



Do we have a “game changer” in treating patients with brain metastasis from renal cell carcinoma?

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Renal cell carcinoma (RCC) is the most common type of kidney cancer. About 25% of patients are diagnosed with metastatic disease at presentation and another 25–30% diagnosed with localized disease will develop metastasis over time (1). The incidence of brain metastasis (BM) ranged from 3–17% in various studies. Historically, the prognosis of patients with brain metastasis was very poor, with a median survival of up to seven months in more contemporary series (2). With targeted therapy, according to the International Metastatic RCC Database Consortium (IMDC) [2005–2011], median survival time has improved, reaching 14.4 months after first-line treatment for patients with brain metastasis *vs.* 19.0 months for those with no brain metastasis (3). The prognosis and preferred treatment strategy for patients with brain metastases depends on several factors, including: number, size and location of brain metastases, neurologic symptoms, performance status, tumor histology, extracranial disease status, previous systemic treatments and additional available treatment options (4,5).

Local therapy remains the most effective type of treatment, including surgery, stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT), or a combination of surgery and radiation.

Surgery as a single modality treatment may give good results with immediate relief of mass-effect related symptoms. However, rates of local failure are relatively high, up to 40% (6,7). The use of surgery in RCC BM is limited to fit patients, usually at a younger age, less

symptomatic, with a Karnofsky Performance Status (KPS) of more than 80, and most importantly, with no more than three metastases. Although there are reports of resection of multiple brain metastasis (8), most of the data available is for patients with one resectable brain metastasis (9). Median survival of patients after craniotomy ranges between 8.5–12.6 months in various reports (4,7,8).

In the past decade, SRS has become the treatment of choice for patients who are not surgical candidates, especially those with multiple metastases (up to 10) (10). This type of treatment may provide 1 year local control rates of up to 90–95% (4,10), with median OS rates of 13.9 months from diagnosis of BM (5,10). Median reported total dose for SRS ranges between 20–22 Gy in different reports, delivered in 1–5 fractions (4). Recommendations of SRS single fraction treatments of maximum doses of 24, 18, and 15 Gy to tumors of 2 cm, between 2–3 cm, and greater than 3 cm, respectively, were given in the RTOG criteria (11,12). Using a dose of 20 Gy in SRS treatment compared to a dose of 16–18 Gy demonstrated better local control rates (12-month local control rates of 81% and 50%, respectively; $P=0.001$) (4).

This treatment option has a number of advantages over surgery, including a higher number of metastases that may be treated at the same time, lower rate of neurological complications, and the opportunity to treat brain metastases in areas not fit for surgery. The main limitations of this type of therapy are the high rates of intracranial failures, up to 50% (13).

Table 1 Local therapy in patients with brain metastasis from RCC

Type of therapy	Patient number	Local recurrence rate (%)	1y LCR (%)	OS (m)	PFS (m)	References
WBRT	447	39–52	7–35	3–7.5		(2,6,9,11,13–15,18)
Surgery	389	31–70	52.8	6–23	6.9	(2,4,7,8,11,14,17)
Surgery + SRS	51	4.2	94	21.9		(2,4)
Surgery + BRT	450	10–20	66–83	5.6–28.1	8.56	(8,9,11,14,17)
SRS + WBRT	428	5–16.7	82–92	5.7–16.1		(4,11,14,18)
SRS	714	0–15	77.1–91.8	6.7–16.8		(2,4,7,10–12,14,18)

SRS, stereotactic radio-surgery; WBRT, whole brain radiotherapy; LCR, local control rate; PFS, progression free survival; OS, overall survival; m, months.

WBRT is another treatment option for patients with BM, but it has several limitations as a single treatment modality in brain metastases from RCC. This tumor type is considered radio-resistant, requiring high doses of radiation for good local control that cannot be delivered to the whole brain. Standard doses usually used for WBRT are not always effective in patients with BM from RCC, leading to a very short median OS, about 4.4 months (14). It remains as the preferred choice for patients with brain metastases not amenable to surgery or SRS, especially for patients with multiple BM (more than 10), poorly controlled systemic disease and a relatively short life expectancy. The standard dose recommended for WBRT in RCC patients with multiple brain metastases is 30 Gy delivered in 10 fractions; dose escalation regimens did not succeed in improving OS in this group of patients in almost all prospective trials (15). Rades *et al.* performed a retrospective analysis of treatment outcomes in 60 RCC patients with BM, treated with WBRT, comparing higher doses (40 Gy in 20 fractions or 45 Gy in 15 fractions) with standard treatment regimens. Higher doses treated patients had a median OS of 1 year and local control rates of 57% for 6 months, compared to lower doses treated patients, with 4 months median OS and local control rates at 6 months of 21% only (15). One of the main limitations of WBRT, especially in high doses, is cognitive impairment. New techniques with sparing of the hippocampal structures showed less cognitive injury, with similar general treatment effectiveness (16).

When considering local therapy, a combined approach may be more effective in all points of view. It includes a combination of surgery with SRS for better local control, or surgery or SRS with WBRT for better intracranial disease control.

In a phase III randomized trial carried out 20 years ago,

the benefit of postoperative WBRT was a 52% reduction in intracranial recurrences (17). More recent retrospective studies supported the point of combined surgery and adjuvant WBRT to improve survival in patients without evidence of extracranial disease but not in patients with uncontrolled systemic disease (14).

A consecutive series of SRS alone, surgery plus SRS, and WBRT plus SRS demonstrated overall survival times of 13.9, 21.9, and 5.9 months, respectively, with local control rates of 84%, 94%, and 88%, respectively (4).

In another trial with 88 patients evaluating the role of SRS and WBRT in brain metastases from RCC, the median OS for SRS only, SRS and WBRT or WBRT only was 12, 16, and 2 months, respectively (18). Although RCC is considered to be a radio-resistant tumor, WBRT might affect microscopic metastases and potential delay in the appearance of new brain metastases. Nevertheless, no significant survival benefit could be demonstrated in these patients. A selection bias might partially explain this result, while WBRT alone was frequently used in patients with a larger number of brain metastases (4).

According to the reported data, aggressive treatment with combined techniques is recommended for local treatment of patients with brain metastases from RCC, including a combination of surgery with adjuvant SRS. In some cases, adding WBI is justified. *Table 1* summarizes the data on local treatments for brain metastasis from RCC.

There is restricted data considering the activity of systemic agents in brain metastases from RCC. From historical treatment options, high-dose interleukin-2 showed overall response rates (ORR) of 5.6%, with the addition 22.3% of the patients with disease stabilization in a group of 18 patients. The median interval between the diagnosis of brain metastases and the beginning of IL-2

Table 2 Systemic therapy in patients with brain metastasis from renal cell carcinoma

Type of treatment	Patient number	Treatment line	Combination with SRS	ORR%	DCR%	PFS (m)	OS (m)	Ref
Sunitinib	16+22	1st	22	0	31	2.3	6.3/11.1*	(20,21)
Sorafenib	29	1st	29	NA	NA	NA	11.1*	(21)
Cabozantinib	12	2nd	5	50	75	5.8	8.8	(22)
Nivolumab	73	2nd+	34	12	25	2.7–4.8	Not reached	(23)

*, in patients, receiving combined therapy with radiation. SRS, stereotactic radio-surgery; ORR, overall response rate; DCR, disease control rate; PFS, progression free survival; OS, overall survival; m, months.

therapy was 7.0 months (range, 1–116 months). Median overall survival in patients with brain metastases was 15.3 months, compared to 48 months in RCC patients without any history of brain metastases (19).

Tyrosine kinase inhibitors (TKIs) are small molecules able to cross the blood-brain barrier, but their therapeutic activity on BM is limited due to the presence of drug efflux transporters. *Table 2* summarizes the data on the effectiveness of TKIs in patients with brain metastases from RCC.

There are two reports of sunitinib activity in patients with BM. Analysis of an open access trial that included 321 patients with brain metastases treated with sunitinib in standard doses demonstrated that 213 (66%) of them were evaluable for tumor response. Complete response was reported for one patient while 25 patients (12%) had a partial response with ORR of 12%, in contrast to 17% ORR in the whole study population. Of the 213 evaluable patients, stable disease was reported for 111 patients (52%) for at least 3 months, following with a clinical benefit rate of 64%. Patients with brain metastases showed a median PFS of 5.6 months, whereas median PFS was 10.9 months in the overall extended access program (EAP) population. Median OS was 9.2 months (95% CI, 7.8–10.9) in patients with brain metastases, contrasting to 18.4 months (95% CI, 17.4–19.2) in the overall EAP population (24). Based on these results, a prospective phase II trial was conducted to better evaluate efficacy of sunitinib in previously untreated patients. Exclusion criteria included cerebral metastasis presenting as hemorrhage, presence of an isolated BM of less than 2 cm amenable to surgery or radiosurgery. The study was stopped after accrual of 17 patients. No objective responses were reported. Best response was disease stabilization, seen in 5 patients (31%). Median TTP was 2.3 months and median OS was 6.3 months (95% CI, 2.1–7.9 months) (20).

Another study based on real life data analyzed the activity of cabozantinib as a second or more treatment line in

patients with newly presented BM from RCC. The analysis was made on 12 patients who presented with BM; most had a single lesion (75%), and all patients were initially or simultaneously treated with local treatment (surgery, SRS or WBRT). Overall response rate was 50%, with a disease control rate of 75%, evaluated according to RECIST criteria. The median duration of response was 4.8 months and median OS was 8.8 months, with a 1 year OS of 50% (22).

A study of combined local and systemic therapy reported efficacy and safety of antiangiogenic agents (sunitinib and sorafenib) with concomitant SRS in patients with cerebral and spinal metastasis from RCC. Of a total of 51 patients with BM, 22 were treated with sunitinib and 29 with sorafenib. Most had been treated with single fraction SRS in a dose of 20 Gy for a median of 2.6 lesions. Local control of cerebral lesions at 12 and 24 months was 100% and 96.6% (SEM 0.03, 95% CI, 78–99%), respectively. Median overall survival of 11 months from SRS was shown in patients with cerebral lesions. Following 36 months from SRS, 25% of the patients were still alive (21). This study supports the approach of combined therapy, with aggressive local treatment added to systemic treatment. Despite the small sample, there is a meaningful difference in survival and local control in these patients, including those on second line systemic therapy.

In recent years, immunotherapy has been showing promising activity in patients with metastatic RCC. There is limited data concerning the immune structure of brain metastases from RCC. These lesions are frequently characterized by lymphocytic infiltration and programmed death-ligand 1 (PD-L1) expression, given the rationale of checkpoint inhibitor evaluation in patients with BM (23).

The GETUG-AFU 26 NIVOREN phase II trial assessed the activity and safety of nivolumab in patients with metastatic clear cell RCC to the brain who failed vascular endothelial growth factor-directed therapies. The rate of overall survival at 1 year was 66.7% (95% CI, 49.6–79.1%)

in patients without local therapy (cohort A), and 58.8% (95% CI, 40.6–73.2%) in those previously treated locally (cohort B). Median intracranial PFS was 2.7 months (95% CI, 2.3–4.6 months) in cohort A and 4.8 months (95% CI, 3.0–8.0) in cohort B. The intracranial activity of nivolumab shown in this study in patients with untreated brain metastases from RCC was very limited. Only four patients (12%) out of 34 had intracranial response. In addition, all the responding patients had limited intracranial tumor burden (up to 10 mm). Actually, the reduction in the risk of intracranial progression was shown only for patients who had received prior focal therapy, compared to those with untreated brain metastases (23) (Table 2).

Checkpoint combinations may show better results, according to their activity in a general population of patients with metastatic RCC, with intermediate and poor IMDC risk groups. This hypothesis is supported by the results of phase II trials in melanoma. The combination of nivolumab with ipilimumab supplied high intracranial response rates among 94 patients with metastatic melanoma to the brain. Complete response rate was 26% and the partial response rate was 30% for a total of 57% intracranial clinical benefit for those patients (25). Combinations of antiangiogenics and immune checkpoint inhibitors may provide improved antitumor immunity in the brain that may deplete myeloid-derived suppressor cells, allowing conversion of “cold tumors” into “hot tumors”. Most probably, these combinations will soon emerge as first-line standard treatment for patients with metastatic RCC, and consecrated trials are awaited to evaluate their impact on patients with BM.

To conclude: local treatment options remain the most important treatment modality of patients with brain metastasis from RCC. Systemic therapy as a single modality is not effective enough. Further dedicated trials with combined therapies of two checkpoint inhibitors or one drug with TKIs are needed to estimate their impact on outcomes in these patients.

The best treatment strategy for patients with brain metastases from clear cell RCC is a combination of local aggressive therapy (surgery, SRS or combination) with the optional use of WBRT, preferably with hippocampal sparing techniques and effective systemic therapy, including second line treatment options (TKI or immunotherapy or combinations).

For each treatment approach, proper patient selection is needed. In patients with poor prognosis or low KPS, uncontrolled primary and lack of further systemic treatment

options—a less aggressive approach may be acceptable.

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Footnote

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