CLINICAL STUDY

Synchronous brain metastases as a poor prognosis factor in clear cell renal carcinoma: a strong argument for systematic brain screening

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Abstract

Purpose Brain metastases (BM) usually represent a poor prognostic factor in solid tumors. About 10% of patients with renal cancer (RCC) will present BM. Local therapies such as stereotactic radiotherapy (SRT), whole brain radiotherapy (WBRT), and surgery are used to achieve brain control. We compared survival between patients with synchronous BM (SynBM group) and metachronous BM (MetaBM group).

Methods It is a retrospective study of patients with clear cell renal cell carcinoma (ccRCC) and BM treated with TKI between 2005 and 2019 at the Centre Léon Bérard in Lyon. We collected prognostic factors: The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score, the TNM stage, the histological subtypes and the Fuhrman grade. Overall survival (OS) was defined from diagnosis of metastatic ccRCC to death. Brain progression-free survival (B-PFS) was defined from focal brain therapy to brain progression or death.

Results 99 patients were analyzed, 44 in the SynBM group and 55 in the MetaBM group. OS in the MetaBM group was 49.4 months versus 19.6 months in the SynBM group, $p = 0.0002$. The median time from diagnosis of metastasic disease to apparition of BM in the MetaBM group was 22.9 months (4.3; 125.7). SRT was used for 101 lesions (66.4%), WBRT for 25 patients (16.4%), surgery for 21 lesions (13.8%), surgery followed by radiation for 5 lesions (3.3%). B-PFS for all patients was 7 months (IC95% [5.0–10.5]).

Conclusions Survival of patients with synchronous BM is inferior to that of patients with metachronous BM. Outcome is poor in both cases after diagnosis of BM. Brain screening should be encouraged at time of diagnosis of metastatis in ccRCC.

Keywords Clear cell renal cell carcinoma · Metastatic · Synchronous brain metastases · Stereotactic radiation · Cabozantinib · Immunotherapy

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Introduction

Brain metastases (BM) usually represent a poor prognostic factor in solid tumors and overall survival in these patients seems to be limited [1]. Moreover, quality of life may be affected by brain damage caused by tumoral lesions, as well as by the different focal treatments (radiotherapy, surgery) [2]. Indeed, the presence of the blood–brain barrier (BBB) limits the delivery and the efficacy of systemic anticancer therapies to the central nervous system (CNS). Multiple mechanisms are involved in this phenomenon: the limited passive diffusion of systemic agents, the presence of active efflux pumps, the different volume of distribution of the drug in the brain parenchyma… [3].

Local therapies have been subsequently developed in order to control tumor progression in the brain. The treatment of BM is based on surgery and radiotherapy: stereotactic radiotherapy (SRT, i.e., radiosurgery or hypofractionated stereotactic radiotherapy, which both have proven their efficacy on renal BM [4]), or whole brain radiotherapy (WBRT) [5]. A combined approach with post-operative SRT following surgery leads to better local control [6, 6]. When surgery is not possible and for patients with up to 3 small lesions, SRT alone compared to SRT followed by WBRT has shown less cognitive deterioration without impact on overall survival with however worse local control [8]. The total volume represented by BM, more than their number, should be a decision criteria for the use of SRT versus WBRT [9]. Unfortunately, despite these different treatment modalities some BM will present local progression or relapse.

About 10% of patients with metastatic renal cell carcinoma (RCC) have brain involvement [10, 11]. A high TN stage at diagnosis could be a predictive factor for the development of BM, as well as the presence of bone or thoracic metastases [10, 10]. However, brain imaging is not routinely recommended for patients with localized or metastatic RCC in the absence of neurological symptoms. The proportion of patients with synchronous BM at diagnosis of metastatic RCC is low, probably less than 5%. Because patients with BM are usually excluded from clinical trials, the efficacy of tyrosine kinase inhibitors (TKI) in this population is not well known, and localized treatments remain mandatory to achieve local control of such lesions. Indeed, for patients with synchronous BM, focal treatment of the CNS is a priority, and has to be planned usually before the start of any systemic treatment.

We hypothesized that patients with synchronous BM present a worse prognosis than patients who developed BM during the course of their disease.

Methods

Study design

We retrospectively reviewed the files of patients with metastatic brain RCC treated with TKI in our institution. Our primary objective was to compare the median overall survival of patients with synchronous BM versus metachronous BM. Our secondary objectives were to describe the efficacy and the side effects of surgery and radiotherapy of the CNS in this population.

Population

Our population sample included all adult patients with clear cell renal cell carcinoma (ccRCC) metastatic to the brain and treated with at least one line of TKI. ccRCC was histologically or cytologically proven. We collected usual prognostic factors: the TN stage, the histological pattern, the Fuhrman nuclear grade and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score (composed of the Karnofsky performance status, the time from diagnosis to systemic treatment, neutrophil count, platelet count, haemoglobin levels and serum calcium levels). Patients treated with interleukine-2 or interferon monotherapy in first line were excluded because of the difference of prognosis of such disease before the era of TKI, as well as patients with non-clear cell subtypes (excepted for sarcomatoid feature). Patients with BM diagnosed within the first 3 months following diagnosis of metastatic disease composed the SynBM group, and patients who developed BM after 3 months composed the MetaBM group.

Treatments and endpoints

Systemic treatments were administered as standard practice according to national approval or within a clinical trial. SRT was defined as any type of hypofractionated focused radiation therapy of the brain (i.e.: hypofractionated radiation therapy and stereotactic radiosurgery). Brain progression was defined by a relapse on the site of the treated BM or by the occurrence of a new BM in a different site, proven by brain imaging (MRI or TDM). Overall survival (OS) was defined from the date of diagnosis of metastatic ccRCC to death or last follow-up. Specific brain overall survival (BM-OS) was defined from the diagnosis of BM to death or last follow-up. Brain progression-free survival (B-PFS) was defined as the time from focal brain therapy to brain progression, death, or last follow-up.

Statistical analysis

Statistical analyses were performed with SAS version 9.4 software (SAS Institute). Survival distributions were evaluated by the Kaplan–Meier method. Log-rank tests were used to compare sub-populations.

Ethics and consent to participate

The study was approved by the General Data Protection Regulation (GDPR) under Protocol MR04 (Non-Human Research, Health Studies and Evaluations) as R201-004-102 number.

Results

Patients

99 patients with ccRCC metastatic to the brain and treated with TKI at the Centre Léon Bérard between January 2005 and December 2019 were analyzed. 44 of them (44%) presented with synchronous BM, and 55 of them (55%) developed metachronous BM. The sex ratio M/F was 3.7 with 78 men and 21 women. The median age was 58.9 years [32.2;83.2]. Characteristics of the population are shown in Table 1. Patients in the two groups were comparable in terms of age, sex, histological features, disease stages, and IMDC scores. Patients were treated with a median of 2 lines of systemic treatment (1 to 8 lines). 89 patients received a TKI in first line: 73 patients received sunitinib, 5 patients pazopanib, and 11 patients sorafenib. The most used TKI for all lines were sunitinib (89 patients), sorafenib (30 patients), axitinib (29 patients), and cabozantinib (17 patients). Only 12 patients received an immune checkpoint inhibitor (ICI), administered between the 2nd and the 6th line. The median follow-up from the diagnosis of metastatic disease to either death or last follow-up was 34.8 months (1.5; 144.8): 19.9 months (1.5; 112.8) in the SynBM group and 46.2 months (7.1; 146.8) in the MetaBM group.

BM characteristics

Seventy-three patients had a progressive systemic disease at diagnosis of the first BM: 39 patients (88.6%) in the SynBM group and 34 patients (61.8%) in the MetaBM group. BM were discovered because of neurological symptoms in 72 patients, 28 patients (63.6%) in the SynBM group and 44 patients (80%) in the MetaBM group, and because of systematic imaging for 27 patients, 16 patients (36.3%) in the SynBM group and 11 patients (20%) in the MetaBM group. 54 patients first presented with a solitary BM: 22 in the SynBM group and 32 the MetaBM group. 10 patients (18%) in the MetaBM group never had a brain imaging before the diagnosis of BM.

Overall survival

OS for the global population was 34.8 months (95%CI [26.7–45.5]). Patients with synchronous BM presented a clinically and statistically significant reduction in median overall survival: median OS in the MetaBM group was 49.4 months (95%CI [34.4–67.7]), versus 19.6 months (95%CI [12.1–30.6]) in the SynBM group, p = 0.0002 (Fig. 1). In the MetaBM group, 80% of patients were alive at 2 years and 38% at 5 years, vs respectively 41% and 14% in the SynBM group. BM-OS in the MetaBM group was 16.4 months (95%CI [6.6–20.0]) vs 19.1 months (95%CI [11.6–29.9]) in the SynBM group, p = 0.23 (Fig. 2). The median time between the apparition of BM and the diagnosis of metastatic disease in the MetaBM group was 22.9 months (4.3; 125.7).

Eighty-seven patients had died at the time of our analysis. There was no significant difference between the 2 groups concerning the cause of death: 30/99 patients died of global progression of the disease (ie systemic plus brain progression), 29 patients of systemic progression, 8 patients (4 in the SynBM group and 4 in the MetaBM group) of brain progression, 18 patients of other or unknown causes.

Local BM treatment

In our 99 patients, 152 focal treatments were performed at diagnosis of BM: SRT for 101 lesions (66.4%), WBRT for 25 patients (16.4%), Surgery for 21 lesions (13.8%), surgery followed by radiation for 5 lesions (3.3%). Brain progression free survival for each treatment was respectively 6.7 months, 3.9 months, 10.4 months and 15.5 months. 58 patients presented with brain progression after a first local treatment. B-PFS for all patients was 7 months (IC95% [5.0–10.5]). (Fig. 3). Ten patients didn't receive any focal treatment for BM: seven patients because of poor performance status and/or fast progression of the disease, and 3 patients because of stability of BM on systemic therapy, and the small lesion size and/or the absence of associated neurological symptoms.

Complications of BM treatments are described in the Table 2. Adverse events occurred in 36% of patients treated with WBRT (intracranial hypertension or symptomatic brain oedema in 28% of cases), versus 23.8% of surgeries, and 20.8% of SRT. Radionecrosis was the most frequent complication of SRT (7.9% of treatments).

Discussion

The presence of BM is a poor prognostic factor in RCC with historical overall survival of less than one year [12, 13]. Since TKI have been developed, the prognosis of these patients seems to have improved, although it remains worse than for patients without brain involvement. Indeed, Dudek et al. [14] showed in their retrospective study on metastatic RCC patients treated with TKI between 2008 and 2010, that OS in patients with BM was 33 months vs 80 months in patients without BM, p = 0.010. With an OS of 34.8 months for all patients in our study, we have concordant results with the current literature. Furthermore, our study is the first to our knowledge that demonstrates the poor prognosis of patients with synchronous BM in patients with ccRCC and brain metastases. However, it is still unclear whether brain
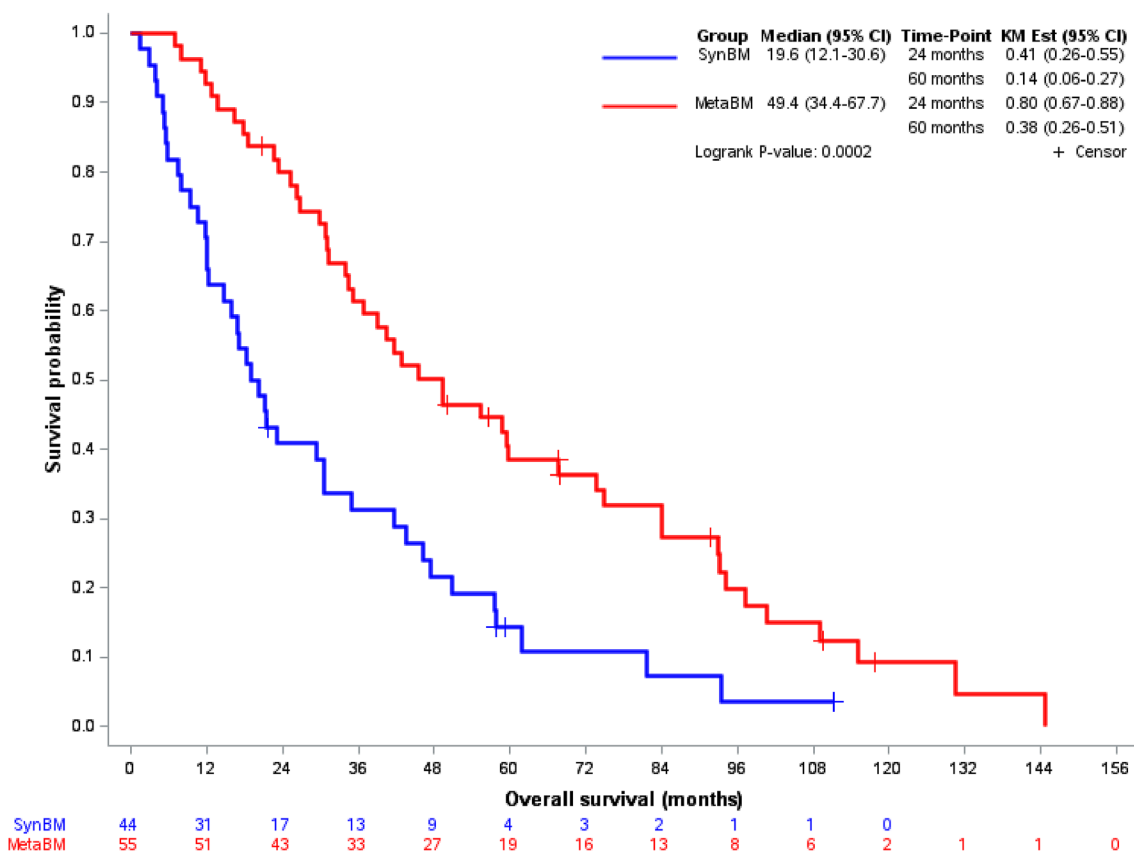
Table 1 Characteristics of patient

	Synchronous brain metastasis		Metachronous brain metastasis		All patients	
	N = 44		N = 55		N = 99	
Clinical characteristics						
Age (years)	57.9	[36.4;82.2]	60.6	[32.2;83,2]	58.9	[32.2;83.2]
Sexe						
Man	36	(81.8%)	42	(76.4%)	78	(78.8%)
Woman	8	(18.1%)	13	(23.6%)	21	(21.2%)
T stage						
1	5	(11.4%)	9	(16.4%)	14	(14.1%)
2	11	(25.0%)	11	(20.0%)	22	(22.2%)
3	25	(56.8%)	30	(54.5%)	55	(55.6%)
4	1	(2.3%)	2	(3.6%)	3	(3.0%)
Unknown	2		3		5	
N stage						
0	22	(50.0%)	25	(45.5%)	47	(47.5%)
1	5	(11.4%)	1	(1.8%)	6	(6.1%)
2	1	(2.3%)	4	(7.3%)	5	(5.1%)
Unknown	16		25		41	
M stage						
0	21	(47.7%)	27	(49.1%)	48	(48.5%)
1	23	(52.3%)	28	(50.9%)	51	(51.5%)
IMDC score						
Favorable	2	(4.5%)	6	(10.9%)	8	(8.1%)
Intermediate	18	(40.9%)	15	(27.3%)	33	(33.3%)
Poor	9	(20.5%)	14	(25.5%)	23	(23.2%)
Unknown	15		20		35	
Histological characteristics						
Majoritary feature						
Clear cell	43	(97.7%)	55	(100.0%)	98	(99.0%)
Sarcomatoid	1	(2.3%)	0	(0.0%)	1	(1.0%)
Minority feature 1						
Clear cell	0	(0.0%)	1	(1.8%)	1	(1.0%)
Sarcomatoid	6	(13.6%)	9	(16.4%)	15	(15.2%)
Oncocytic	0	(0.0%)	1	(1.8%)	1	(1.0%)
Eosinophilic	3	(6.8%)	4	(7.3%)	7	(7.1%)
None	35		40		75	
Minority feature 2						
Sarcomatoid	1	(2.3%)	0	(0.0%)	1	(1.0%)
Rhabdoid	1	(2.3%)	0	(0.0%)	1	(1.0%)
None	42		55		97	
Furhman grade						
1	1	(2.3%)	0	(0.0%)	1	(1.0%)
2	10	(22.7%)	15	(27.3%)	25	(25.3%)
3	12	(27.3%)	22	(40.0%)	34	(34.3%)
4	11	(25.0%)	13	(23.6%)	24	(24.2%)
Unknown	10		5		15	
Systemic treatments						
Number of lines administered/patient	2.0	[1.0–7.0]	3.0	[1.0–8.0]	2.0	[1.0–8.0]
Molecules administered (any line)						
Sunitinib	41	(93.2%)	48	(87.3%)	89	(89.9%)
Everolimus	9	(20.5%)	23	(41.8%)	32	(32.3%)

Table 1 (continued)

	Synchronous brain metastasis		Metachronous brain metastasis		All patients	
	N = 44		N = 55		N = 99	
Sorafenib	13	(29.5%)	17	(30.9%)	30	(30.3%)
Axitinib	14	(31.8%)	15	(27.3%)	29	(29.3%)
Bevacizumab	8	(18.2%)	11	(20.0%)	19	(19.2%)
Cabozantinib	6	(13.6%)	11	(20.0%)	17	(17.2%)
Pazopanib	4	(9.1%)	8	(14.5%)	12	(12.1%)
Nivolumab	3	(6.8%)	9	(16.4%)	12	(12.1%)
Temsirolimus	4	(9.1%)	4	(7.3%)	8	(8.1%)
Gemcitabine + 5-Fluorouracile	2	(4.5%)	4	(7.3%)	6	(6.1%)
Interferon alpha	2	(4.5%)	0	(0.0%)	2	(2.0%)
Adriamycine	1	(2.3%)	0	(0.0%)	1	(1.0%)

IMDC international metastatic renal cell carcinoma database consortium

Group	Median (95% CI)	Time-Point	KM Est (95% CI)
SynBM	19.6 (12.1-30.6)	24 months	0.41 (0.26-0.55)
		60 months	0.14 (0.06-0.27)
MetaBM	49.4 (34.4-67.7)	24 months	0.80 (0.67-0.88)
		60 months	0.38 (0.26-0.51)

Logrank P-value: 0.0002   + Censor

|													
SynBM	44	31	17	13	9	4	3	2	1	1	0		
MetaBM	55	51	43	33	27	19	16	13	8	6	2	1	1	0

Abbreviations : SynBM = synchronous brain metastases ; MetaBM = metachronous brain metastases

Fig. 1 Overall survival from the diagnosis of metastatic ccRCC (OS) in SynBM and MetaBM groups. *SynBM* synchronous brain metastases; *MetaBM* metachronous brain metastases

imaging should be systematically performed at the diagnosis of metastatic disease. Choi et al. [15], in their retrospective study of 93 patients with RCC and BM did not show any difference in survival between patients with synchronous or metachronous BM. However, they chose to consider OS from the time of BM diagnosis with similar results to ours (9.9 months for patients with metachronous BM vs 14.5 months for patients with synchronous BM, p = 0.4780).

Abbreviations : SynBM = synchronous brain metastases ; MetaBM = metachronous brain metastases
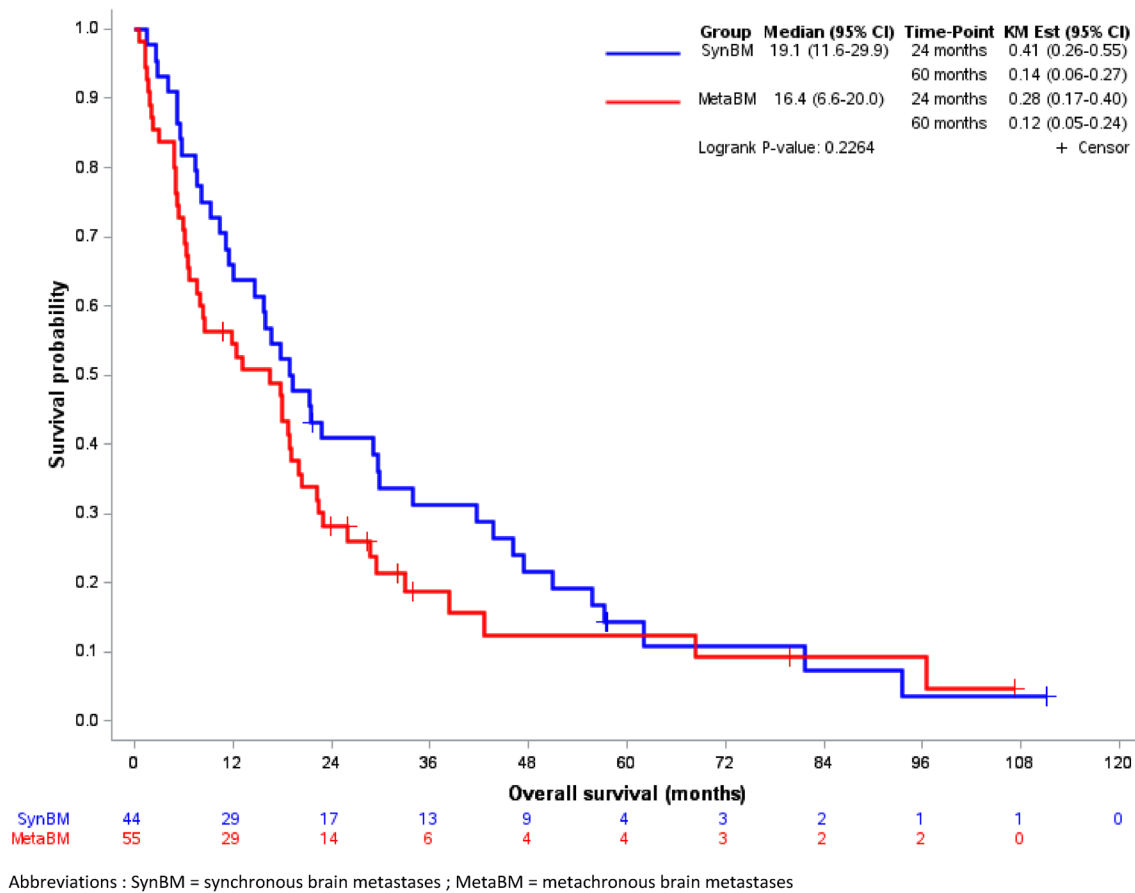
Fig. 2 Overall survival from the diagnosis of BM (BM-OS^{OSbm}) in SynBM and MetaBM groups. *SynBM* synchronous brain metastases; *MetaBM* metachronous brain metastases

We chose in our study to consider OS from the diagnosis of metastatic RCC because the question of brain screening at this phase of the disease is controversial. OS was significantly different between our 2 groups (49.4 months in the MetaBM group vs 19.6 months in the SynBM group, p = 0.0002) whereas BM-OS was not (p = 0.23). With a median time to develop BM of 26.7 months in the Choi study and 22.9 months in our study, we can extrapolate that the low BM-OS in the MetaBM group may be explained by the secondary drug resistance developed by RCC because of previous exposure to systemic therapies before the occurrence of BM. Furthermore, we can note that the apparition of metachronous BM seems to be an evolutionary turning point in the cancer disease, as patients at this point present a similar OS to patients with a diagnosis of synchronous BM.

Focal treatments were associated to systemic therapies in 89% of our patients in this study. Khan et al. recently showed in their meta-analysis of seven studies that the combination of SRT with TKI in patients RCC with BM was associated with better OS and better local control compared to patients who didn't received TKI [16]. In our study, SRT

was used most of the time, followed by surgery. Better PFS was obtained with surgery followed by SRT orsurgery alone. Indeed, patients who are eligible to surgery must have good performance status and solitary or a small number of lesions [5], which are two favorable prognostic factors [17]. Surgery followed by focal radiation is the most efficient approach for brain control [7] but was used only 5 times, probably because the data that support this combined approach have only been recently published, and because not all lesions are accessible to surgical resection. WBRT was associated with the lowest PFS, probably because it was used for patients with advanced brain diseases. It may suggest that these patients with a poor prognosis could better benefit from exclusive supportive care without specific brain therapy, especially because of the cognitive impairment WBRT can cause [8]. SRT alone was the most used focal therapy in our study: indeed, it is an attractive option because of its efficiency on brain control even for multiple small lesions (4) [18, 18], its feasibility and acceptability, with less cognitive impairment [8]. The most frequent adverse event of SRT was radionecrosis (7.9% of patients), which is concordant with
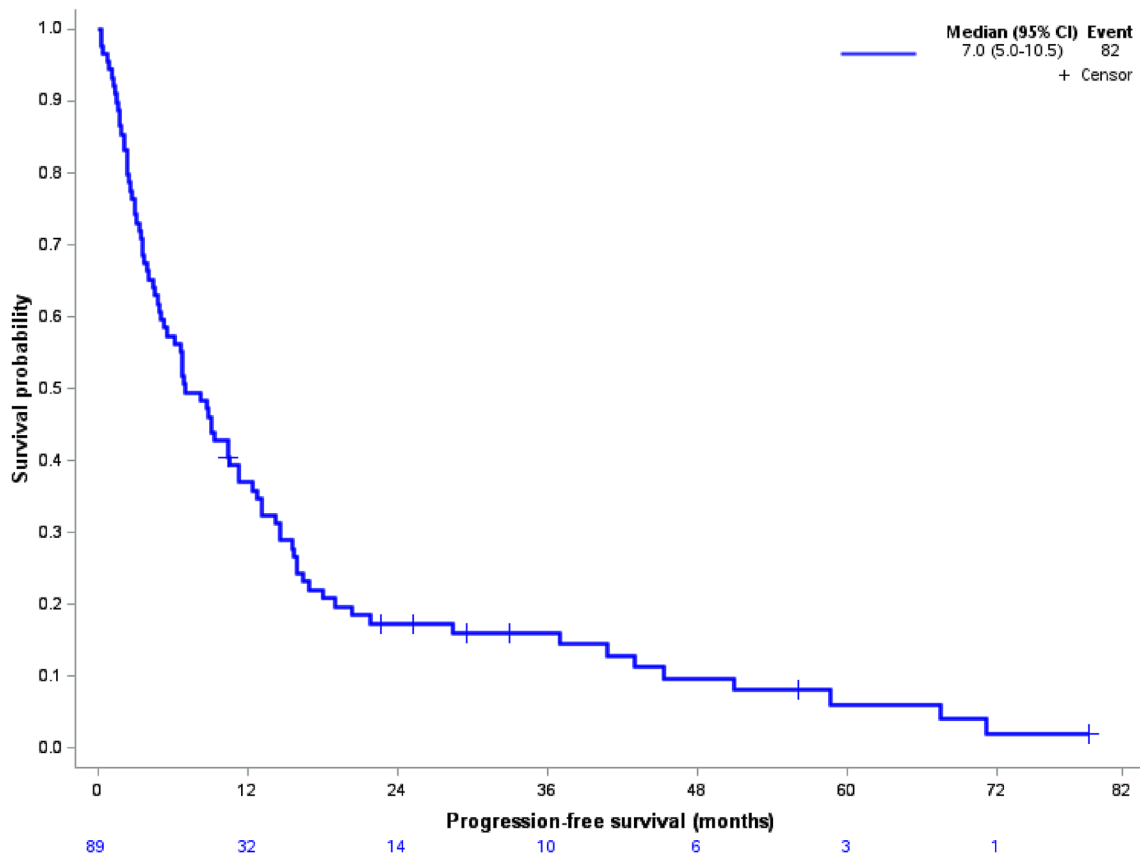
Fig. 3 Survival before brain progression for all patients

Table 2 Complications of brain focal therapies

| | Focal treatment of brain metastasis | | | | | | | | | All | |
| | Surgery | | WBRT | | Sur-gery + SRT | | SRT | | | | |
	N = 21		N = 25		N = 5		N = 101			N = 152	
None	16	(76.2%)	16	(64.0%)	5	(100.0%)	80	(79.2%)		117	(77.0%)
Intracranial hypertension or symptomatic oedema	0	(0.0%)	7	(28.0%)	0	(0.0%)	10	(9.9%)		17	(11.2%)
Radionecrosis	0	(0.0%)	0	(0.0%)	0	(0.0%)	8	(7.9%)		8	(5.3%)
Bleeding	2	(9.5%)	0	(0.0%)	0	(0.0%)	2	(2.0%)		4	(2.6%)
Seizure	3	(14.3%)	1	(4.0%)	0	(0.0%)	1	(1.0%)		5	(3.3%)
Cognitive impairment	0	(0.0%)	1	(4.0%)	0	(0.0%)	0	(0.0%)		1	(0.7%)

WBRT whole brain radiotherapy, *SRT* stereotactic radiotherapy

the literature [4]. Furthermore, Wolf et al. showed that in patients treated with stereotactic radiosurgery, local control and overall survival are better for subcentimetimetric lesions [19], independently of the histology of the primitive tumor and the number of BM. This is another argument in favor of systematic brain screening in order to propose patients early and optimal focal therapy.

Most of our patients received sunitinib, which was the most used TKI in first line in France at the time of our study. The role of TKI on BM remains unclear. Sunitinib and sorafenib seem to reduce the occurrence of BM [20, 21], and several case reports and small cohorts showed brain responses to sunitinib [22, 23] and more recently cabozantinib [24, 25]. However no prospective trial succeeded in demonstrating a benefit of TKI on BM so far [26]. Therefore,

focal therapy with surgery and/or radiotherapy remains essential to achieve brain control. Cabozantinib is a reversible inhibitor targeting multiple tyrosine kinases such as VEGFR, AXL, RET and MET. BM tumor cells from renal primary overexpress MET in 35% of cases [27]. A retrospective trial of 12 patients with BM treated with cabozantinib reported intracerebral tumor control in 9 patients (75%), including 4 patients who didn't received focal therapy to the brain [25]. A phase II trial (ET19-006-CABRAMET, NCT03967522) is currently ongoing to assess the efficacy of cabozantinib in patients with RCC and brain metastases who have not previously received focal brain therapy.

We also note that only 12 patients received nivolumab in our study. Indeed, efficacy of ICI monotherapy on brain metastases has not been demonstrated in renal carcinoma. Flippot et al. in the BM subgroup of the prospective phase 2 NIVOREN trial, did not show any response with nivolumab on untreated BM, excepted for infracentimetric lesions [28]. However, the combination of ipilimumab plus nivolumab has already shown efficacy on untreated BM in melanoma [29], and encouraging signals in renal cancer with BM [30].

Our study presents several limitations: it is a retrospective analysis. We analyzed patients over a period of 14 years; the improvement of anti-cancer therapies during this period, especially for SRT, could have induced some heterogeneity in the population. In order to limit this bias, we chose not to include patients treated before the TKI era. It however gives interesting results to support early brain screening for patients with metastatic RCC.

Conclusion

Patients with ccRCC diagnosed with synchronous BM have a poorer prognosis than patients who develop BM later on. Nevertheless, the diagnosis of BM is of poor prognosis with a survival of 16–19 months regardless of synchronous or metachronous situation. Whenever possible, focal treatment (surgery or stereotactic radiotherapy) of BM should be used. The use of WBRT should be carefully discussed due to its frequent side effects. Using a combination of systemic and focal treatments results in a median OS from diagnosis of metastatic disease of 1.6 years when BM are synchronous, compared to more than 4 years when BM are metachronous. Because synchronous BM is of poor prognosis, brain imaging should be performed at the time of diagnosis of metastasis in order to deliver optimal focal therapy to provide a better brain control and preserve patients quality of life. Specific clinical trials should also be encouraged.

Declarations

References

1. Cagney DN et al (2017) Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. Neuro-Oncol 19(11):1511–1521. https://doi.org/10.1093/neuonc/nox077
2. Soffietti R et al (2013) 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 31(1):65–72. https://doi.org/10.1200/JCO.2011.41.0639
3. Muldoon LL et al (2007) Chemotherapy delivery issues in central nervous system malignancy: a reality check. J Clin Oncol 25(16):2295–2305. https://doi.org/10.1200/JCO.2006.09.9861
4. Lesueur P et al (2018) Radiosurgery or hypofractionated stereotactic radiotherapy for brain metastases from radioresistant primaries (melanoma and renal cancer). Radiat Oncol 13(1):138. https://doi.org/10.1186/s13014-018-1083-1
5. Soffietti R et al (2017) Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). Neuro-Oncol 19(2):162–174. https://doi.org/10.1093/neuonc/now241
6. Kumar AMS et al (2018) Postoperative hypofractionated stereotactic brain radiation (HSRT) for resected brain metastases: improved local control with higher BED10. J Neurooncol 139(2):449–454. https://doi.org/10.1007/s11060-018-2885-6
7. Mahajan A et al (2017) Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol 18(8):1040–1048. https://doi.org/10.1016/S1470-2045(17)30414-X
8. Brown PD et al (2016) Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA 316(4):401. https://doi.org/10.1001/jama.2016.9839
9. Niranjan A, Monaco E, Flickinger J, Lunsford LD (2019) Guidelines for multiple brain metastases radiosurgery. In: A. Niranjan,

L. D. Lunsford, and H. Kano, Eds. S. Karger AG, Progress in Neurological Surgery, vol. 34, pp. 100–109

10. Bianchi M et al (2012) Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. Ann Oncol 23(4):973–980. https://doi.org/10.1093/annonc/mdr362

11. Chandrasekar T, Klaassen Z, Goldberg H, Kulkarni GS, Hamilton RJ, Fleshner NE (2017) Metastatic renal cell carcinoma: Patterns and predictors of metastases—A contemporary population-based series. Urol Oncol Semin Orig Investig 35(11):661.e7-661.e14. https://doi.org/10.1016/j.urolonc.2017.06.060

12. Decker DA, Decker VL, Herskovic A, Cummings GD (1984) Brain metastases in patients with renal cell carcinoma: prognosis and treatment. J Clin Oncol 2(3):169–173. https://doi.org/10.1200/JCO.1984.2.3.169

13. Bennani O et al (2014) Brain metastasis from renal cell carcinoma. Neurochirurgie 60(1–2):12–16. https://doi.org/10.1016/j.neuchi.2013.12.001

14. Dudek AZ et al (2013) Brain metastases from renal cell carcinoma in the era of tyrosine kinase inhibitors. Clin Genitourin Cancer 11(2):155–160. https://doi.org/10.1016/j.clgc.2012.11.001

15. Choi SY et al (2017) Prognostic factors for survival of patients with synchronous or metachronous brain metastasis of renal cell carcinoma. Clin Genitourin Cancer 15(6):717–723. https://doi.org/10.1016/j.clgc.2017.05.010

16. Khan M, Zhao Z, Arooj S, Liao G (2020) Impact of Tyrosine Kinase Inhibitors (TKIs) combined with radiation therapy for the management of brain metastases from renal cell carcinoma. Front Oncol 10:1246. https://doi.org/10.3389/fonc.2020.01246

17. Sperduto PW et al (2020) Survival in patients with brain metastases: summary report on the updated diagnosis-specific graded prognostic assessment and definition of the eligibility quotient. J Clin Oncol. https://doi.org/10.1200/JCO.20.01255

18. Yamamoto M et al (2014) Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 15(4):387–395. https://doi.org/10.1016/S1470-2045(14)70061-0

19. Wolf A et al (2018) Toward the complete control of brain metastases using surveillance screening and stereotactic radiosurgery. J Neurosurg 128(1):23–31. https://doi.org/10.3171/2016.10.JNS161036

20. Massard C, Zonierek J, Gross-Goupil M, Fizazi K, Szczylik C, Escudier B (2010) Incidence of brain metastases in renal cell carcinoma treated with sorafenib. Ann Oncol 21(5):1027–1031. https://doi.org/10.1093/annonc/mdp411

21. Verma J, Jonasch E, Allen P, Tannir N, Mahajan A (2011) Impact of tyrosine kinase inhibitors on the incidence of brain metastasis in metastatic renal cell carcinoma: TKIs and Brain Metastasis in mRCC. Cancer 117(21):4958–4965. https://doi.org/10.1002/cncr.26138

22. Gore ME et al (2011) Sunitinib in metastatic renal cell carcinoma patients with brain metastases. Cancer 117(3):501–509. https://doi.org/10.1002/cncr.25452

23. Lim ZD, Mahajan A, Weinberg J, Tannir NM (2013) Outcome of patients with renal cell carcinoma metastatic to the brain treated with sunitinib without local therapy. Am J Clin Oncol 36(3):258–260. https://doi.org/10.1097/COC.0b013e3182467b9a

24. Négrier S et al (2018) Activity of cabozantinib in radioresistant brain metastases from renal cell carcinoma: two case reports. J Med Case Reports 12(1):351. https://doi.org/10.1186/s13256-018-1875-9

25. Peverelli G et al (2019) Cabozantinib in renal cell carcinoma with brain metastases: safety and efficacy in a real-world population. Clin Genitourin Cancer 17(4):291–298. https://doi.org/10.1016/j.clgc.2019.05.002

26. Chevreau C et al (2014) A phase II trial of sunitinib in patients with renal cell cancer and untreated brain metastases. Clin Genitourin Cancer 12(1):50–54. https://doi.org/10.1016/j.clgc.2013.09.008

27. Derosa L et al (2017) Inter and intra-tumor heterogeneity of PD-L1 and MET expression in metastatic renal cell carcinoma (mRCC). J Clin Oncol 35(Suppl_15):4569–4569. https://doi.org/10.1200/JCO.2017.35.15_suppl.4569

28. Flippot R et al (2019) Safety and efficacy of nivolumab in brain metastases from renal cell carcinoma: results of the GETUG-AFU 26 NIVOREN multicenter phase II study. J Clin Oncol 37(23):2008–2016. https://doi.org/10.1200/JCO.18.02218

29. Tawbi HA et al (2018) Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 379(8):722–730. https://doi.org/10.1056/NEJMoa1805453

30. Emamekhoo H et al (2019) Safety and efficacy of nivolumab plus ipilimumab (NIVO+IPI) in patients with advanced renal cell carcinoma (aRCC) with brain metastases: Interim analysis of CheckMate 920. J Clin Oncol 37(15_suppl):4517–4517. https://doi.org/10.1200/JCO.2019.37.15_suppl.4517