were no treatment-related deaths. Late complications after SRS have not been observed so far. Details of adverse effects related to SRS are given in Table 2 and details of grade III/IV adverse effects of systemic therapy are given in Table 3.

Thirty patients had tumour-associated pain syndromes not related to vertebral instability. The median visual analogue scale pain score before treatment was 5 (range 1–8). After SRS, the median pain score was significantly lowered to 0 (range 0–2, $P < 0.001$). Pain relief occurred as early as 1 hour and within 7 days after SRS.

In the 55 patients treated for spinal metastases the mean age was 60.2 years (range 18.3–84.4 years). With 105 treated spinal lesions the median number of lesions per patient was 1.9 (range 1–5) with 1.3 treatments per patient during the follow-up period (range 1–10). The median dose per lesion was 20 Gy (range 19–20 Gy) with a mean volume of 30.1 ± 30.4 $cm^3$ (range 0.5–152.8). Tumour-associated pain was observed in 30 patients. In these patients the median pretreatment pain score on a visual analogue scale was 5 (range 1–8), which fell significantly, to 0 (range 0–2) ($P < 0.001$) within 1 week after SRS. Twenty-three patients were treated with sunitinib and 32 with sorafenib. No relevant adverse effects were seen, except in one patient who developed temporary abdominal pain. Only two lesions were not controlled after 6 months; in those two lesions a new enhancing area directly adjacent to the treated lesion was observed and successfully retreated by SRS.

The local control rate of spinal lesions at 12 and 24 months was 94.1% (SEM 0.03, 95% CI 85–98%) and 90.4% (SEM 0.05, 95% CI 77–96%), respectively (Fig. 1).

The median overall survival was 17.4 months with an actuarial survival after 12 and 24 months of 0.704 (SEM 0.07, 95% CI 0.54–0.82) and 0.49 (SEM 0.08, 95% CI 0.32–0.64), respectively (Fig. 2).

The median age of the 51 patients treated for cerebral lesions was 64.2 years (range 30.5–83.5 years). With a total of 135 treated lesions, patients had a median of 2.6 treated lesions (range 1–9) with a median of 1.05 treatments/patient during the follow-up period (range 1–2). The median dose of radiation per lesion was 20 Gy (range 20–20) with a mean volume of 1.65 ± 3.0 $cm^3$ (range 0.1–26.6). The local control rate of cerebral lesions at 12 and 24 months was 100% and 96.6% (SEM 0.03, 95% CI 78–99%), respectively (Fig. 1).

The median overall survival was 11.1 month with an actuarial survival after 12 and 24 months of 0.51 (SEM 0.082, 95% CI 0.34–0.65) and 0.25 (SEM 0.8, 95%CI 0.11–0.42), respectively (Fig. 2).

Twenty-two patients with cerebral lesions were treated with sunitinib and 29 were treated with sorafenib. In five patients there was an asymptomatic reaction to radiation, three patients had convulsions after SRS, with one of them having the same symptoms before SRS. No radiation-related necrosis was noted. In two patients, asymptomatic bleeding into the treated cranial lesion was found on restaging, none of them reaching clinical significance. One patient experienced fatal cerebral bleeding while on treatment with sunitinib 3 months after SRS.

In a univariate analysis of prognostic factors for overall survival, age < 65 years, previous radiation, surgery, systemic therapy, and disease-free interval turned out to be of no prognostic significance. Only the general condition of the patient as classified with the Karnfosky performance status >70 was a statistical predictor of overall survival ($P$ = 0.001, hazard ratio 0.29, 95% CI 0.16–0.57). Also, in a multivariate Cox proportional model the Karnfosky performance status was the only significant predictor of overall survival ($P$ = 0.006, hazard ratio 0.40, 95% CI 0.21–0.76).

## DISCUSSION

Treatment of patients with metastatic RCC has been dramatically changed with the introduction of the anti-angiogenic therapies sorafenib, sunitinib and temsirolimus but the cure rate for patients not eligible for surgery remains about 2%, and so multidisciplinary approaches to treat the underlying disease are warranted. Little is known about the control of spinal and cerebral lesions by systemic treatment alone, as the evaluation criteria used in phase III study protocols either exclude patients with cerebral lesions or disregard osseous lesions when evaluating remission. We have previously shown that single-session spinal and cerebral SRS is feasible, safe and effective, with the major benefits being short treatment times in an outpatient setting and rapid recovery from symptoms [8,9,21,23]. In our experience SRS not only stabilizes lesions, but also prevents further local problems in patients undergoing systemic therapy. From previous series we have learned that SRS itself has very few and mild adverse effects, such as local rash or mild and transient fatigue or dysphoria [8,10,14,23]. In addition, we have seen several patients who experience a rebound of tumour growth after cessation of anti-angiogenic therapy. Taken together, we chose to investigate the feasibility of integrating SRS into our multidisciplinary treatment approach, continuing the underlying systemic therapy and performing SRS treatment simultaneously.

Although sunitinib is regarded as a first-line standard therapy in patients with metastatic RCC, most of our patients were treated with sorafenib (41 sunitinib vs 65 sorafenib). The disproportionate use of sorafenib in this cohort reflected two major issues, the first being the availability of sorafenib before sunitinib at our centre in study protocols. The other issue is that patients with severe metastatic spread (which was most of the patients in our study) are in the later course of the disease and so are mainly treated second line or later. Now that SRS with simultaneous anti-angiogenic therapy has shown promising efficacy, even patients with earlier stages of disease should be treated with SRS to prevent local complications, especially from spinal lesions.

Overall survival of our patients was extremely high. Patients with spinal lesions had a median overall survival of 17.4 months but remained stable with 40% still being alive after 36 months. It is notable that this survival is not calculated from the beginning of the first-line systemic therapy, but from SRS in the later course of the disease. The overall survival under systemic therapy is therefore even longer. Taking into account that there were only a few sites that had to be retreated, SRS can not only be regarded as a palliative treatment but as definitive tumour control of the selected lesions. In consequence, indication for SRS should be given even early in the course of the disease.

Patients with cerebral lesions had a median overall survival of 11.1 month from SRS; 36 months after SRS 25% of the patients were still alive. So far, no comparable overall survival data for other radiotherapeutic treatments of brain lesions can be found in the literature.

The influence of systemic therapy on overall survival should not be underestimated, but the high local tumour control rate of over 98% after SRS adds a valuable palliative tool to the therapeutic approach of metastatic RCC. Systemic therapy need not to be paused during SRS and therefore the rebound phenomena with their negative influence on tumour burden and, eventually, survival are avoided.

In the present study no statistically different effect of SRS on local tumour control was seen between the two treatment groups, but this was mainly because of differences in the size of the two treatment arms. In both arms, local tumour control rate was comparable and did not differ from the whole cohort.

Local skin toxicities, especially those expected under sorafenib treatment, were not found. SRS did not alter the adverse effect profile of the underlying anti-angiogenic therapy, and did not induce other adverse events. So far, little is known of the toxicity of radiotherapy and simultaneous anti-angiogenic therapy. Several series hint towards the possibility of this combined approach, especially with high-dose radiotherapy regimens [26,27].

We found tumour haemorrhage in three patients as a previously reported adverse effect of any high-dose radiation therapy (stereotactic, gamma-knife, cyber-knife) [9,18,20]. All events were grade II. There were only radiographic hints of bleeding within the treated lesions, without any further clinical implication. There are some reports, especially for bevacizumab treatment, of tumour haemorrhage, mainly in the gastrointestinal tract – but our patients were not treated with bevacizumab. So far we have seen very few patients with a treatment-related haemorrhage while on sorafenib or sunitinib and these were mainly related to gastrointestinal lesions. No further tumour haemorrhage was observed in the patients with the combined approach reported.

One patient died who had cerebral bleeding 3 months after SRS while he was still on sunitinib. Death was not related directly to the bleeding but to a rapidly general tumour growth in all other lesions not treated by SRS. It is not possible to estimate whether the cerebral lesion in this patient was controlled or not by SRS so the patient's death was considered to be the result of disease progression and not related to treatment. As previously reported, we found no factors that were predictive of local tumour control by SRS. In particular, histology has been shown not to influence tumour control, rendering SRS effective in any metastatic lesion [23].

The fact that the local tumour control rate was lower in patients with spinal lesions may be explained by the difference in tumour size of the treated lesions, which was significant. Hence, the only limitation on SRS seems to be lesion size; we have adopted a maximum of 3 cm for cranial lesions and 4 cm for spinal lesions. Therefore, the present results apply to a subgroup of patients with localized metastatic lesions. In patients with generalized lesions, such as multiple osseous lesions, the impact of SRS remains unclear.

Cerebral lesions in any metastatic disease are usually related to a devastating prognosis. In historical series, patients with cerebral metastases of RCC had a median survival of 6–8 weeks. Systemic therapy has improved overall survival but it had already been shown that fiducial-free stereotactic radiation therapy alone could improve the survival to a median of 9.9 months [9]. None of our patients died from growth of the SRS-treated cerebral tumour; deaths were the result of progression of the underlying disease. Hence SRS is highly effective in patients with RCC and should be regarded as the treatment standard if available to the patient.

The significance ($P = 0.038$) between the overall survival of patients with spinal and cerebral lesions and the parallel Kaplan–Meier curves after the median overall survival hints at the control by SRS of disease in the brain, rendering the course of the disease unaffected by the appearance of cerebral metastases and relating it to the effects of the underlying systemic therapy. Cerebral SRS of cerebral metastases seems to be performed in the later course of the disease although the interval between initial diagnosis of RCC and SRS did not differ significantly.

The univariate and multivariate analyses prove that the only prognostic factor for overall survival of the patients was performance status. This is in accordance with many other predictive models of survival for patients with metastatic RCC [28,29].

Simultaneous anti-angiogenic treatment and SRS is a non-invasive, safe and effective treatment method for patients with spinal or cerebral metastases from RCC. Local tumour and pain control are excellent. Adverse effects of systemic anti-angiogenic therapy were not altered by SRS. Single fraction delivery as an outpatient procedure allows convenient integration of SRS into oncological treatment concepts. Further studies need to identify the limits of SRS for extracranial and extraspinal metastatic RCC lesions.

## CONFLICT OF INTEREST

None declared.

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Abbreviation: **SRS**, stereotactic radiosurgery.