doi:10.4149/neo_2016_012

The efficacy of stereotactic radiotherapy for metastases from renal cell carcinoma

W. MAJEWSKI[1,*], M. TABOR[2], P. BANASZEK[2], G. GLOWACKI[1], W. ROKICKI[3], A. TUKIENDORF[4]

[1]Radiotherapy Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch; [2]Students' Scientific Association at Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch; [3]Department and Clinic of Ophthalmology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland; [4]Department of Epidemiology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch

**Correspondence: wmajewski1@poczta.onet.pl*

Received February 9, 2015 / Accepted July 30, 2015

Our purpose was to evaluate the efficacy of stereotactic radiotherapy (SRT) for intracranial and extracranial metastases in patients with renal cell carcinoma. The retrospective analysis of 85 patients (151 tumors) treated with SRT was performed. SRT was the sole treatment in 35% of tumors, the other 65% had received additional treatment such as surgery, palliative radiotherapy, immunotherapy or chemotherapy. In 60% and 40% of patients SRT was delivered to brain and extracranial lesions, respectively. The assessment of the efficacy of SRT was based on a radiological imaging (Computed Tomography or Magnetic Resonance Imaging) and estimation of Local Control (LC) as well as Overall Survival (OS). Single fraction was used for 104 tumors and fractionated treatment for 47 tumors. The crude LC for evaluable lesions was 81%, stratified by tumor location: brain LC=94%, extracranial tumors LC=70% (p=0.049). The median OS was 9.4 months; 1-year and 2-year OS were 40% and 29%, respectively. The additional treatment did not lead to a better local response (p=0,543), but resulted in a benefit in OS (7 vs 13 months, p=0,01). A positive relationship between the biologically effective dose (BED) and local response was noted, but the BED was influenced by a tumor volume (R=-0,38; p<0,00001). The presence of multi-organ metastases reduced the OS rate (8.7 vs 19.1 months; p=0,01). The interval between the diagnosis of the metastasis and its treatment with SRT was inversely related to OS (P=0.0001). SRT results in a good local response, which is more beneficial for brain than extracranial lesions. The local efficacy of the SRT depends on the radiation dose. Multidisciplinary treatment and earlier application of SRT improves the prognosis of patients.

Key words: stereotactic radiotherapy, renal cell carcinoma, prognostic factors

The most common locations of distant metastases in patients with renal cell carcinoma are lungs, brain, bones, liver and adrenal glands [1]. In case of a limited number of lesions, local therapies, especially very precise and non-invasive ones may be used additionally to conventional systemic or palliative treatment [2]. Stereotactic radiosurgery or stereotactic radiotherapy (SRS or SRT) are such a local treatment modalities, which allows for high dose irradiation of a very precisely defined area, leaving surrounding tissues intact. Such high dose of radiation is given in one or few fractions. SRS/SRT was mainly used for brain metastases, but it can be also performed for extracranial lesions [3-5].

Although renal cell carcinoma (RCC) is considered rather as a non-radiosensitive tumor, some benefit of postnephrectomy conventionally fractionated radiotherapy (RT) was reported [6]. However, the administration of high doses of radiation in one or few fractions causes quite different molecular effect and seems to overcome the radioresistance [7]. In a clinical practice, SRT is associated with a relatively good prognosis as compared to the prognosis of patients receiving only palliative treatment [8-18]. The role of SRT in case of "radioresistant" tumors as compared to the surgery is a matter of debate. The randomized trials are unfortunately lacking. From a practical point of view the non-invasive SRT may be potentially more convenient and attractive for patients, of course if it yields satisfactory local control. It may be also a reasonable non-invasive option for patients with disseminated disease. Quite often so called "radioresistant" tumors like RCC, melanoma and sarcoma are grouped together, but their behavior is not exactly the same. So, the important issue

is to analyze them separately. There is also a necessity to define a role of potential factors which may influence the efficacy of SRT separately for various histological types of tumors.

The study was planned to evaluate the applicability and efficacy of that method in a population of patients with RCC. The emphasis was put on the assessment of factors potentially influencing the results, especially those treatment-related, which may have a practical utility.

Patients and methods

A retrospective analysis of 85 patients with RCC who underwent stereotactic radiotherapy (SRT) between 2008-2012 was performed. The total number of tumors was 151 (148-metastases to solid organs, 3- local recurrences). All patients had histopathological diagnosis of RCC and previous radical nephrectomy was performed in all cases.

The mean age of all patients was 61 years (33-89 years). In this study group, 75% (n=64) were male and 25% (n=21) female. Disease progression after previous nephrectomy occurred after 34 months, on the average. The mean time since the disease progression to the stereotactic radiotherapy was 10.3 months. The clinical features, frequency, distribution and locations of all metastases being treated with SRT are shown in Table 1 .

The mean number of lesions treated with SRT per patient was 1.8. In 74% (n=63) patients, despite of the lesions in the organ treated with SRT, a progression of the disease occurred in other organs. The remaining 26% (n=22) of patients presented tumors located only in one organ.

SRT was the exclusive form of a treatment in 35% (n=53) of all tumors, while the other 65% (n=98) of tumors received additional form of treatment such as surgery, palliative radiotherapy, immunotherapy or chemotherapy (Table 1).

If the surgical metastatectomy was used it usually (91%) preceded SRT. The SRT was performed then in case of local recurrence. Systemic treatment was also generally used before referral of patients to SRT (81%).

SRT was performed with a linear accelerator. Multiple beams techniques were used, and the radiation dose was

Table 1. The characteristics of a study group

		The percentage of the treated tumors N=151	The percentage of the treated patients N=85
The tumor location	BRAIN	60% (n=90)	65% (n=55)
	LUNGS	30% (n=45)	32% (n=27)
	LIVER	5% (n=8)	6% (n=5)
	POSTOPERATIVE BED	2% (n=3)	2,5% (n=2)
	ADRENAL GLANDS	2.5% (n=4)	2.5% (n=2)
	LYMPH NODES	0,5% (n=1)	1% (n=1)
The histopathological type of a cancer	CLEAR CELL CARCINOMA	82% (n=124)	82% (n=70)
	OTHER	18% (n=27)	18% (n=15)
Grading*	G1	7% (n=10)	7% (n=6)
	G2	33% (n=50)	31% (n=26)
	G3	31% (n=47)	31% (n=27)
	G4	3% (n=5)	5% (n=4)
	NO DATA	26% (n=39)	26% (n=22)
ECOG Performance score**	0	-	25% (n=21)
	1	-	66% (n=56)
	2	-	8% (n=7)
	3	-	1% (n=1)
The number of lesions being treated in one patient	1	-	48% (n=41)
	2	-	36% (n=30)
	3-4	-	14% (n=12)
	≥5	-	2% (n=2)
The type of an additional treatment	NO ADDITIONAL TREATMENT	35% (n=53)	39% (n=33)
	PALLIATIVE RADIOTHERAPY	35% (n=53)	36% (n=31)
	CHEMOTHERAPY	40% (n=61)	35% (n=30)
	SURGERY	15% (n=23)	14% (n=12)
	IMMUNOTHERAPY	15% (n=22)	12% (n=10)

*- Grading was performer according to Fuhrman Nuclear Grade

**-Performance status: ECOG 0: Fully active, ECOG 1: ambulatory and able to carry out light or sedentary work, ECOG 2: ambulatory but not able to carry out work, ECOG 3: capable of only limited self-care

specified at the isocenter. BrainLab system was used for brain metastases and ExactTrack or Real-time Position Mangement Respiratory Gating for extracranial tumors. The most common irradiation schedules used for stereotactic radiotherapy were: 8–14 Gy/1 fx; 15–20 Gy/1 fx; 21–24 Gy/2 fx; 36–60 Gy/3 fx (Table 2). The mean tumor volume was 9.3 cm^3. For brain metastases the tumor volume was on average 5.7 ± 8.4 cm^3, for lungs 11.7 ± 16.3 cm^3, and for liver 26.1 ± 25.8 cm^3.

The planning treatment volume (PTV) was specified by adding approximately 5-10 mm around the tumor.

Methods and statistical analysis. The efficacy of the SRT was assessed with a radiological imaging performed before and after the treatment. A total of 49% (n=74) of the lesions were evaluated post-treatment with a radiological imaging (Computed Tomography- CT, Magnetic Resonance Imaging-MRI). The rest of the patients did not have any imaging for assessing the treatment effect. This was due to the follow-up in the other health facilities or because of a systemic progression of the disease with a deterioration a general status and referring a patient to the symptomatic palliative care.

The pre-treatment tumor volume was calculated on CT/MRI images used for radiotherapy planning with standard software tools. The local response to SRT was evaluated using the RECIST criteria comparing follow-up CT/MRI images to the pre-treatment ones. Complete remission (CR) have been scored in case of a disappearance of the tumor. Partial remission (PR) is a reduction of a sum of two largest dimensions of a tumor by ≥30%. Progressive disease (PD) is an increase in a sum of two largest dimensions of the tumor by ≥ 20%. A stable disease (SD) is considered when the change in the sum of the largest dimensions does not fulfil the criteria for PR and PD. The crude Local Control (LC) was calculated as a sum of complete, partial remission and stable disease.

The mean time from the SRT to the follow-up radiological assessment was 7.6 ± 7.1 months. After over a year since the SRT (an average of 13.5 months) 44 metastases were evaluated with subsequent radiological imaging. If the surgery of the metastasis was performed after SRT such cases were defined as a progression.

Overall Survival (OS) was calculated using the Kaplan-Meier estimator, and the results were compared using the log-rank test. Censored observations were in alive patients at the date of last examination or information on patients' status. A frailty model which is a Cox's proportional hazards model incorporating random effects was applied in the statistical analysis of factors related to OS [19].

Local responses between the groups of patients were compared using non-parametric tests. A correlation was calculated with a non-parametric Spearman's coefficient. Because of different radiation schedules, they were recalculated using biologically effective dose (BED) formula [BED= Total dose (1 + dose per fraction/α/β)], assuming α/β-5. The results were considered as statistical significant for p<0,05. All analyzes except for Cox model were performer using software STATISTICA 10.0 Statsoft.

Results

Local control (LC). In 47% (n=35) of all evaluated tumors (n=74) a local regression was observed. In 34% (n=25) the effect was assessed as stable disease, and in 19% (n=14) local progression was recorded. The crude LC rate for all evaluated lesions was 81%. About 80% of tumors achieving LC at first radiological assessment remained without evidence of progression, on the second imaging (after an average of 13,5 months after SRT). In the remaining 20% local progression appeared. Thus, after 13.5 months the crude LC rate was 65%. The recurrences outside the stereotactically irradiated volume but in the treated organ occurred in 29% of evaluable patients (26%-cranial SRT patients, 32% extracranial SRT patients).

The LC rate stratified by a tumor location was: for brain LC=94%, and for extracranial location LC=70% (Table 3). The differences between cranial and extracranial tumor location were statistically significant (p=0.049).

Any additional treatment of metastases with other modalities did not lead to a statistically better local response to subsequent stereotactic radiotherapy (p=0.543). A detailed comparison of the exclusive SRT and SRT combined with palliative conventional RT did not reveal any significant role neither for cranial nor for extracranial tumors (Table 3). The histopathological grading did not have a significant role (p=0.13). Also the influence of the tumor volume on the effect of SRT was not significant (p=0.32). A positive relationship between the BED (BED α/β=5) and local response was noted. For patients with a progressive disease a mean BED was 78 Gy, for patients with stable disease- 89 Gy, for patients with partial remission- 103 Gy and for those with complete remission it was 158 Gy (p=0.02). However, there was a correlation between the BED and the tumor volume, which might influence the results (Spearman's R= -0.38; p<0.00001). The BED cut-off point of 100 Gy did not differentiate between patients with a better and worse local outcome. But, if the BED of 120 Gy was selected as a cut-off point the differences in the local treatment effect became significant (Table 3).

The example of tumor regression in a lung after SRT is shown in Figure 1a and 1b.

Overall survival (OS). The median follow-up was 30 months. The observation lasted until the death or the last contact with the patient. Information about the patients was

Table 2. The irradiation schedules for all of the tumors (n=151)

		TOTAL DOSE [Gy]				
		8 – 14	15 – 20	21 – 24	25 – 35	36 – 60
NUMBER OF FRACTIONS	1	**13**	**85**	6	0	0
	2	1	13	**10**	2	1
	3	0	0	3	0	**12**
	4	0	0	0	0	2
	5	0	0	0	0	2
	6	0	0	0	0	1

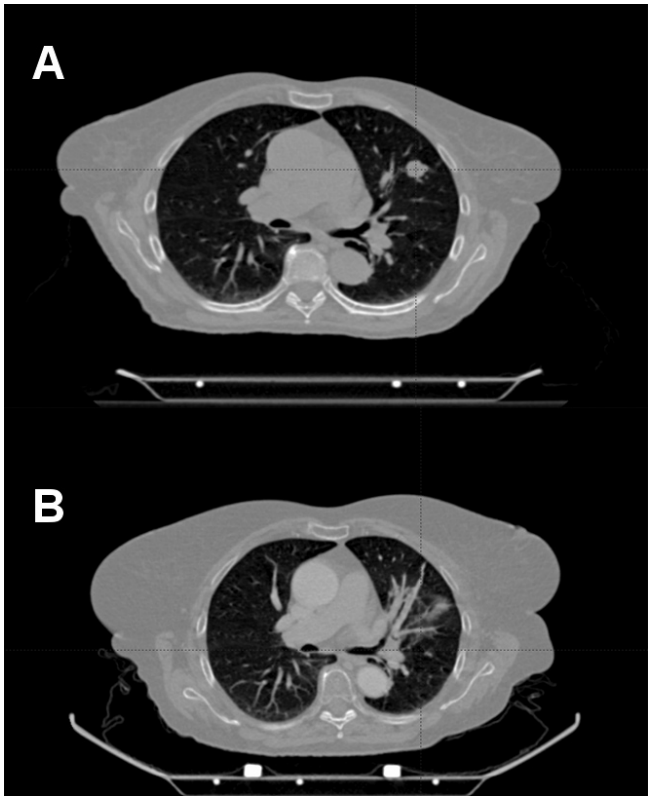

Figure 1. (A) The CT image of the patient with a lung metastasis before SRT. (B) The CT image of the same patient showing a complete regression after SRT with 3 x 20 Gy

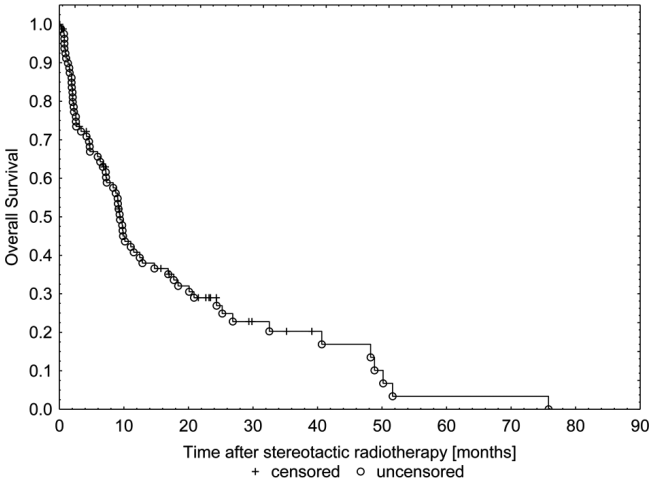

Figure 2. Overall Survival in a whole patients' group

also obtained from the registries. During the follow-up 75% (n=63) of the patients had died. The median OS from the time of SRT treatment was 9.4 months. The percentages of OS after 6, 12, 24, 36 months were 66%, 40%, 29%, 20% respectively (Figure 2).

There was a statistically significant difference in OS after SRT according to whether the SRT has been used alone or with any other additional treatment (p=0.01). The median OS for patients being treated exclusively with SRT was 7 months, while it was 13 months for patients being treated with additional modalities. Coming into details, no beneficial effect of conventional palliative radiotherapy added to SRT was observed in the whole group (p=0.39). When analyzed separately additional RT was not important for extracranial SRT (p=0.75). Although whole-brain radiotherapy (WBRT) was not important for cranial SRT either, it revealed some statistical trend (p=0.075, Figure 3).

Table 3. Treatment effect and crude local control rates by selected factors for evaluable patients

Factor		CR+PR	SD	PD	LC
Tumor Location	**Cranial**	59%	35%	6%	**94%**
p=0.024	**Extracranial**	37.5%	32.5%	30%	**70%**
Biologically Effective Dose (BED)	**BED ≥ 100**	47%	38%	15%	**85%**
p=0.61	**BED <100**	47,5%	30%	22,5%	**77,5%**
Biologically Effective Dose (BED)	**BED ≥ 120**	80%	13%	7%	**93%**
p=0.018	**BED < 120**	39%	39%	22%	**78%**
Mean Tumor diameter	**< 2 cm**	50%	39%	11%	**89%**
p=0.32	**2-3 cm**	55%	20%	26%	**75%**
	> 3 cm	38%	33%	40%	**71%**
Cranial Irradiation	**No**	54%	38%	8%	**92%**
p=0.87	**Yes**	62%	33%	5%	**95%**
Extracranial palliative irradiation	**No**	39%	33%	27%	**72%**
p=0.71	**Yes**	29%	29%	42%	**58%**
Tumor Grade	**G1+G2**	55%	34%	10%	**89%**
p=0.13	**G3+G4**	39%	29%	32%	**68%**

CR-Complete Remission, PR-Partial Remission, SD-Stable Disease, PD-Progressive Disease LC- Local Control
LC= CR+PR+SD

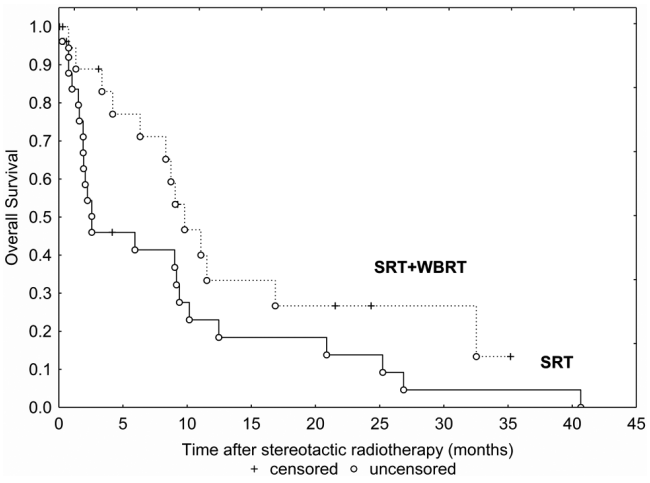

Figure 3. Overall Survival in a subgroup of patients with brain metastases according to the treatment given: SRT or SRT+WBRT

In a multivariate analysis, the important factors with respect to overall survival were patients' general condition (ECOG) and age, which might be expected, and the BED. However, we found also an important role of the time from diagnosis of metastasis to its treatment with the SRT (HR=0.93; p=0.000). Following the Weibull's regression, the predictions of survivals as a function of the interval since the diagnosis of progression (metastases) to its treatment with SRT are presented in Figure 4a and Figure 4b, for cranial and extracranial SRT, respectively.

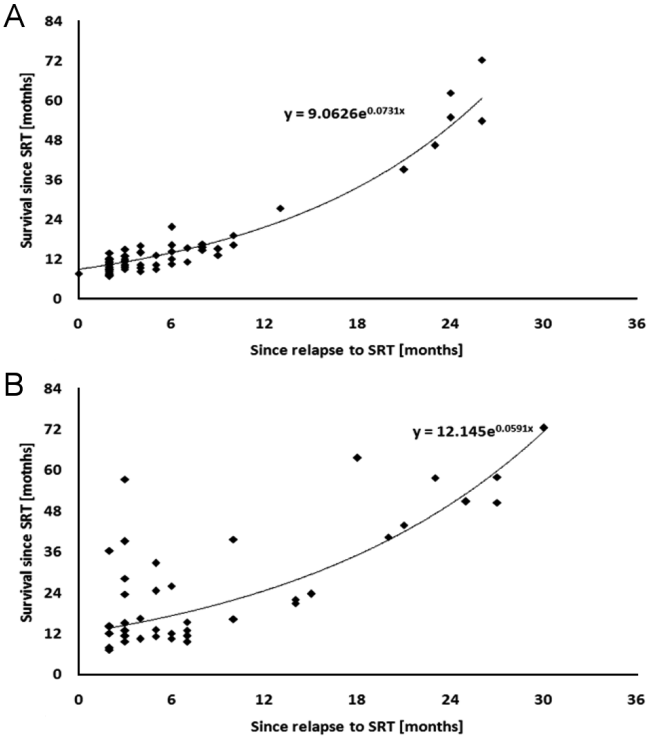

Figure 4. (A) A model of survival since SRT as a function of interval between the diagnosis of metastasis and its treatment with SRT (cranial metastases). (B) A model of survival since SRT as a function of interval between the diagnosis of metastasis (recurrence) and its treatment with SRT (extracranial metastases)

Discussion

The LC rate for RCC's brain metastases after SRT usually exceeds 80% [8-12], and the main cause of deaths is systemic progression, rather than a recurrence in the brain. The studies comparing directly SRT to neurosurgery for RCC are lacking. But, some studies focusing on tumors of a various histopathological origin suggest a comparable treatment outcome [20]. This indicates SRT to be a valuable option in patients with brain metastases, maybe also for those with "radioresistant" tumors.

In case of RCC brain metastases the results obtained using SRT may be relatively good. For example, in the study of Kim et al. [10], the median progression-free survival was especially encouraging in a good-response group which consisted of patients, who had received local regression of the tumor (29 months). A tumor regression was observed in 68.2%, stable disease in 16.5% and progression in 15.3%, with a median OS of 10 months in a whole group.

The ECOG phase II trial in 31 patients with brain metastases from RCC, melanoma or sarcoma treated with sole SRS/SRT [12] revealed local recurrence in 19% and 32% after 3 and 6 months, respectively, but the recurrences outside the irradiated area were 16% and 32%. The median OS was 8.3 months. These results may justify the irradiation of the whole brain (WBRT) in "radioresistant" tumors. The percentage of patients with recurrences outside the irradiated volume in a present study (26%) was similar to the above and others observation [9,12] But on the other hand the question is whether such non-radioresponsive tumors do benefit from conventional WBRT?

The application of SRT as the sole method, or in combination with other treatments has also become an important issue in many studies on RCC [8,14,21,22], but no firm conclusions may be drawn presently. With regard to other common histopathological types of brain metastases it is believed, at present, that the survival times for patients treated with SRT+WBRT and SRT alone do not differ significantly. But, the WBRT may result in worse quality of life, however a better in-brain local control can be expected [3,23]. For RCC it seems that WBRT does not improve the treatment outcome either and it may be generally omitted [9]. Although our study also did not confirm the beneficial effect of this combination for subgroup with RCC brain metastases we observed some statistical trend (p=0.075). However, our study was retrospective and the compared subgroups were small, so the results should be interpreted with caution. We found that any combined treatment in the whole group of cranial and extracranial lesions

(systemic therapy, RT or surgery) with SRT yielded a better outcome in terms of OS (7 months vs 13 months) but not in terms of LC. This seems logical, taking into account the possibility of extending the time to disease progression especially after the use of a systemic treatment. On the other hand, the preselection could also have an important role. Those patients in a better general condition and with a better response to any treatment could be proposed another treatment option. Therefore, in our opinion any firm conclusions on that issue would be possible when based on a randomized trial

The LC for brain tumors in a present study was good (94%) with regression rate of 59% of the lesions and median OS of 8.5 months. That may indicate the SRT may be a "reasonable" alternative to surgery, especially in those tumors in which an adequately high biological effective dose may be given, as derived from own analysis. However, it should be stated that unlike the classical neurosurgical removal of the tumor, the local control in a SRT means no tumor progression with possibility of leaving it in a stable form. Unfortunately, in a majority of patients (85%) with brain metastases they were not isolated or were associated with dissemination to other organs. So, possibly such patients may not be candidates for invasive neurosurgery and SRT could be a good option.

Unlike the above, the results on extracranial SRT were not so encouraging with LC of 70%. The data in the literature on SRS/SRT for extracranial metastases reveal more or less similar results to those obtained for brain metastases. The average LC rate exceeds quite often 80% [13,15,16,17,18]. The local response for extracranial metastases mostly depends on the total dose and schedule of irradiation [15,18]. In case of bone metastases, better results were obtained with a high single dose than with lower doses given in single-fraction or with multifraction treatment (3-year local progression-free survival rates were 88%, 21% and 17% respectively) [18]. Stinauer and al. [15] reported better results for BED >100. Assuming the α/β ratio for RCC between 3 and 5, it means that the radiation dose should be higher than 3 x 8-10 Gy, which is quite often used in a clinical practice [24], also in our center. Moreover, our results suggest that a cut-off point for BED of 100 Gy did not differentiate patients with better or worse treatment outcome. However if BED of 120 Gy or higher was used the local treatment effect was significantly better. It may indicate the application of radiation schedules of 3 x 12 Gy or higher or at least 22 Gy in one fraction. Of course, those are rough approximations assuming the validity of linear-quadratic model for SRT, which may be questionable. But the general impression is that an adequately high biological dose of irradiation should be used for "radioresistant" tumors like RCC.

So, our study indicates that extracranial tumors do not respond so well to the SRT as brain tumors (LC 70% vs 94%), and states the relationship between the radiation dose (BED) and better local response. Although, that latter relationship was probably influenced by a typical tendency in a SRT to treat smaller tumors with larger doses. Therefore, the difference between the effect on brain and extracranial tumors may be due to the lower volume of metastatic lesions in the brain and also more uniform standards for brain stereotactic radiotherapy. It should be noted, however, that the volume effect in our analysis was not statistically significant. The worse results for extracranial metastases could be probably caused by a large volume of the metastases and suboptimal doses of radiation in some cases. Possibly also the SRT in the brain may be less prone to target positioning uncertainties, due to better and more precise treatment planning and positioning. We cannot exclude also some differences in an environmental influence of tumor location on the clinical behavior after SRT. We believe that smaller tumors which are suitable for delivering high radiation doses (BED ≥120) are still good candidates for extracranial SRT and may be alternative to surgery. In other cases which are medically fit, the surgical treatment would be preferable.

An interesting finding coming from our study was the important role of the interval between the diagnosis of metastasis and its treatment with SRT. With prolongation of that time the OS decreased. Such results were also reported by others [25]. It is difficult to explain, but probably too long interval may lead to the tumor enlargement influencing the possibility of delivering the adequate radiation dose. The secondary seeding or more aggressive tumor behavior with prolongation of that time may be also taken into account. It should be stressed, however, that the excessive prolongation of that interval was observed generally in patients given pre-SRT other treatment (palliative RT, systemic therapy). Some differences between cranial and extracranial SRT could be explained by a lesser influence of systemic treatment on the growth of cranial metastases than extracranial ones.

Nowadays, when the targeted therapy is commonly used, it is important to consider the role of the SRT as a part of the multi-disciplinary proceeding [14,21]. The local treatment is important because efficient systemic therapy may improve the life expectancy even in disseminated disease. And some studies show a really good response and tolerance of SRT for brain metastases given together with chemotherapy (sunitynib/sorafenib) [14]. So, assuming the role of the interval to application of the SRT as discussed above, the early incorporation of SRT could be considered.

A limitation of this study is a relatively high percentage of lesions not being assessed radiologically (≈50%). However, this reflects the clinical reality outside the framework of a clinical trial, which was also observed in other studies, where the percentage of radiological assessment was about 60% [22]. Therefore, the evaluation of survival was undoubtedly a valuable complement to the present analysis that increased the credibility of this study.

Conclusions

Treatment of metastases from renal cell carcinoma with the SRT results in a good local response. The local control is better

for brain metastases than extracranial ones. The local efficacy of the SRT seems to depend on the total dose of radiation. Multidisciplinary treatment and earlier application of the SRT appeared to improve the prognosis in patients with metastatic renal cell carcinoma.

References

[1] BHAT S. Role of surgery in advanced/metastatic renal cell carcinoma. Indian J Urol 2010; 26: 167–176 http://dx.doi.org/10.4103/0970-1591.65381

[2] European Association of Urology Guidelines 2014 edition. Avaible from: http: //www.uroweb.org/guidelines/online-guidelines. [5 January 2015]

[3] AOYAMA H, SHIRATO H, TAGO M, NAKAGAWA K, TOYODA T, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006; 295: 2483–2491 http://dx.doi.org/10.1001/jama.295.21.2483

[4] KONDZIOLKA D, PATEL A, LUNSFORD LD, KASSAM A, FLICKINGER JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. Int J Radiat Oncol Biol Phys 1999; 45: 427–434 http://dx.doi.org/10.1016/S0360-3016(99)00198-4

[5] TIMMERMAN RD, KAVANAGH BD, CHO LC, PAPIEZ L, XING L. Stereotactic body radiation therapy in multiple organ sites. J Clin Oncol 2007; 25: 947–952 http://dx.doi.org/10.1200/JCO.2006.09.7469

[6] MAKAREWICZ R, ZARZYCKA M, KULINSKA G, WINDORBSKA W. The value of postoperative radiotherapy in advanced renal cell cancer. Neoplasma 1998; 45: 380–383

[7] DE MEERLEER G, KHOO V, ESCUDIER B, JONIAU S, BOSSI A, et al. Radiotherapy for renal-cell carcinoma. Lancet Oncol 2014; 15: e170–177 http://dx.doi.org/10.1016/S1470-2045(13)70569-2

[8] FOKAS E, HENZEL M, HAMM K, SURBER G, KLEINERT G, et al. Radiotherapy for brain metastases from renal cell cancer: should whole-brain radiotherapy be added to stereotactic radiosurgery?: analysis of 88 patients. Strahlenther Onkol 2010; 186: 210–217 http://dx.doi.org/10.1007/s00066-010-2055-z

[9] KANO H, IYER A, KONDZIOLKA D, NIRANJAN A, FLICKINGER JC, et al. Outcome predictors of gamma knife radiosurgery for renal cell carcinoma metastases. Neurosurgery 2011; 69: 1232–1239 http://dx.doi.org/10.1227/NEU.0b013e31822b2fdc

[10] KIM WH, KIM DG, HAN JH, PAEK SH, CHUNG HT, et al. Early significant tumor volume reduction after radiosurgery in brain metastases from renal cell carcinoma results in long-term survival. Int J Radiat Oncol Biol Phys 2012; 82: 1749–1755 http://dx.doi.org/10.1016/j.ijrobp.2011.03.044

[11] MARKO NF, ANGELOV L, TOMS SA, SUH JH, CHAO ST, et al. Stereotactic radiosurgery as single-modality treatment of incidentally identified renal cell carcinoma brain metastases. World Neurosurg 2010; 73: 186–193 http://dx.doi.org/10.1016/j.surneu.2009.02.011

[12] MANON R, O'NEILL A, KNISELY J, WERNER-WASIK M, LAZARUS HM, et al. Phase II trial of radiosurgery for one to three newly diagnosed brain metastases from renal cell carcinoma, melanoma, and sarcoma: an Eastern Cooperative Oncology Group study (E 6397). J Clin Oncol 2005; 23: 8870–8876 http://dx.doi.org/10.1200/JCO.2005.01.8747

[13] RANCK MC, GOLDEN DW, CORBIN KS, HASELLE MD, LIAUW SL, et al. Stereotactic body radiotherapy for the treatment of oligometastatic renal cell carcinoma. Am J Clin Oncol 2013; 36: 589–595 http://dx.doi.org/10.1097/COC.0b013e31825d52b2

[14] STAEHLER M, HASEKE N, NUHN P, TULLMANN C, KARL A, et al. Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma. BJU Int 2011; 108: 673–678 http://dx.doi.org/10.1111/j.1464-410x.2010.09895.x

[15] STINAUER MA, KAVANAGH BD, SCHEFTER TE, GONZALES R, FLAIG T, et al. Stereotactic body radiation therapy for melanoma and renal cell carcinoma: impact of single fraction equivalent dose on local control. Radiat Oncol 2011; 6: 34 http://dx.doi.org/10.1186/1748-717X-6-34

[16] SVEDMAN C, SANDSTROM P, PISA P, BLOMGREN H, LAX I, et al. A prospective Phase II trial of using extracranial stereotactic radiotherapy in primary and metastatic renal cell carcinoma. Acta Oncol 2006; 45: 870–875 http://dx.doi.org/10.1080/02841860600954875

[17] WERSALL PJ, BLOMGREN H, LAX I, KALKNER KM, LINDER C, et al. Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. Radiother Oncol 2005; 77: 88–95 http://dx.doi.org/10.1016/j.radonc.2005.03.022

[18] ZELEFSKY MJ, GRECO C, MOTZER R, MAQSANOC JM, PEI X, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. Int J Radiat Oncol Biol Phys 2012; 82: 1744–1748 http://dx.doi.org/10.1016/j.ijrobp.2011.02.040

[19] HA ID, NOH M, LEE Y. Frailty Models via H-likelihood. Version 1.1. Vienna (2012): R Foundation for Statistical Computing.

[20] MUACEVIC A, KRETH FW, HORSTMANN GA, SCHMID-ELSAESSER R, WOWRA B, et al. Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. J Neurosurg 1999; 91: 35–43 http://dx.doi.org/10.3171/jns.1999.91.1.0035

[21] GORE ME, HARIHARAN S, PORTA C, BRACARDA S, BJARNASON GA, et al. Sunitinib in metastatic renal cell carcinoma patients with brain metastases. Cancer 2011; 117: 501–509 http://dx.doi.org/10.1002/cncr.25452

[22] SAMLOWSKI WE, MAJER M, BOUCHER KM, SHRIEVE AF, DECHET C, et al. Multidisciplinary treatment of brain metastases derived from clear cell renal cancer incorporating stereotactic radiosurgery. Cancer 2008 113: 2539–2548 http://dx.doi.org/10.1002/cncr.23857

[23] SOFFIETTI R, KOCHER M, ABACIOGLU UM, VILLA S, FAUCHON F, et al. A European Organisation for Research

and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality of life results. J Clin Oncol 2013; 31: 65–72 http://dx.doi.org/10.1200/JCO.2011.41.0639

[24] JERECZEK-FOSSA BA, PIPERNO G, RONCHI S, CATALANO G, FODOR C, et al. Linac-based stereotactic body radiotherapy for oligometastatic patients with single abdominal lymph node recurrent cancer. Am J Clin Oncol 2014; 37: 227–233 http://dx.doi.org/10.1097/COC.0b013e3182610878

[25] CELEJEWSKA A, TUKIENDORFF A, MISZCZYK L, SKLADOWSKI K, WYDMANSKI J, et al. Stereotactic radiotherapy in epithelial ovarian cancer brain metastases patients. J Ovarian Res 2014; 7: 79 http://dx.doi.org/10.1186/s13048-014-0079-1