Impact of Stereotactic Radiosurgery Dose on Control of Cerebral Metastases from Renal Cell Carcinoma

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Abstract. *Aim: Renal cell carcinoma (RCC) is a relatively radioresistant tumor and may require for higher radiation doses than other tumor types. Patients and Methods: Nineteen patients treated with 20 Gy of stereotactic radiosurgery (SRS) alone for one to three cerebral metastases were compared to nine patients treated with 16-18 Gy. Results: SRS with 20 Gy led to significantly better local control than did 16-18 Gy (81% vs. 50% at 12 months; p<0.001). Results were also significant on multivariate analysis (risk ratio: 6.30; p=0.033). SRS dose did not associate with freedom from new cerebral metastases (75% vs. 62% at 12 months; p=0.42) or survival (16% vs. 56% at 12 months; p=0.46). On multivariate analyses, better survival was associated with higher Karnofsky performance score (p<0.001) and absence of extracranial metastatic disease (p=0.006). Conclusion: In patients treated with SRS alone, local control of cerebral metastases from RCC was better after 20 Gy than after 16-18 Gy.*

Between 4% and 11% of patients with renal cell carcinoma (RCC) develop cerebral metastases (1-3). This proportion will likely increase because systemic treatment of metastatic RCC has been improving and now includes several targeted-therapies such as sunitinib, sorafenib, axitinib and everolimus (4-6). Many systemic agents are not able to cross the blood-brain barrier. A considerable number of the patients who are treated systemically will have a response of their extracranial metastases, resulting in longer survival. Since the risk of developing cerebral metastases increases with duration of survival, more patients with brain metastases from RCC can be expected in the future. Therefore, the treatment of cerebral lesions from RCC will likely become more important. The majority of patients with cerebral metastases receive radiotherapy, either as whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or as combination of both WBRT and SRS. Since a randomized trial suggested a significant increase in neurocognitive deficits with the addition of WBRT to SRS, many oncologists favor SRS alone, particularly for relatively radioresistant tumor types such as RCC (7). If SRS alone is administered, uncertainty exists regarding the optimal dose. Studies comparing different doses of SRS alone for cerebral metastases from RCC are lacking. Therefore, the present study was performed. We compared two SRS doses in patients with one to three cerebral metastases from RCC, 16-18 Gy and 20 Gy, with respect to local control of the irradiated cerebral lesions, freedom from new cerebral metastases and survival.

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Patients and Methods

In this study, 19 patients treated with linear-accelerator-based SRS alone of 20 Gy for one to three cerebral metastases were compared to nine patients treated with 16-18 Gy. Investigated end-points of this retrospective study included local control of the irradiated cerebral lesions, freedom from new cerebral metastases and survival. SRS doses were prescribed to the outer margin of the metastases, which represented isodose levels ranging from 80% to 90%. In addition to the SRS dose, seven potential prognostic variables were evaluated: age (≤65 *vs.* >65 years, median age=65.5 years), gender, Karnofsky performance score (KPS 60-70 *vs.* KPS 80-100), number of cerebral metastases (1 lesion *vs.* 2-3 lesions), site of the cerebral metastases (supratentorial alone *vs.* infratentorial with/without supratentorial), extracranial metastatic disease (no *vs.* yes) and time from the first diagnosis of renal cell carcinoma until SRS (≤18 *vs.* >18 months).

The statistical analyses were performed using the Kaplan–Meier method and the log-rank test for the univariate analyses. Those

Table I. *Local control of treated lesions (univariate analysis).*

	Local control at 6 months (%)	Local control at 12 months (%)	*p*-Value
Dose of stereotactic radiosurgery			
16-18 Gy (N=9)	50	50	
20 Gy (N=19)	100	81	0.020
Age			
≤65 years (N=14)	83	73	
>65 years (N=14)	80	64	0.96
Gender			
Female (N=7)	75	75	
Male (N=21)	83	67	0.81
Karnofsky performance score			
60-70 (N=8)	67	67	
80-100 (N=20)	84	70	0.72
Number of cerebral metastases			
1 (N=16)	85	65	
2-3 (N=12)	80	80	0.82
Site of cerebral metastases			
Supratentorial alone (N=19)	76	61	
Infratentorial with/without supratentorial (N=9)	100	100	0.15
Extracranial metastatic disease			
No (N=11)	80	67	
Yes (N=17)	84	72	0.98
Time from first diagnosis of renal cell carcinoma until radiosurgery			
≤18 months (N=14)	70	58	
>18 months (N=14)	92	79	0.16

Table II. *Freedom from new cerebral metatsases (univariate analysis).*

	Local control at 6 months (%)	Local control at 12 months (%)	*p*-Value
Dose of stereotactic radiosurgery			
16-18 Gy (N=9)	75	75	
20 Gy (N=19)	69	62	0.42
Age			
≤65 years (N=14)	83	72	
>65 years (N=14)	59	59	0.52
Gender			
Female (N=7)	69	69	
Male (N=21)	72	65	0.92
Karnofsky performance score			
60-70 (N=8)	64	64	
80-100 (N=20)	74	68	0.63
Number of cerebral metastases			
1 (N=16)	85	85	
2-3 (N=12)	53	40	0.064
Site of cerebral metastases			
Supratentorial alone (N=19)	82	75	
Infratentorial with/without supratentorial (N=9)	44	44	0.099
Extracranial metastatic disease			
No (N=11)	73	73	
Yes (N=17)	69	60	0.34
Time from first diagnosis of renal cell carcinoma until radiosurgery			
≤18 months (N=14)	80	69	
>18 months (N=14)	64	64	0.54

variables that were significant ($p<0.05$) or showed a strong trend ($p<0.10$) in the univariate analyses, were included in multivariate analyses (Cox proportional hazards model).

Results

One major end-point of this study was local control of the cerebral metastases treated with radiosurgery. On univariate analysis, a significant positive association with local control was found only for the SRS dose ($p=0.020$) (Figure 1 and Table I). A dose of 20 Gy resulted in better local control rates than did 16-18 Gy. The local control rates at 6 months were 100% and 50%, respectively, and the local control rates at 12 months were 81% and 50%, respectively (Figure I and Table I). In the Cox proportional hazards model, SRS dose remained significant [risk ratio (RR)=6.30; 95% confidence interval (CI)=1.16-47.62; $p=0.033$].

On univariate analyses of freedom from new cerebral metastases, no investigated factor was significant. However, the number of cerebral metastases ($p=0.064$) and the site of the cerebral metastases ($p=0.099$) showed trends for positive associations with freedom from cerebral metastases (Table II). The SRS dose had no significant impact on this endpoint ($p=0.43$). In the Cox proportional hazards model, neither the number of cerebral metastases [RR=3.00; 95% CI=0.77-14.64; $p=0.12$] nor the metastatic site [RR=2.39; 95% CI=0.57-9.32; $p=0.22$] reached significance.

In the univariate survival analysis (Table III), the Karnofsky performance score achieved significance ($p<0.001$) and extracranial metastatic disease showed a trend ($p=0.067$). In contrast, the SRS dose was not significant ($p=0.46$). According to the Cox proportional hazards model, both the Karnofsky performance score (RR=10.34; 95% CI=2.85-43.86; $p<0.001$) and extracranial metastatic disease (RR=5.28; 95% CI=1.56-23.73; $p=0.006$) had a significant impact on survival.

Discussion

Much research has been performed to improve the results of the treatment of RCC (8, 9). Since systemic treatment has improved, patients with RCC live longer due to better control of their extracranial disease. Therefore, more patients are at-risk of developing cerebral metastases. In cases of one to three cerebral lesions, many patients receive SRS-alone or SRS-plus-WBRT. SRS beams are also subject matter of current research (10). The addition of WBRT to SRS is currently under debate. Findings from one randomized trial of 58 patients determined

Table III. *Survival (univariate analysis).*

	Local control at 6 months (%)	Local control at 12 months (%)	*p*-Value
Dose of stereotactic radiosurgery			
16-18 Gy (N=9)	89	16	
20 Gy (N=19)	63	56	0.46
Age			
≤65 years (N=14)	79	55	
>65 years (N=14)	64	39	0.82
Gender			
Female (N=7)	57	43	
Male (N=21)	76	48	0.84
Karnofsky performance score			
60-70 (N=8)	25	13	
80-100 (N=20)	90	61	<0.001
Number of cerebral metastases			
1 (N=16)	75	54	
2-3 (N=12)	67	36	0.24
Site of cerebral metastases			
Supratentorial alone (N=19)	84	49	
Infratentorial with/without supratentorial (N=9)	44	44	0.53
Extracranial metastatic disease			
No (N=11)	91	60	
Yes (N=17)	59	39	0.067
Time from first diagnosis of renal cell carcinoma until radiosurgery			
≤18 months (N=14)	71	26	
>18 months (N=14)	71	64	0.11

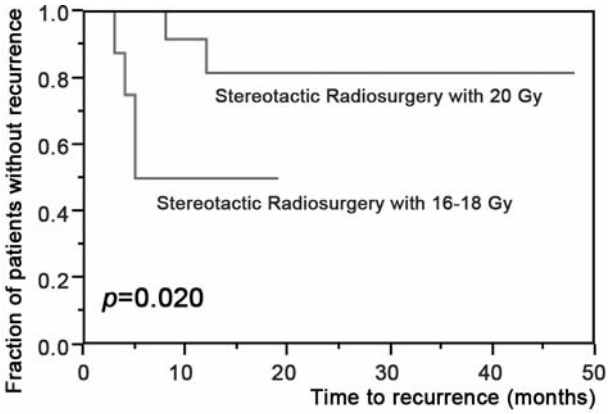

Figure 1. *Comparison of 16-18 Gy and 20 Gy with respect to local control of the irradiated cerebral metastases.*

that WBRT increases toxicity in terms of neurocognitive dysfunction (7). However, it was also shown that the addition of WBRT improves local control of the irradiated cerebral lesions and freedom from new cerebral metastases (11-13). It has been suggested that control of the disease within the brain is of major importance for avoiding neurocognitive deficits. Since benefits of WBRT in addition to SRS are not clear, many oncologists favour SRS alone. However, for SRS alone, the optimal dose needs to be defined, in particular for relatively radioresistant tumor types such as RCC.

Therefore, the present study was conducted. It compared two SRS doses, 16-18 Gy and 20 Gy. According to the results of this study, local control of the irradiated lesions was significantly better after 20 Gy than after 16-18 Gy. However, this benefit did not translate into significantly improved survival, mainly because more patients in the 20-Gy-treated group developed new cerebral metastases than in the 16-18-Gy-treated group. These results agree with the findings of previous studies comparing different doses of SRS alone for lung cancer and melanoma (14-15). In both studies, a higher SRS dose resulted in significantly improved local control without a significant survival benefit. The results of the present study of SRS also agree with previous studies that compared different radiation doses for WBRT of patients with cerebral metastases from relatively radioresistant tumors in general and from RCC in particular (16-17).

An additional finding of the present study was the fact that improved survival was significantly associated with higher Karnofsky performance score and absence of extracranial metastatic disease at the time of SRS. The findings agree with those of two previous studies investigating predictive factors of survival in RCC patients treated with SRS for cerebral metastases (18, 19). The Karnofsky performance score had an impact on survival in both studies, and extracranial metastatic disease in at least one study.

In summary, the present study showed that in patients with RCC with one to three cerebral metastases, SRS with 20 Gy resulted in significantly better local control of the irradiated lesions than SRS with 16-18 Gy. Therefore, patients with a limited number of cerebral metastases from RCC who are candidates for SRS alone should receive 20 Gy rather than 16-18 Gy whenever possible.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there exist no conflict of interest related to this study.

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