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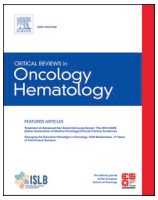

Global management of brain metastasis from renal cell carcinoma

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ABSTRACT

During the last decade, major improvements have been made in the treatment of renal cell carcinoma (RCC) with the development and use of multiple tyrosine kinase inhibitors and immune checkpoint inhibitors. Brain metastases in RCC patients (BM-RCC) is associated with poor outcome and their management represents a challenge for clinicians. In most of case, brain metastases in this context require local intervention such as radiotherapy, stereotactic radiotherapy/stereotactic radiosurgery and whole brain radiation therapy. Despite efficacy in extracranial metastases, systemic therapies have modest antitumoral effect on cerebral lesions. In this review, we highlight the benefits and pitfalls of the available therapies in BM-RCC.

1. Introduction

Renal cell carcinoma (RCC) is the 7th most common malignancy with 338,000 new cases and 144,000 related deaths worldwide annually (Ferlay et al., 2015). The most common histology is clear cell renal cell carcinoma (ccRCC) accounting for 80% of all kidney cancers (Escudier et al., 2019). RCC represents one of the most frequent malignancies associated with increased risk of brain metastases (BM); although BM prevalence is only 1.5% at the RCC diagnosis, it increases to 10-15% with the disease course evolution (Sun et al., 2019; Barnholtz-Sloan et al., 2004; Bianchi et al., 2012; Schouten et al., 2002; Achrol et al., 2019; Berghoff et al., 2016a). White race, sarcomatoid differentiation, T2–4 disease and infiltrated lymph nodes are associated with BM development (Sun et al., 2019; Berghoff et al., 2016a; Howlader et al., 2020). In addition to systemic therapy, management of BM usually requires local therapy including neurosurgery, whole brain radiation therapy (WBRT) and/or hypofractionated stereotactic radiotherapy/stereotactic radiosurgery (HFSRT/SRS) (Escudier et al., 2019; Soffietti et al., 2017a).

Patients with BM from RCC (BM-RCC) experience poor outcome, with a median overall survival (OS) that does not exceed 10 months and an impaired quality of life (Sperduto et al., 2012). Several scores exist to predict survival (Table 1) and involve some clinical features (Karnofsky performance score (KPS), age, extra-cranial metastatic spread, interval time between initial RCC diagnosis and BM occurrence) and some BM characteristics (number of BM, cumulative intracranial tumor volume superior or inferior to 4 cm^3) associated with survival outcome (Sperduto et al., 2012; Ali et al., 2017; Hansen et al., 2019; Dziggel et al., 2014). However, these analysis were performed before the common use of immune checkpoint inhibitors (ICIs), that drastically improve the prognosis of patients compared to tyrosine kinase inhibitors (TKI) monotherapy (Choueiri and Motzer, 2017). Our objective is to review the management of BM-RCC in the era of ICI-based strategies.

2. Particularities of brain metastasis from RCC

Metastatic process involves multiple proliferative and survival pathways that enhance migration of tumor cells into systemic circulation. Reaching and surviving in brain environment require specific mechanisms that include production of mitogenesis-associated enzymes and matrix metalloproteinases; these enzymes enhance the endothelial permeability and the extra- or intravasation of tumor cells, as well as multiple interaction with stromal cells (Achrol et al., 2019). These adaptative ways render BM-RCC management challenging (Fig. 1).

2.1. Blood Brain Barrier (BBB) impermeability

In BBB, endothelial cells are joined by tight junctions, without fenestration and are strongly covered by pericytes and astrocytes; moreover, multiple efflux transporters such as P-glycoprotein (P-gp), multidrug resistance–associated proteins (MRP) family and breast cancer–resistant protein (BCRP) are present in the luminal membrane of endothelial cells of the BBB. These structures significantly limit the penetration of therapeutic drugs into central nervous sytem (Achrol

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et al., 2019; Deeken and Löscher, 2007; Arvanitis et al., 2020). However, BBB could be altered in the metastatic process, due to modifications in tight junction structure, enlargement of perivascular space, fenestrations in endothelium, increased pinocytic transport activity and decreased efflux transporter concentration (Deeken and Löscher, 2007; Bart et al., 2000; Zhang et al., 1992). Furthermore, cranial radiation therapy (RT) was also shown to impair BBB through enlargement of the blood vessel lumen, thickening of the vessel wall, hypertrophy of adjacent astrocytes and decreased P-gp expression (Deeken and Löscher, 2007; Arvanitis et al., 2020; Bart et al., 2000).

2.2. Brain tissue as a specific immune environment

Astrocytes play an important role in the tumor microenvironment; the gap junctions between tumor cells and astrocytes enhance the transfer of metabolites between these cells. Moreover, brain infiltration by tumor cells enhances the activation of immune cells and the secretion of Tumor Necrosis Factor (TNF) or Interferon-α by the astrocytes, increasing chemoresistance and proliferation of tumor cells (Achrol et al., 2019).

Immune evasion plays a key role in BM process. Tumor cells release tumor-associated antigens, named neoantigens that are captured by antigen-presenting cells (APC) through the major histocompatibility complex class I. APC migrate to lymphoid organs, where they activate effector T-cells, which in turn infiltrate tumors and kill cancer cells. Different mechanisms have been developed by tumor cells to evade immune recognition; one such strategy involves the expression of cell-surface molecules, named immune checkpoints on tumor cells and tumor-specific lymphocytes, that are able to inhibit activated T-cells. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death-1 (PD-1) and its ligand PD-L1 are the most well-known immune checkpoint. Activation of T-cells requires interaction between CD28 on T-cell and B7 on APC. CTLA-4 expressed on T-cell exerts its inhibitory effect by competing with CD28 and by binding to B7, resulting in T-cell inactivation in lymphoid tissues. In the same way, PD-1 is an inhibitory receptor expressed on T-cells. When binding to PD-1, PD-L1 expressed on tumor cells transmits an inhibitory signal into T-cells (Flippot et al., 2018; Finn, 2008; Sheu and Shih, 2010). Immune evasion could thus participate in the BM process; tumor environment is marked by low density of T-cells and high density of immunosuppressive cells in glioblastoma and by high count of TILs expressing PD-L1 in brain metastases from RCC (Arvanitis et al., 2020; Galea et al., 2007; Farber et al., 2016; Berghoff et al., 2016b; Berghoff et al., 2015). ICIs are monoclonal antibodies that target immune checkpoints and, by disrupting inhibitory signals, reactivate immune system (Flippot et al., 2018). While the penetration of large molecules such as monoclonal antibodies through the BBB is generally poor, ICIs could have an indirect intracranial action by enhancing systemic immune reaction and T-cell activation. These activated T-cells cross the BBB and infiltrate BM (van Bussel et al., 2019). Corticosteroids are frequently used in BM in order to rapidly alleviate BM-related symptoms or to decrease RT-induced oedema; this could represent a problem when using ICIs, as this immune response may be counteracted by corticosteroids due to their immunosuppressive action and their capacity to restore the impermeability of the BBB (Arvanitis et al., 2020; Farber et al., 2016).

2.3. Discordance between brain metastases and primary tumor

Heterogeneity represents an important issue when considering treatment of cancer; during tumoral progression, multiple clones emerge progressively, harbouring molecular discordances that explain tumoral heterogeneity (Venkatesan and Swanton, 2016). The genomic analysis of paired biopsies in 60 metastatic RCC (mRCC) patients showed a 78% rate of mutation discordance between primary tumor and metastases (Becerra et al., 2018; Psutka et al., 2016). Compared to primary tumors, BM present more frequently expression of endothelial growth factor receptor (EGFR) and c-MET as well as mutation in phosphatase and tensin homologue (*PTEN*), phosphoinositol 3-kinase (*PIK3CA*), and cyclin dependent kinase inhibitor 2A (*CDKN2A*) (Schiefer et al., 2015; Brastianos et al., 2015; Derosa et al., 2017). This could be crucial for identifying tailored treatment in BM-RCC based on these molecular targets.

2.4. Renal cancer as a radioresistant tumor: considering brain protection

RCC is historically considered as a radioresistant tumor with a low α/β ratio estimated between 2.6 and 6.9 Gy (while classical radiosensitive tumor exhibit α/β ratio superior to 10 Gy) (Deschavanne and Fertil, 1996; Ning et al., 1997). Conventional RT has currently no place in the management of localized RCC, as radical RT treatment with

Table 1
Comparison between different prognostic scores for brain metastases renal cell carcinoma patients. BM: Brain metastases, KPS: Karnofsky performance status, WBRT: Whole brain radiation therapy.

Score	KPS	Age	Extracranial metastases	Number of BM	Cumulative intracranial volume	Time between diagnosis and WBRT	Probability of 6-month survival according to groups		
							Most favourable	Intermediate	Least favourable
DS-GPA RCC (Sperduto et al., 2012)	90-100: 2 points 70-80: 1 point < 70: 0 point			1: 2 points 2-3: 1 point >3: 0 point			3,5-4 points: 50,0%	2,5-3 points: 33,3%	1,5-2 points: 22,7%
DS-GPA-CITV (Ali et al., 2017)	90-100: 2 points 70-80: 1 point < 70: 0 point			1: 2 points 2-3: 1 point >3: 0 point	<4 cm^3 : 2 points ≥4 cm^3 : 0 point				
Dziggel score (Dziggel et al., 2014)	≥70: 4 points < 70: 1 point	≥65: 2 points < 65: 4 points	None: 6 points Present: 2 points				12-14 points: 75%	9-11 points: 31%	5-8 points: 12%
WBRT-30-RCC (Hansen et al., 2019)	>60: 4 points ≤ 60: 2 points		None: 6 points Present: 2 points	1-3: 4 points ≥4: 2 points		≤ 33 months: 2 points ≥ 34 months: 4 points	16-18 points: 66,7%	12-14 points: 38,5%	8-10 points: 6,7%

conventional dose per fraction (1.8-2.0 Gy) would result in high total dose and excessive toxicity in surrounding normal tissues (Escudier et al., 2019; Siva et al., 2017; De Meerleer et al., 2014). This is particularly challenging when considering brain irradiation and prevention of RT-induced cerebral damage. The cytotoxic effect of HFSRT/SRS (higher or equal doses per fraction than 6.0 Gy) is more predominantly related to activation of ceramide-mediated apoptosis and direct acute damage to vascular endothelial cells compared to conventionally fractioned RT. This highlights the more efficient role of HFSRT/SRS in sterilizing radioresistant tumor lesion such as RCC (Siva et al., 2017; De Meerleer et al., 2014).

2.5. Targeting angiogenesis as a challenge in brain metastases

Loss of *Von Hippel Lindau* (*VHL*) gene is found in more than 90% of RCC and leads to increase in amount of the transcription factor Hypoxia-inducible factor (HIF). In normoxic condition, HIF-1α is sequestered by the Van Hippel Lindau protein (pVHL) that promotes its proteasomal degradation. In hypoxia, pVHL is inactivated, allowing HIF-1α to migrate into the nucleus to stimulate the transcription of multiple genes implicated in angiogenesis (Vachhani and George, 2016; Baldewijns et al., 2010). This results in subsequent production of multiple pro-angiogenic factors such as vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1), platelet derived growth factors (PDGF), angiopoietin or matrix metalloproteinase 2 (MMP-2). All these growth factors bind to their specific tyrosine kinase receptors (TKR) located on surface of tumor and endothelial cells (Vachhani and George, 2016; Muacevic et al., 2005; Yagasaki et al., 2003; Nanus et al., 1993; Nakagawa et al., 1997). Binding to these TKR activates the tyrosine kinase activity and the phosphorylation of multiple signalling cascade such as the PI3K-AKT-mTOR pathway and the RAS-RAF-MEK pathway (Vachhani and George, 2016; Guo et al., 2015). This angiogenic switch results in highly vascularized tumors composed of dysfunctional and abnormal vessels. The effect of HIF-1α on radiosensitivity is not clear; in one hand, HIF-1α increases the radiosensitivity of tumor cells by enhancing apoptosis, metabolism and proliferation but in other hand, induction of proangiogenic factors such as VEGF protect tumor vasculature from HFSRT/SRS-induced acute vascular damage (Moeller and Dewhirst, 2006). Treatment with TKIs allow a strong angiogenic inhibition that could induce bleeding or thrombotic complications due to endothelial homeostasis deregulation. The highly angiogenic profile of renal tumors and the frequent use of TKIs could result in spontaneous or treatment-related haemorrhages. This is particularly life-threatening when intra-cranial bleeding occurs spontaneously or within BM (Muacevic et al., 2005; Yagasaki et al., 2003; Wowra et al., 2002). TKIs can also, by impairing angiogenic architecture, reduce oxygen supply and enhance intra-tumoral hypoxia. This chronic hypoxia stimulates adaptative mechanisms and increases invasiveness of tumor cells and radioresistance; furthermore, at high doses, antiangiogenic TKIs reduce BBB permeability by reducing VEGF concentration and may reduce the delivery of drugs (Arvanitis et al., 2020; Gray et al., 1953).

2.6. Brain metastases as an exclusion criterion in clinical trials

BM represent an exclusion criter in most of randomized prospective trials due to the poor local control (LC) induced by systemic treatment and the poor outcome of these patients (Motzer et al., 2009; Motzer et al., 2007; Sternberg et al., 2010; Escudier et al., 2007a; Escudier et al., 2007b; Choueiri et al., 2016; Choueiri et al., 2017; Motzer et al., 2013; Motzer et al., 2015; Motzer et al., 2018; Rini et al., 2019). Majority of the data come from case reports and retrospective analysis, reflecting the difficulty to draw any conclusion concerning the management of these patients.

3. Local therapies

3.1. Surgical resection with or without postoperative radiotherapy

In RCC patients with low number of metastatic brain lesions, surgery should be considered if feasible. Compared to RT, surgery induces a rapid cerebral decompression, shortens steroid duration and provide tissue for diagnosis or complementary analysis (Achrol et al., 2019; Soffietti et al., 2017b). Innovative technics such as neuronavigation, cortical mapping or magnetic resonance imaging-guided surgery allow safe and minimally invasive neurosurgery (Soffietti et al., 2017b).

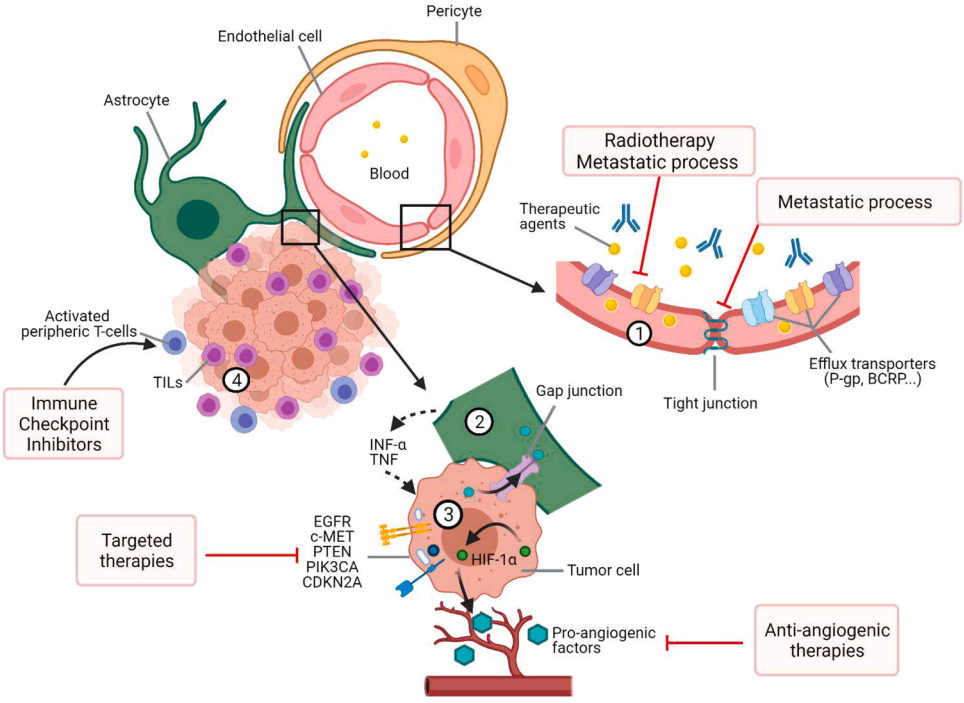

Fig. 1. Overview of the challenges of BM from renal cell carcinoma. 1) The BBB consists in endothelial cells (EC) expressing efflux transport and joined by tight junctions. These ECs are surrounded by pericytes and astrocytes. These mechanisms limit permeability of therapeutics drugs. However, the metastatic process and radiotherapy decrease the number of efflux transporter, which increase the permeability of peripheral molecules. Moreover, tight junction can be impaired by the metastatic development, leading also to an increased permeability of the BBB. 2) Gap junctions allow transfer of several metabolites between tumor cells and astrocytes and induce secretion of INF-α and TNF by astrocytes, leading to chemoresistance. 3) Molecular profile of renal cancer cells should be considered when developing therapeutic agents, including highly angiogenic profile, molecular discordance between primary and brain metastases, and intrinsic radioresistance. 4) Cerebral tissue was historically considered as an immune-desert environment, but recent analysis highlighted high presence of T-cells and other immune effectors. BBB: Blood brain barrier, BM: Brain metastases, INF-α: Interferon-α, TNF: Tumor necrosis factor.

Limitations of surgery include high number of BM, inaccessibility, unresectability and inoperability due to patient comorbidities.

Achieving 'en bloc' resection remains an important goal as piecemeal resection is more often associated with leptomeningeal spreading (Suki et al., 2009). Interestingly, compared to other cancers, 'en bloc' resection is more frequently achieved in BM-RCC, suggesting a well-circumscribed aspect of BM-RCC. This could explain why the rate of leptomeningeal carcinomatosis in BM-RCC was lower than in other aetiology (lung, melanoma, and breast) after surgical resection (Suki et al., 2009).

The role of adjuvant RT after surgical resection of BM from any cancer type remains unclear. In a prospective randomized trial enrolling patients with single BM from any origin, 49 patients received postoperative WBRT and 46 patients received no further treatment. Postoperative RT resulted in fewer brain recurrences and less frequent deaths from neurologic causes compared to surgical resection alone; there was, however, no significant difference in OS (Patchell et al., 1998). Furthermore, in a phase III study, 194 patients with BM from various origins were randomized between postoperative HFSRT/SRS (n = 98) or postoperative WBRT (n = 96). Patients treated with postoperative HFSRT/SRS had better cognitive outcome compared to postoperative WBRT and similar OS. However, LC and intracranial control seem to be improved by WBRT compared to HFSRT/SRS (Brown et al., 2017).

In BM-RCC patients, the role of peri-operative RT remains also unclear. In a retrospective analysis, 50 BM-RCC patients were treated with surgical resection, including 7 who had preoperative WBRT, 22 who received postoperative WBRT and 21 who did not receive any WBRT. Multivariate analysis identified different good prognosis factors such as the concomitant pulmonary metastases resection, the supratentorial location of BM, the left-sided primary tumor, and the absence of previous neurologic deficit. Intra-tumoral haemorrhage was found in 23 resected patients including 4 patients who required further surgical management (Wroński et al., 1996). Addition of WBRT (7 in preoperative and 22 in postoperative setting) did not improve OS (13.3 versus 14.5 months respectively, $p = 0.61$) or intracranial control (52% versus 62% respectively) compared to resection alone ($n = 21$) (Wroński et al., 1996).

Preoperative HFSRT/SRS may provide a better LC compared to postoperative HFSRT/SRS, potentially decreasing the risk of radionecrosis and leptomeningeal recurrence (Prabhu et al., 2019; Patel et al., 2016). In a retrospective analysis, compared to other primary tumors (n = 104), BM-RCC patients (n = 13) underwent less local recurrence (hazar ratio (HR) 0.1 compared to non-small cell lung carcinoma histology, $n = 50$, $p < 0.001$). Furthermore, RCC histology appeared as a favourable criteria in term of local recurrence, symptomatic radionecrosis and leptomeningeal recurrence rates (Prabhu et al., 2018).

3.2. WBRT as single modality

WBRT is the most commonly used treatment for BM, providing rapid attenuation of neurological symptoms and improving quality of life; WBRT is poorly invasive and is effective when surgery is medically contraindicated or unfeasible (Khuntia et al., 2006). A major adverse event (AE) is neurocognitive dysfunction that can persist over time. This is challenging as OS improves in RCC patients, with increasing risk of developing BM, receiving WBRT and experiencing this AE. However, the role of WBRT on cognitive functions is not clearly defined because of potential cofounding factors such as baseline neurocognitive impairment or difficulty to assess the cognition (Khuntia et al., 2006; Li et al., 2007). The most common regimens are 30 Gy (10 fractions of 3 Gy) and 20 Gy (5 fractions of 4 Gy); both regiments are comparable regarding OS and neurological function outcome (Tsao et al., 2018).

In the diagnosis-specific graded prognostic assessment (DS-GPA) cohort of 78 BM-RCC patients who received WBRT as unique treatment, the median OS was 5.08 months, which was inferior to other local treatment modalities (10.78 months for SRS alone, 12.12 months for SRS + WBRT, 12.91 for surgery plus SRS, 15.52 months for surgery plus WBRT and 8.80 months for surgery plus SRS plus WBRT). This could be explained by the fact that patients assigned to WBRT alone had poor clinical characteristics (patients unable to underwent surgery, high number of BM and no possibility to treat with HFSRT/SRS) (Sperduto et al., 2012). Other retrospective studies reported median OS ranging from 3.0 to 4.4 months when using WBRT alone (Wroński et al., 1996; Nieder et al., 2011).

Due to the historical notion of RCC radioresistance, escalated doses in WBRT have been evaluated in BM-RCC patients. In a retrospective study of 60 patients, two escalated dose schedules (40 Gy in 20 fractions of 2 Gy for 4 weeks or 45 Gy in 15 fractions for 3 weeks, $n = 29$) were compared to conventional dose (30 Gy in 10 fractions of 3 Gy, $n = 31$); the primary endpoints were OS and LC. Compared to conventional group, the 6-month OS was significantly increased for group with escalated dose (29% versus 52%, respectively; $p = 0.003$) as well as the 12-month OS (13% versus 47%, respectively). The 6-month LC rate was also improved, reaching 21% and 57% for conventional group and for escalated dose group, respectively ($p = 0.013$). No difference for grade $\geq$ 2 AEs and cognitive dysfunction was reported (Rades et al., 2010). However, there is no prospective trial evaluating escalated dose WBRT in BM-RCC management. Furthermore, due to absence of benefit of dose-escalated WBRT in other tumor types in prospective trials, conventional schedule remains recommended in BM-RCC patients (Tsao et al., 2018).

3.3. HFSRT/SRS

HFSRT/SRS is more appropriate for multiple or inaccessible oligometastic lesions compared to surgery and allows higher rate of LC with less cognitive deterioration compared to WBRT. However, compared to WBRT, due to its very limited irradiation area, HFSRT/SRS provides a shorter distant brain progression-free survival (PFS) (O'Neill et al., 2003; Alexander et al., 1995). When using high dose per fraction (defined as $>$ 6 Gy per fraction for HFSRT/SRS), the linear quadratic model describing the survival of irradiated cells is not applicable and the HFSRT/SRS efficacy is not dependant of the intrinsic radiosensitivity of the tumor (Alexander et al., 1995; Wolf et al., 2018; Malaise et al., 1987). However, the size of the lesions seems to be an important predictive factor of LC, OS and HFSRT/SRS-related toxicity (Wolf et al., 2018; Shaw et al., 2000). The maximal tolerated doses in unique fraction were shown to be 24 Gy for $<$21 mm BM, 18 Gy for 21-30 mm BM and 15 Gy for 31-40 mm BM (Shaw et al., 2000). Practically, single fraction of 24 Gy is allowed for small and well-located lesion while hypofractionation (3-5 fractions) is widely used for larger lesions or BM resection cavities, and dose reduction is required for BM in critical areas closed to brainstem or optical pathways (Shaw et al., 2000; Soltys et al., 2010; Kased et al., 2008; Lesueur et al., 2018).

Several case series have been reported for BM-RCC patients treated with HFSRT/SRS only (Table 2). Compared to radiosensitive tumors, HFSRT/SRS achieved similar LC ranging between 50% and 100% (Achrol et al., 2019; Rades et al., 2015; Staehler et al., 2011). Moreover, when using HFSRT/SRS, LC of BM-RCC patients seems similar to LC observed in radioresistant BM from other origin such as melanoma (Lesueur et al., 2018; Jensen et al., 2008; Manon et al., 2005).

In case of brain progression in mRCC patients treated with systemic treatment, brain HFSRT/SRS could maintain the current systemic therapy and delay the switch to further treatment line. Barata et al. analysed outcome of mRCC patients treated by HFSRT/SRS for BM; patients were stratified in two groups, the group STAY ($n = 43$) in which the systemic treatment was continued and the group SWITCH ($n = 23$), in which the systemic treatment was changed. In both groups, the duration of systemic treatment following HFSRT/SRS was comparable (5.2 versus 5.0 months, respectively; $p = 0.549$) as well as the OS (24.2 versus 27.1 months, respectively; $p = 0.381$) (Barata et al., 2018).

Table 2
Summary of studies providing individual data for treatment of brain metastases in renal cell carcinoma patients by stereotactic radiosurgery (series for which another local therapy was performed are not included). BM: Brain metastases, Ds-GPA: Diagnosis-specific graded prognostic assessment, IMDC: International metastatic renal cell carcinoma database consortium KPS: Karnofsky performance status, LC: Local control, N: Number of, NA: Not assessed, OS: Overall survival, RPA: Recursive partitioning analysis, HFSRT/SRS: hypofractionated stereotactic radiotherapy/Stereotactic radiosurgery, WBRT: Whole-brain radiotherapy.

	N patients	N brain metastases	Total dose (Gy)	N fractions	LC (median follow-up)	Median OS (months)	Factor associated with poorer OS
(Ikushima et al., 2000)	10	24	42 (prescribed at the isocentre)	7	88% (5,2 months)	25,6	
(Noel et al., 2004)	21	NA	Mean of 17,3 (prescribed to the 70% isodose)	1	NA	15	
(Samlowski et al., 2008)	20	NA	15-24 (prescribed to the 95% isodose)	1	NA	6,2	No immunotherapy nor high dose interleukin-2 after HFSRT/SRS
(Fokas et al., 2010)	51	NA	15-22	1	55% (at 3 years)	12	Extra cranial disease, high RPA class
(Marko et al., 2010)	19	59	Mean of 21,3 (prescribed to the 60% isodose)	1	95% (NA)	12,58	
(Sperduto et al., 2012)	131	NA	NA		NA	10,78	KPS < 70, N of BM >3
(Staehler et al., 2011)	51	135	20 (prescribed to the 50% isodose)	1	100% (at 12 months)	11,1	KPS ≤70
(Lo et al., 2011)	14	22	15-22 (prescribed to the 50% isodose)	1	95,5% (6,1 months)	NA	
(Ippen et al., 2015)	36	138	12-30 (prescribed to the 76% isodose)	1-5	92,8% (10 months)	13,6	High RPA class, KPS < 70, score index for radiosurgery <6, low Ds-GPA, low basic score for BM, initial number of BM > 3, prior WBRT
(Rades et al., 2015)	9	NA	16-18 (prescribed to the 80-95% isodose)	1	50% (at 12 months)	16% at 12 months	
	19		20 (prescribed to the 80-95% isodose)		81% (at 12 months)	46% at 12 months	
(Barata et al., 2018)	57	NA	10-24	1-3	88% (28,8 months)	NA	
(Haque et al., 2018)	813	NA	NA	NA	NA	9	Advanced age, high comorbidity index, T3-4, node-positive disease, non- race, treatment at non-academic centers and absence of chemotherapy and/or nephrectomy
(Wardak et al., 2019)	38	243	12-24 (prescribed to the 50% isodose)	1	86,1% (12 months)	13,8	Unfavourable IMDC risk group only if < 5 lesions

It is important to note that HFSRT/SRS does not increase risk of cerebral bleeding; symptomatic intracranial haemorrhage occurring post-HFSRT/SRS was observed in 1.9%-12.0%; this incidence is similar to those observed during the normal course of the disease (Wowra et al., 2002; Muacevic et al., 2004; Shuto et al., 2010).

3.4. *WBRT + HFSRT/SRS*

Compared to WBRT alone, addition of HFSRT/SRS to WBRT (WBRT + HFSRT/SRS) may improve LC and OS (Andrews et al., 2004; Sanghavi et al., 2001; Kondziolka et al., 1999; Aoyama et al., 2006). Outcome of 88 BM-RCC patients was retrospectively assessed regarding the local cerebral treatment; 51 patients underwent HFSRT/SRS alone, 20 patients underwent WBRT alone and 17 patients underwent WBRT + HFSRT/SRS. The OS was significantly increased for HFSRT/SRS and WBRT + HFSRT/SRS compared to WBRT alone (12-month OS of 52%, 70% and 30%, respectively; $p < 0.001$). WBRT + HFSRT/SRS improved significantly LC compared to HFSRT/SRS alone (12-month LC of 70% versus 49%, respectively; $p = 0.032$). However, there was no OS difference between HFSRT/SRS alone and WBRT + HFSRT/SRS ($p = 0.703$). A limitation of this retrospective analysis is the poor prognosis of the WBRT group patients who presented a higher number of BM and a poorer recursive partitioning analysis score. (Fokas et al., 2010). In a retrospective analysis, 66 BM-RCC patients were stratified in 3 groups; 36 were treated with HFSRT/SRS alone, 24 with surgical resection + HFSRT/SRS and 6 with WBRT + HFSRT/SRS; compared to HFSRT/SRS alone, resection + HFSRT/SRS resulted in a similar LC (92.8% versus 96.0% respectively), a higher median distant brain metastasis free survival (DBMFS) (19 versus 7 months respectively) and a longer OS, even if that last endpoint did not reach significance (13.6 versus 21.9 months, respectively $p = 0.053$). For the WBRT + HFSRT/SRS group, LC was similar to other groups (93.2%) but median DBMFS and OS were inferior (3.5 and 5.9 months respectively). Among all groups, the rate of acute and long term grade ≥ 3 toxicity was only 4.5% ($n = 3/66$, 1 in surgical resection + HFSRT/SRS group and 2 in HFSRT/SRS alone group) and 1.5% ($n = 1/66$, 1 in HFSRT/SRS alone group) respectively, showing that HFSRT/SRS alone or in combination is a safe modality of treatment for BM-RCC patients (Ippen et al., 2015). Unfortunately, all these studies were retrospective with a limited number of patients.

4. Systemic Therapies

4.1. *Tyrosine kinase inhibitors*

TKIs have significantly improved outcome of mRCC patients. Most of these TKIs not only inhibits VEGF receptor (VEGFR)-1, -2, and -3, but also target other TKR such as PDGF receptor (sunitinib, pazopanib, sorafenib, and axitinib), fibroblast growth factor receptor (lenvatinib), and MET and AXL (cabozantinib). These molecules have been approved for treating mRCC, based on phase III randomized trials in first-line metastatic setting or beyond. They were shown to improve outcome of patients in term of PFS, OS and objective response rate (ORR). However, their efficacy on BM remains difficult to determine, as BM represented a major exclusion criter in these trials (Motzer et al., 2009; Motzer et al., 2007; Sternberg et al., 2010; Escudier et al., 2007a; Escudier et al., 2007b; Choueiri et al., 2016; Choueiri et al., 2017; Motzer et al., 2013).

In the overall mRCC population, sunitinib resulted in a median OS and PFS of 26.4 and 11 months respectively, with an ORR reaching 47% when administered in first-line setting (Motzer et al., 2009). A phase II trial investigated the efficacy of sunitinib in 16 BM-RCC patients

ineligible for local treatment and naive of prior systemic therapy. When regarding the BM response, there was no objective response and only 5 (31%) patients had stable disease (SD). Regarding other survival endpoints, median time-to-progression and median OS were 2.3 and 6.3 months, respectively (Chevreau et al., 2014). In the final expanded-access trial evaluating sunitinib in daily practice, 324 (7%) patients among the 4543 enrolled patients had BM; the systemic ORR was 9% (1% of complete response (CR) and 8% of partial response (PR)), which was lower than the systemic ORR observed in the overall population (16%). These BM-RCC patients had also a lower PFS and OS compared to the overall population (5.3 vs 9.4 and 8.2 vs 18.7 months, respectively) (Table 3) (Gore et al., 2015). Only few cases were reported about pazopanib efficacy in treatment for BM-RCC (Gooch et al., 2016). Sunitinib and pazopanib poorly penetrate the BBB, due to interaction with the efflux transporters P-gp and BCRP. It was shown preclinically that the brain concentration of sunitinib or pazopanib were significantly increased in knock-down mice for P-gp and BCRP or in case of pharmacological inhibition of these proteins (Minocha et al., 2012). Sunitinib and pazopanib do not increase the rate of neurological AEs, which also suggests a lack of activity in brain (Motzer et al., 2009; Motzer et al., 2007; Sternberg et al., 2010). Cases reports of seizures induced by sunitinib and pazopanib are, in most of cases, due to posterior reversible encephalopathy syndrome (PRES), which are induced by secondary hypertension rather than direct neurological action (Cumurciuc et al., 2008; Chelis et al., 2012).

Although spectacular responses were reported in few patients, sorafenib efficacy for BM treatment is not well demonstrated (Valcamonico et al., 2009; Walid and Johnston, 2009). In a retrospective analysis of 139 patients from the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), overall incidence of BM was significantly reduced among patients receiving sorafenib (at a dose of 400 mg twice daily) compared to placebo (3% versus 12% respectively, $p < 0.05$) (Massard et al., 2010). In the expanded access program for mRCC patients treated by sorafenib, 47 patients had BM previously treated with local therapy and were evaluable for ORR; there was no CR (0%), 2 PR (4%), 33 SD (70%) and 12 progressive disease (PD) (26%) but BM specific response was not reported (Table 3). There was no cerebral bleeding, and the incidence of seizure did not exceed 6% in this trial with sorafenib (Henderson et al., 2007; Stadler et al., 2010; Lagas et al., 2010). However, careful follow-up of patients should be done as another study suggests an increased incidence of intracranial bleeding among BM-RCC patients treated with sunitinib and sorafenib (Pouessel and Culine, 2008).

Axitinib presents a strong affinity for VEGFR-1, -2, and -3, providing longer PFS and better ORR, but similar OS, compared to sorafenib in second-line setting of mRCC treatment (Motzer et al., 2013; Rini et al., 2011). The penetration through the BBB by axitinib is also limited by the efflux transporters P-gp and BCRP suggesting a poor activity to control BM from RCC (Poller et al., 2011). Patients with BM were excluded from the major trials evaluating axitinib efficacy in RCC patients; only few case reports of BM-RCC responding to axitinib are published (Rini et al., 2011; Hutson et al., 2013; Shimura et al., 2017).

Cabozantinib is an inhibitor of VEGFR-2 but also of MET and AXL, which are two receptors that are associated with poor prognosis in mRCC and resistance to classical VEGFR inhibitors (Choueiri et al., 2016; Choueiri et al., 2017; Yakes et al., 2011). Cabozantinib has shown to improve ORR, PFS and OS compared to everolimus in mRCC after failure of TKI and is thus currently approved in this setting; cabozantinib has also shown significant PFS and ORR benefits compared to sunitinib in first-line treatment in intermediate- or poor-risk IMDC risk group in the phase II CABOSUN trial (Choueiri et al., 2016; Choueiri et al., 2017). The rational of evaluating cabozantinib in BM-RCC is based on the discordance rate in MET expression between RCC primary tumor and BM; MET overexpression reached 35% in BM while it was 0% in primary tumors (Derosa et al., 2017). Compared to other TKIs, cabozantinib could also more easily penetrate BBB and reach a concentration 20% of peak plasma levels in preclinical model (Zhang et al., 2010). Retrospective analysis of cabozantinib in BM showed moderate response

Table 3
Summary of major studies providing results of targeted therapy and immunotherapy in patients with brain metastases from renal cell carcinoma. BM: Brain metastases, CR: Complete response, N: Number of, NA: Not assessed, OS: Overall survival, PD: Progressive disease, PFS: Progression-free survival, PR: Partial response, SD: Stable disease.

	Study design	N patients with BM	Systemic therapy	Local therapy	Response	Median PFS	Median OS
(Chevreau et al., 2014)	Prospective, Phase II	16	Sunitinib	None	SD : 31,3% and PD : 68,7%	NA	6,3
(Gore et al., 2015)	Retrospective, expanded-access trial	324	Sunitinib	NA	CR: 1%, PR: 8%, SD:33% and PD (or SD<3months): 24%	5,3	8,2
(Henderson et al., 2007)	Retrospective, expanded-access trial	65	Sorafenib	Previous local therapy	CR: 0%, PR: 4%, SD: 70% and PD: 26%	NA	NA
(Albiges et al., 2021)	Retrospective, early access program	69	Cabozantinib	NA	NA	NA	11,3
(Peverelli et al., 2019)	Retrospective	12	Cabozantinib	Previous local therapy in 42%, Concurrent local therapy in 42%, None in 16%	CR: 0%, PR: 50%, SD: 25% and PD: 25% Brain-specific response: CR: 22%, PR: 33%, SD: 45% and PD: 0%	5,8	8,8
(Bodnar et al., 2019)	Retrospective	10	Cabozantinib	NA	NA	6,4	45% at 12 months
(Flippot et al., 2019)	Prospective, Phase II	39	Nivolumab	None	CR: 0%, PR: 21%, SD: 30% and PD: 49% Brain-specific response: CR: 12%, PR: 0%, SD: 38% and PD: 50%	2,4	66,7% at 12 months
		34	Nivolumab	Previous local therapy	NA	2,5	28,8% at 12 months
(De Giorgi et al., 2019)	Retrospective, expanded-access trial	32	Nivolumab	NA	CR: 3,1%, PR: 15,6%, SD: 34,4% and PD: 40,6%	NA	NA
(Emamekhoo et al., 2019)	Prospective, phase IIIb/IV	28	Nivolumab + Ipilimumab	None	PR : 28,6%	9	NR
(Jonasch et al., 2020)	Prospective, phase III	23	Avelumab + Axitinib	Previous local therapy	NA	4,9	NR

(Table 3) (Peverelli et al., 2019; Ciccarese et al., 2018; Négrier et al., 2018; Uche et al., 2019; Bodnar et al., 2019; Albiges et al., 2021). The CABOREAL study investigated cabozantinib use in real-world population, including 69 BM-RCC patients; OS was significantly lower than in patients without BM regardless the number of previous lines of systemic therapy (11.3 versus 15.5 months respectively, p = 0.0066) (Albiges et al., 2021). In a second retrospective study, 12 BM-RCC patients received cabozantinib in second or third-line setting; median PFS and OS were respectively 5.8 and 8.8 months. Among 9 patients evaluable for initial BM specific response (including 5 patients who received local therapy concomitantly), CR occurs in 2 patients, PR in 3 patients and SD in 4 patients (Peverelli et al., 2019).

A third retrospective analysis investigated the use of cabozantinib after at least one line of systemic treatment in 115 patients including 10 with BM. Compared to non-BM-RCC patients, BM-RCC patients had significant lower median PFS (14.2 versus 6.4 months, respectively; p = 0.0037) and 12-month OS (73% versus 45%, respectively; p = 0.0106). Intracranial activity of cabozantinib was not reported (Bodnar et al., 2019). Use of cabozantinib for BM treatment in patients with RCC is currently investigated in the prospective phase II CABRAMET study (NCT03967522).

Everolimus is recommended alone in third-line or in combination with lenvatinib in second-line treatment of mRCC (Escudier et al., 2019). Everolimus targets the mammalian Target of Rapamycin protein (mTOR), providing distinct antiangiogenic properties compared to anti-VEGFR TKIs (Lane et al., 2009). Due to its good brain biodisponibility, everolimus has been evaluated alone or in combination in various cerebral disease but not in BM from RCC (Van Swearingen et al., 2018; Franz et al., 2013; Meikle et al., 2008; Hurvitz et al., 2018).

Combination of bevacizumab plus interferon α-2a (IFN-α-2a) was shown to increase PFS compared to IFN-α-2a alone, but OS benefits are not clear (Escudier et al., 2007b; Rini et al., 2010). Bevacizumab has been investigated in various cerebral disease such has glioblastoma, BM from lung cancer or radionecrosis following HFSRT/SRS with conflicting results (Gilbert et al., 2014; Besse et al., 2015; Gonzalez et al., 2007). For BM-RCC, few data are available as these patients were excluded from pivotal phase III studies (Escudier et al., 2007b; Rini et al., 2010). In a small retrospective study, 4 BM-RCC patients were treated with bevacizumab and IFN-α-2a, which resulted in 1 CR (patient with concurrent neurosurgery), 2 PR (1 patient with no concurrent local therapy and 1 patient with concurrent HFSRT/SRS) and 1 SD (patient with no concurrent local therapy). A potential interest of bevacizumab is improving the quality of life by reduction of corticosteroids use, due to oedema regression or WBRT delaying (Zustovich et al., 2013).

4.2. Immunotherapies-based strategies

ICIs are monoclonal antibodies that target immune checkpoints, and thereby disrupt the inhibitory signals and reactivate immune system. PD-L1 inhibitors include atezolizumab, durvalumab and avelumab, PD-L1 inhibitors include nivolumab and pembrolizumab, and CTLA-4 inhibitors include ipilimumab and tremelimumab (Flippot et al., 2018; Finn, 2008; Sheu and Shih, 2010).

4.2.1. Nivolumab monotherapy

Nivolumab is an ICI antibody targeting PD-1 on T-cells, which inhibits the interaction between PD-1 and its ligands PD-L1 and PD-L2 (Topalian et al., 2012). In mRCC, nivolumab is superior to everolimus regarding OS, ORR and toxicity profile after failure of prior TKI. However, BM-RCC patients were excluded from this phase III trial (Motzer et al., 2015). The 'Groupe d'étude des tumeurs urogénitales', in the phase II GETUG-AFU 26 NIVOREN trial has investigated the efficacy of nivolumab in two cohorts of mRCC patients with asymptomatic BM. The cohort A (n = 39) had no history of previous local treatment for BM while the cohort B (n = 34) had been previously treated by surgery or RT for BM. Both groups receive nivolumab for newly diagnosed BM, without any local or other systemic therapy. In the cohort A, intracranial response rate was lower than the extracranial response (12% versus 21%) and no objective response was reported in patients with multiple or >1 cm BM. Median intracranial PFS was 2.7 months (95% confident interval (CI), 2.3 to 4.6 months) in cohort A and 4.8 months (95% CI, 3.0 to 8.0 months) in cohort B. The 12-month OS was 67% (95% CI, 49.6% to 79.1%) in cohort A and 59% (95% CI, 40.6% to 73.2%) in cohort B. In cohort A, 72% of patients required subsequent local therapy (WBRT, HFSRT/SRS and/or neurosurgery) and 51% required corticosteroids while in cohort B, local therapy was required in 21% and corticosteroids in 27%. Nivolumab was well tolerated, with no unexpected toxicity (Flippot et al., 2019). In the Italian open-access trial for nivolumab in mRCC, among 389 evaluated patients, 32 (8.2%) had asymptomatic BM. OS and ORR did not significantly differ compared to patients without BM (Table 3) (De Giorgi et al., 2019). A retrospective study investigating patterns of mRCC progression on nivolumab highlighted that the first site of new metastatic lesion was the brain; however, these patients had a long-lasting control of their disease with spectacular OS, suggesting that cerebral progression naturally occurs after long course of the disease in mRCC (Zahoor et al., 2018).

4.2.2. Nivolumab and Ipilimumab

Ipilimumab is another ICI antibody which targets CTLA-4 on T-cells. By linking to B7 present at the surface of dendritic cells, CTLA-4 inhibits the immune response against tumoral cells (Melero et al., 2007). The combination of nivolumab and ipilimumab (NIVO + IPI) has proven its superiority compared to sunitinib in first line intermediate/poor risk mRCC in the phase III CheckMate 214 trial (Motzer et al., 2018). For BM-RCC patients, the ongoing CheckMate 920 provided interim results in 28 patients; the ORR was 28.6%, the median PFS was 9.0 months, and the median OS has not yet been reached. Incidence of grade ≥3 immune-mediated AEs is the primary endpoint and occurred, until now, in 6 patients (21.4%) within 100 days (Table 3) (Emamekhoo et al., 2019). There was no brain-specific AE such as cerebral haemorrhage (Motzer et al., 2018; Emamekhoo et al., 2019). At this time, the population size is too weak, and the follow-up is not yet long enough to clearly conclude to a benefit of NIVO + IPI in BM-RCC patients.

4.2.3. Pembrolizumab/Avelumab and Axitinib

Both pembrolizumab and avelumab have recently been evaluated in combination with axitinib in first-line mRCC patients compared to sunitinib. Both pivotal phase III trials demonstrated improved ORR and PFS with an acceptable safety profile (Rini et al., 2019; Motzer et al., 2019). No patient with BM were included in the pembrolizumab-axitinib trial (Rini et al., 2019). However, 46 patients with asymptomatic BM were included in the avelumab-axitinib trial: 23 patients in the experimental group and 23 patients in the sunitinib group (Jonasch et al., 2020). In this specific population, there was no significant difference in PFS between both arms (4.9 months for avelumab-axitinib versus 2.8 months for sunitinib, HR 0.90; 95% CI 0.43-1.88). New BM appeared in 8 patients in the avelumab-axitinib arm and 10 in the sunitinib arm suggesting that both these therapies are ineffective to prevent BM development (Table 3) (Jonasch et al., 2020).

5. Combination of local and systemic therapies

Even if inclusion of BM-RCC patients in prospective trials is difficult (frail patients, corticosteroids use, low incidence), improvements in local and systemic therapies seem to result in better outcome for BM-RCC patients (Suarez-Sarmiento et al., 2019) (Table 4).

The challenge is now to evaluate the current strategies, such as combination of RT, TKI and/or ICIs in BM-RCC. Combination of TKIs and local therapy showed promising results due to better control of systemic disease and the possibility of continuing the systemic treatment used before occurrence of BM. Some data showed that targeted therapy may provide better LC when combined with local therapy while not

Table 4
Summary of studies evaluating local therapies for the treatment of brain metastases in renal cell carcinoma patients reporting individual data for concurrent systemic therapy used. 5-Fu: 5-Fluorouracil, BM: Brain metastases, DBMFS: Distant brain metastases-free survival, HFSRT/SRS: Hypofractionated stereotactic radiotherapy/ stereotactic radiosurgery, IFN-α: Interferon-α, IL-2: Interleukin-2, LC: Local control, mTOR: Mammalian target of rapamycin, N: Number of, NA: Not assessed, NS: Neurosurgery, OS: Overall survival, PD: Progressive disease, PFS: Progression-free survival, RT: Radiotherapy, TKI: Tyrosine kinase inhibitor, WBRT: Whole-brain radiotherapy

	Systemic therapy	N patients	Local therapy	1 year LC	p	Median DBMFS (months)/ Distant Brain control	p	Median OS (months)	p
(Mori et al., 1998)	Adjuvant systemic chemotherapy/ immunotherapy (IL-2, IFN-α, or IL-2 plus 5-Fu)	7	HFSRT/SRS (n = 7), HFSRT/SRS + WBRT (n = 28)	NA		NA		16	0,02
	No adjuvant systemic chemotherapy/ immunotherapy	28						5	
(Wowra et al., 2002)	Adjuvant systemic chemotherapy and/or immunotherapy	28	HFSRT/SRS (n = 40), WBRT + HFSRT/SRS (n = 8), NS + HFSRT/SRS (n = 27)	NA		NA		7,2	0,021
	No adjuvant systemic chemotherapy and/or immunotherapy	47						15,2	
(Muacevic et al., 2004)	Chemotherapy/ immunotherapy	32	HFSRT/SRS (n = 54), NS + HFSRT/SRS (n = 31)	NA		NA		7,8	0,1
	No chemotherapy/ immunotherapy	53						13,4	
(Samlowski et al., 2008)	Immunotherapy (IL-2 and/or INF-α) after HFSRT/SRS	9	HFSRT/SRS (n = 20), WBRT + HFSRT/SRS (n = 12)	NA	NA	23,2/NA	0,07/ NA	17,1	0,0007
	No immunotherapy after HFSRT/SRS	23				15/NA		5,4	
	Antiangiogenic agent after HFSRT/SRS (bevacizumab, sunitinib, sorafenib, or thalidomide)	13		NA	NA	NA		9,2	0,13
	No antiangiogenic agent after HFSRT/SRS	19						4,5	
(Kano et al., 2011)	Prior chemotherapy/ immunotherapy	94	HFSRT/SRS (n = 79), NS + HFSRT/SRS (n = 22), WBRT + HFSRT/ SRS (n = 57)	NA	0,63	NA	NA/ 0,15	NA	0,005 (in favor of no previous chemotherapy/ immunotherapy)
	No prior chemotherapy/ immunotherapy	64							
(Cochran et al., 2012)	Targeted therapy (TKI, mTOR inhibitors, and/or bevacizumab)	24	HFSRT/SRS (n = 52), WBRT + HFSRT/SRS (n = 9)	93,3%	0,01	NA	NA/ 0,98	16,6	0,04
	Conventional Therapy (Cytokins, metastasectomy, cytotoxic chemotherapy or follow-up)	37		60,0%				7,2	
(Verma et al., 2013)	TKI post-BM occurrence (sunitinib, sorafenib, and pazopanib)	40	WBRT (n = 13), HFSRT/SRS (n = 34), NS (n = 16), None (n = 33)	90%	0,18	NA/43,2% at 1-year	0,39	23,6	0,0001
	TKI pre-BM occurrence			53%		NA/0% at 1-year		2,08	
	Never TKI (IFN-α, IL-2, 5-Fu, or gemcitabine)	41		74%		NA/49% at 1-year		4,41	
(Du et al., 2016)	Targeted therapy (sunitinib, sorafenib, temsirolimus, pazopanib, axitinib, everolimus and imatinib)	26	NS (n = 16), RT (n = 39), NS + RT (n = 9)	NA		NA		9,9	0,018
	No targeted therapy	90						4,8	
(Bates et al., 2017)	Concurrent targeted therapy (sunitinib, sorafenib, pazopinib, or temsirolimus)	7	Different combination of NS, WBRT and HFSRT/SRS	NA		NA	NA/ 0,86	7,3	NA
	No concurrent targeted therapy	18						4,1	

providing better DBMFS (Cochran et al., 2012; Bates et al., 2017; Verma et al., 2013). Verma et al. showed that TKI-naive patients at the time of BM occurrence had better OS, LC and DBMFS compared to patients who developed BM during TKI treatment (Verma et al., 2013).

The combination of RT and ICIs involves complex immunologic mechanisms that could potentially result, through synergic action, in improved anti-tumoral response. Chen et al evaluated outcome of 260 patients with a broad spectrum of malignancies and BM (including 33 BM-RCC) in a retrospective trial. These patients were treated by HFSRT/SRS alone, concurrent HFSRT/SRS + ICIs and non-concurrent HFSRT/SRS + ICIs. Even if the OS was significantly higher in concurrent HFSRT/SRS + ICIs compared to other groups, there was no significant difference between the 3 groups for 1-year LC (82%, 79% and 88% for HFSRT/SRS alone, non-concurrent HFSRT/SRS + ICIs and concurrent HFSRT/SRS + ICIs respectively). However, concurrent HFSRT/SRS + ICIs patients had less probability to develop ≥ 3 new BM following HFSRT/SRS (p = 0.045), but the authors suggest that it could be potentially due to a better extracranial control rather than synergistic immune effect

between ICIs and HFSRT/SRS (Chen et al., 2018). Whether this association HFSRT/SRS + ICIs could increase the rate of radionecrosis remains unknown (Hwang et al., 2018). Martin et al. reported a retrospective series of 480 patients with BM from various histology, including 41 mRCC. All patients were treated with HFSRT/SRS and 24% of them (12% for mRCC) received concurrent ICI. The incidence of symptomatic radionecrosis after approximatively 2 years was significantly lower for patients treated with HFSRT/SRS only compared to patients treated by HFSRT/SRS + ICI (6.8% versus 20% respectively, $p < 0.001$). A prospective phase II trial investigating the combination of nivolumab and HFSRT/SRS (15-20 Gy in a single fraction) for the treatment of BM-RCC, lung carcinoma (both small cell and non-small cell carcinoma) and melanoma is ongoing. The primary endpoint is the intracranial PFS, and the estimated study completion date is in June 2021 (NTC02978404).

6. Conclusion

In conclusion, BM-RCC remains a major challenge and need a multidisciplinary approach to provide the best treatment for the patient. Recent progresses have significantly improved the outcome of mRCC patients but only retrospective and modest trials are available for the application of these new therapies to the specific BM-RCC subgroup. Further prospective studies are needed to investigate the impact of the new therapies as well as their potential combination.

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Julien Pierrard: Conceptualization, Writing - original draft, Writing - review & editing. **Thaïs Tison:** Writing - review & editing. **Guillaume Grisay:** Writing - review & editing. **Emmanuel Seront:** Writing - original draft, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors report no declarations of interest.

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