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ORIGINAL RESEARCH

An Italian multicenter retrospective real-life analysis of patients with brain metastases from renal cell carcinoma: the BMRCC study

V. Internò[1], F. Massari[2], R. Rudà[3], B. A. Maiorano[4], O. Caffo[5], G. Procopio[6], S. Bracarda[7], F. Atzori[8], A. Passarelli[9], M. Bersanelli[10], M. Stellato[6,11], G. Fornarini[12], L. Galli[13], C. Ortega[14], E. Zanardi[15], L. Incorvaia[16], G. Facchini[17], J. R. Giron Berrios[18], R. Ricotta[19], M. Santoni[20], C. Funaioli[21], P. Trerotoli[22], C. Porta[1,22†] & M. Rizzo[1,23†‡§*]

[1]Medical Oncology Unit, Azienda Ospedaliera Universitaria Policlinico di Bari, Bari, Italy; [2]Medical Oncology Unit, IRCCS Azienda Ospedaliera Universitaria di Bologna, Bologna, Italy; [3]Division of Neuro-Oncology, Department of Neuroscience 'Rita Levi Montalcini', University of Torino, Torino, Italy; [4]Medical Oncology Unit, IRCCS Fondazione Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy; [5]Department of Medical Oncology, Azienda Provinciale per i Servizi Sanitari di Trento, Trento, Italy; [6]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy; [7]Medical and Translational Oncology Unit, Department of Oncology, Azienda Ospedaliera Santa Maria, Terni, Italy; [8]Medical Oncology Unit, University Hospital of Cagliari, Cagliari, Italy; [9]Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli, Italy; [10]Medical Oncology Unit, University Hospital of Parma, Parma, Italy; [11]Department of Medical Oncology, Fondazione Policlinico Campus Bio-Medico, Roma, Italy; [12]Department of Medical Oncology, IRCCS Azienda Ospedaliera Universitaria San Martino, Genova, Italy; [13]Medical Oncology Unit, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; [14]Oncology Unit—ASL Cuneo 2—'Michele e Pietro Ferrero' Hospital, Verduno, Cuneo, Italy; [15]Academic Unit of Medical Oncology, IRCCS Ospedale Policlinico San Martino, Genova, Italy; [16]Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy; [17]ASL Napoli 2 Nord, Oncology Operative Unit, 'S. Maria delle Grazie' Hospital—Pozzuoli, Napoli, Italy; [18]Department of Medical Oncology, Belcolle Hospital of Viterbo, Viterbo, Italy; [19]Oncology Unit, IRCCS MultiMedica, Sesto San Giovanni, Milano, Italy; [20]Oncology Unit, Macerata Hospital, Macerata, Italy; [21]Medical Oncology Unit, ASST 'Santi Paolo e Carlo', Milano, Italy; [22]Department of Interdisciplinary Medicine, University of Bari 'Aldo Moro', Bari, Italy; [23]Division of Translational Oncology, IRCCS Istituti Clinici Scientifici Maugeri, Pavia, Italy

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Background: The treatment of patients with brain-spread renal cell carcinoma (RCC) is an unmet clinical need, although more recent therapeutic strategies have significantly improved RCC patients' life expectancy. Our multicenter, retrospective, observational study investigated a real-world cohort of patients with brain metastases (BM) from RCC (BMRCC).

Patients and methods: A total of 226 patients with histological diagnosis of RCC and radiological evidence of BM from 22 Italian institutions were enrolled. Univariate and multivariate models were performed to investigate the impact of clinicopathological features and multimodal treatments on both overall survival (OS) from the BM diagnosis and intracranial progression-free survival (iPFS).

Results: The median OS from the BM diagnosis was 18.8 months (interquartile range: 6.2-43 months). Multivariate analysis confirmed the following as positive independent prognostic factors: a Karnofsky Performance Status >70% [hazard ratio (HR) = 0.49, 95% confidence interval (CI) 0.26-0.92, $P = 0.0026$] and a single BM (HR = 0.51, 95% CI 0.31-0.86, $P = 0.0310$); in contrast, the following were confirmed as worse prognosis factors: progressive extracranial disease (HR = 1.66, 95% CI 1.003-2.74, $P = 0.00181$) and only one line of systemic therapy after the BM occurrence (HR = 2.98, 95% CI 1.62-5.49, $P = 0.029$). Subgroup analyses showed no difference in iPFS according to the type of the first systemic treatment [immunotherapy (IT) or targeted therapy (TT)] carried out after the BM diagnosis (HR = 1.033, 95% CI 0.565-1.889, $P = 0.16$), and revealed that external radiation therapy (eRT) significantly prolonged iPFS when combined with IT (10.7 months, 95% CI 4.9-48 months, $P = 0.0321$) and not when combined with TT (9.01 months, 95% CI 2.7-21.2 months, $P = 0.59$).

Conclusions: Our results suggest a potential additive effect in terms of iPFS for eRT combined with IT and encourage a more intensive multimodal therapeutic strategy in a multidisciplinary context to improve the survival of BMRCC patients.

Key words: renal cell carcinoma, brain metastases, radiotherapy, targeted therapy, immunotherapy

*Correspondence to: Dr Mimma Rizzo, Medical Oncology Unit, Azienda Ospedaliera Universitaria Policlinico di Bari, Bari, Italy. Tel: +39-0805594508
E-mail: rizzo.mimma@gmail.com (M. Rizzo).
Twitter handle: @mimma_rizzo

†Co-senior authors.
‡Present address: Medical Oncology Unit, Azienda Ospedaliera Universitaria Policlinico di Bari, Bari, Italy.
§Previous address: Division of Translational Oncology, Scientific Clinical Institute Maugeri (ICS Maugeri), Pavia, Italy.

INTRODUCTION

The incidence of brain metastases (BM) in metastatic renal cell carcinoma (mRCC) patients ranges between 2% and 15%,[1-3] although a single-center surveillance study using magnetic resonance imaging (MRI) reported a higher incidence of 30%.[4] Indeed, available epidemiological data should be regarded as inaccurate, since screening for BM is not systematically carried out.

Among patients with mRCC at the time of diagnosis, ~5% have synchronous BM, while among those with radically resected localized disease, around 17% will develop metachronous encephalic spread;[5] early encephalic metastases are generally multiple, in contrast with late encephalic metastases which are generally solitary.[6,7]

BM frequently cause neurological symptoms and have a high propensity for bleeding due to the typical neovascularization features.[8,9]

Several retrospective series have identified the number of BM, the presence of extracranial metastases, and patient's performance status at the time of BM diagnosis as negative prognostic factors,[10-12] although the overall prognosis of these patients appears to be heterogeneous.

Indeed, although the median overall survival (OS) of patients with BM is lower with respect to patients without encephalic disease, median survival ranges from 3 to almost 25 months from the first evidence of BM.[4] In a retrospective cohort of patients treated at the University of California Los Angeles, between 1989 and 2006, the median OS after the BM diagnosis was 10.7 months, with survival rates of 48%, 30%, and 12% at 1 year, 2 years, and 5 years, respectively.[13]

In the era of targeted therapies (TTs), an International Metastatic RCC Database Consortium (IMDC) report of mRCC patients treated between 2005 and 2011 showed a median OS after first-line TT of 14.4 months for patients with BM, as compared to 19.0 months for those without BM.[14]

In the era of immunotherapy (IT), available figures (mainly from retrospective series) are still too heterogeneous to extract reliable survival rates.

An optimal approach for treating patients with brain-spread RCC remains an unmet need, despite the survival improvement achieved for mRCC due to the advent of TT and immune checkpoint inhibitors (ICIs).[15-18] Indeed, specific trials aimed at investigating the benefit of standard treatments in mRCC patients with BM are warranted.

In general, the cornerstone of the treatment of BM is represented by a multimodal therapeutic approach, which includes encephalic radiotherapy (eRT), with stereotactic radiosurgery (SRS) when possible or whole-brain radiotherapy (WBRT), surgical resection (as an alternative to eRT), and systemic treatments, although the prognosis of these patients remains poor.[19]

Here we retrospectively report a cohort of mRCC patients with BM, with the aim of investigating the possible impact of clinicopathological features and treatment strategies on intracranial progression-free survival (iPFS), the primary objective of the present study.

PATIENTS AND METHODS

Study population

Patients aged ≥18 years, with a cytological and/or histological confirmed diagnosis of RCC, and radiological evidence of BM, observed between 1 January 2008 and 31 December 2021 in 22 Italian institutions, were included in the BMRCC study. Ethical committee approval was obtained from all participating centers, while written informed consent for clinical data collection was obtained from all patients. The features extracted from patients' charts included age, sex, Karnofsky Performance Status (KPS), histological subtype of RCC, presence of sarcomatoid differentiation, TNM (tumor—node—metastasis) stage, type and time of kidney surgery, IMDC risk group, site(s) of metastases, time of intracranial metastatic diagnosis, number and site of BM, occurrence and typology of neurologic signs/symptoms and specific drugs used for their palliation, type and time of systemic and/or local treatments (single-agent TT, single-agent ICI, combined TT plus ICI, SRS or WBRT), radiological response to local and systemic treatments, date of intracranial progression, and date of death. Patients with insufficient data on encephalic radiological response were excluded from this study. Follow-up included physical examinations and laboratory tests every 3-6 weeks, and computed tomography (CT) scans of at least the thorax and abdomen every 2-4 months, according to physicians' practice or when systemic disease progression was clinically suspected. MRI of the brain was carried out whenever BM were evidenced by means of CT, and every 2-4 months thereafter, according to physician practice, or when encephalic disease progression or complications were clinically suspected.

Statistical analysis

Quantitative variables were summarized as means and standard deviation or median and interquartile range (IQR). Comparisons between independent groups were carried out using Student's t-test for an independent sample of Wilcoxon, as appropriate according to the Gaussian distribution of the data. Qualitative variables were summarized as counts and percentages. Comparisons between groups were carried out by the chi-square test.

Intracranial progression-free survival (iPFS) was defined as the time from the BM diagnosis to their progression according to the Response Assessment in Neuro-Oncology criteria;[20] for the purpose of this analysis, OS was defined as the time from the BM diagnosis to death. Both were summarized as median and IQR. The survival analysis for treatment comparison was conducted with the Kaplan—Meier curves. The log-rank test assessed the related differences by treatment and prognostic factors (such as eRT or neurological symptoms). Comparisons between pairs were adjusted according to Bonferroni in those cases with more than two levels for variables. The prognostic analysis was conducted with the Cox proportional hazards regression model. Factors tested in the univariate regression

were: sex (M/F), age (≤55 versus >55 years), KPS (>70% versus ≤70%), BM number (1 versus 2-3 versus >3) and localization (supratentorial versus infratentorial versus both), time of diagnosis (synchronous versus metachronous BM), presence of extracranial disease (yes/no), neurological symptoms (yes/no), local treatments carried out (neurosurgery versus eRT versus both), type (IT versus TT versus IT + TT), and number (1 versus 2 versus 3) of systemic therapies carried out after the BM diagnosis. A multivariable Cox regression model was also applied without any variable selection method. As a measure of fitting, a generalized R-square based on the likelihood ratio test was used. Statistical significance was assessed for *P* value <0.05 and confidence levels were set at 95% in confidence intervals (CIs). All analyses and data management were carried out by SAS 9.4 for PC Windows (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics

Table 1 summarizes the clinical and pathological characteristics of the whole population of patients; 81% of patients ($n = 182$) were male and the median age at the time of BM diagnosis was 59 years. Approximately 80% of patients ($n = 180$) also had extracranial metastases, and BM were mostly metachronous to the RCC diagnosis (74%, $n = 167$). The median time to the BM occurrence from the RCC diagnosis was 18 months. The predominant brain metastatic site was the supratentorial region (66%, $n = 148$), while 13% ($n = 30$) of patients showed BM in the posterior cranial fossa, and 21% ($n = 48$) in both encephalic regions. Almost half of the patients (52%, $n = 119$) had a single BM, while a quarter of them ($n = 53$) had more than three BM. Bleeding signs were detected in 10% of the patients ($n = 23$). The primary histological diagnosis was clear cell carcinoma in 96% ($n = 217$), while papillary carcinoma was evidenced in 3% of the cases ($n = 7$); the presence of sarcomatoid differentiation was reported in only 1% ($n = 2$) of patients. At the diagnosis of BM, 78% ($n = 178$) of patients had a good performance status (KPS > 70%) and only 2% ($n = 4$) had KPS < 40%. Forty-four percent ($n = 100$) of patients had neurological symptoms, and all of them received palliative steroids. As far as local treatments are concerned, surgical resection of the BM was carried out in a quarter (25%) of the patients ($n = 53$), while 70% of them ($n = 158$) received eRT, either SRS ($n = 106/158$, 67%) or WBRT ($n = 52/158$, 33%). Notably, as many as 45% ($n = 101/226$) of BM patients did not receive any systemic treatment after the BM diagnosis. On the other hand, systemic IT or TT therapy following the BM diagnosis was carried out in 54% ($n = 122/226$) of patients: TT in 73% ($n = 89/122$) and IT in 27% ($n = 33/122$). After the diagnosis of BM, 31% of patients ($n = 39/125$) received two sequential lines of systemic therapy and 25% ($n = 32/125$) of patients received three sequential lines of systemic therapy.

Table 2 summarizes local and systemic treatment outcomes.

Factors associated with OS. At the time of data lock, 139 patients had died, while 87 were still alive. The mOS from the BM diagnosis was 18.8 months (IQR: 6.2-43 months). Table 3 shows the results of univariate and multivariate analyses of clinicopathological factors potentially related to the prognosis. Univariate analysis revealed a worse prognosis in male patients ($P = 0.004$), in patients with a KPS ≤ 70% ($P = 0.04$), multiple BM (1 versus 2-3, $P < 0.0001$; 1 versus >3, $P = 0.0154$), extracranial disease progression concomitant with the BM diagnosis ($P = 0.045$), and a single line of systemic therapy after the BM diagnosis (1 versus 2, $P < 0.0001$; 1 versus 3, $P = 0.0177$).

Neither the location of BMs (supra versus infratentorial, $P = 0.6788$) nor the presence of neurological symptoms ($P = 0.4766$) impacted on OS. Multivariate analysis

Table 1. Main characteristics of the study sample

		N (226)	%
Sex	M	182	81
	F	44	19
Age at BMs onset, years (mean)		59	
RCC histology	Clear cell	217	96
	Papillary	7	3
	Sarcomatoid differentiation	2	1
Timing of BMs with respect to RCC diagnosis	Synchronous	59	26
	Metachronous	167	74
Number of BMs	1	119	52
	2-3	54	24
	>3	53	24
BMs location	Supratentorial	148	66
	Infratentorial	30	13
	Both	48	21
Extracranial metastases	Yes	180	80
	No	46	20
Symptomatic BM	Yes	100	44
	No	126	56
KPS at BMs onset	>70	178	78
	70 ≤ × ≥ 40	44	20
	≤40	4	2

Table 1 summarizes the main characteristics of the study population and the underlying metastatic disease, such as the occurrence of BM (metachronous or synchronous), their encephalic location and number.
BMs, brain metastases; KPS, Karnofsky Performance Status; RCC, renal cell carcinoma.

Table 2. Local and systemic treatments

		N (226)	%
Neurosurgery	Yes	53	23
	No	173	77
eRT	Yes	158	70
	No	68	30
Type of eRT	SRS	106	67
	WBRT	52	33
Systemic treatment after BMs onset	IT	33	15
	TT	89	39
	Other	106	46
Number of systemic therapies after BMs onset	1	54	43
	2	39	31
	3	32	25

Table 2 lists both local and systemic treatments carried out.
BMs, brain metastases; eRT, encephalic radiotherapy; SRS, stereotactic radiosurgery; IT, immunotherapy; TT, targeted therapy; WBRT, whole-brain radiotherapy.

Table 3. Results of Cox regression for overall survival

Factors	Effect tested	Univariate analysis			Multivariate analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	Female versus male	0.47	0.31-0.84	**0.004**	0.59	0.28-0.93	0.08
Age at BMs onset (years)	≤ 55 years versus > 55 years	0.79	0.55-1.17	0.24	0.91	0.59-1.38	0.94
KPS	> 70% versus ≤ 70%	1.59	0.44-0.99	**0.04**	0.49	0.26-0.92	**0.0026**
Year of BMs onset	After the year 2017 (included) versus before 2017	0.93	0.65-1.33	0.6824	0.95	0.57-1.57	0.833
Extracranial metastatic disease status at BMs onset	PD versus controlled disease (CR, PR, SD, NED)	1.24	0.76-2.03	**0.045**	1.66	1.003-2.74	**0.00181**
BMs site	Supra- versus infratentorial	2.16	1.15-4.06	0.6788	1.78	0.79-3.99	0.8889
Neurological symptoms	Yes versus no	1.13	0.81-1.58	0.4766	0.99	0.63-1.57	0.9882
Number of BMs	1 versus 2-3	0.55	0.36-0.83	**<0.0001**	0.49	0.29-0.83	**0.0112**
	1 versus >3	0.31	0.21-0.48	**0.0154**	0.51	0.31-0.86	**0.0310**
	2-3 versus >3	0.58	0.37-0.7	0.578	1.05	0.6-1.94	0.7899
Number of therapeutic systemic lines after BMs onset	1 versus 2	3.46	2.12-5.6	**<0.0001**	2.09	1.29-3.41	**0.0004**
	1 versus 3	9.79	3.47-27.64	**0.0177**	2.98	1.62-5.49	**0.029**

Table 3 shows the results of the Cox regression model applied to assess the effect of each variable on the risk of death. All risk factors were evaluated to assess the assumption for proportional hazard with a multivariable Cox model with the dependent OS. Statistical significance was set at $P < 0.05$ and are indicated in bold.
BMs, brain metastases; CI, confidence interval; CR, complete response; HR, hazard ratio; KPS, Karnofsky Performance Status; NED, no evidence of disease; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

confirmed the following as positive independent prognostic factors: a KPS > 70% [hazard ratio (HR) = 0.49, 95% CI 0.26-0.92, $P = 0.0026$] and a single BM (HR = 0.51, 95% CI 0.31-0.86, $P = 0.0310$); in contrast, the following were confirmed as worse prognosis factors: progressive extracranial disease (HR = 1.66, 95% CI 1.003-2.74, $P = 0.00181$) and only one line of systemic therapy after the BM occurrence (HR = 2.98, 95% CI 1.62-5.49, $P = 0.029$). Neurological symptoms and location of BMs showed no prognostic value in the multivariate analysis ($P = 0.9888$ and $P = 0.888$, respectively).

Impact of treatments on survival. We then explored the intracranial efficacy of systemic treatments, as their impact on both OS and iPFS from the BM occurrence and the additive role, if any, of eRT on the efficacy of the different systemic treatments used.

No OS difference was observed between patients treated with TT as compared to those treated with IT (HR = 0.57, 95% CI 0.31-1.06, $P = 0.0727$) (Figure 1A), with the median OS (mOS) being 16.7 months (95% CI 6.8-36.4 months) and 22.7 months (95% CI 7-23.8 months), respectively.

Also median iPFS did not differ significantly when considering the systemic treatments carried out (HR = 1.033, 95% CI 0.565-1.889, $P = 0.16$), and the median iPFS was 10.7 months (95% CI 4.5-48 months) and 9.3 months (95% CI 3.9-21 months) for patients treated with IT and TT, respectively (Figure 1B).

Regarding brain-specific treatments, those who received eRT showed only a modest benefit in terms of iPFS compared to not treated patients, but no statistically significant differences were detected (HR = 0.99, 95% CI 0.68-1.47, $P = 0.982$).

Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101598, shows the iPFS according to the locoregional treatment and the type of radiotherapy received: this analysis did not show a statistically significant result, with the exception of the longer iPFS (*P* value = 0.022) of patients who received WBRT without surgery compared to those who received no brain-directed treatment (no RT and no surgery).

We also tested (Figure 2A and B) whether the combination of eRT with an IT or TT could influence iPFS, in order to identify the strategy that has the major impact on BM growth, reduces neurological complications, and improves patients' quality of life, if any. For this purpose, we divided the study population into four groups based on the treatment received: (A) IT plus eRT ($n = 25$), (B) IT without eRT ($n = 8$); (C) TT without eRT ($n = 18$), and (D) TT plus eRT ($n = 57$).

Patients in group A achieved a statistically significant iPFS (10.7 months, 95% CI 4.9-48 months) as compared to group B (5.5 months, 95% CI 4.3-20.8 months, $P = 0.0321$), while a similar iPFS was seen between group C (9.9 months, 95% CI 5.3-22.3 months) and group D (9.01 months, 95% CI 2.7-21.2 months, $P = 0.59$).

DISCUSSION

For decades, BM have been related to a particularly poor prognosis, leading to their exclusion from enrollment into clinical trials. Furthermore, limited information is available on the biological and genetic pathways underlying the spread of cancer cells to the brain, the clinicopathological features of BM, and even less on the results that can be achieved on BM by means of systemic treatments. In recent years, the Food and Drug Administration issued guidance on the inclusion of patients with BM in clinical trials to alert the oncology community to this population,[21] while a framework to support the management of patients with central nervous system metastases in clinical trials has been published.[22]

Compared to other solid tumors, RCC growth depends on a complex relationship between immune response (often inhibited) and angiogenesis (almost always exasperated). Indeed, basic research models suggest that the slow growth (or even the regression) of distant metastases which can be clinically observed after the resection of the primary tumor could be due to the suppression of the cross-talk between

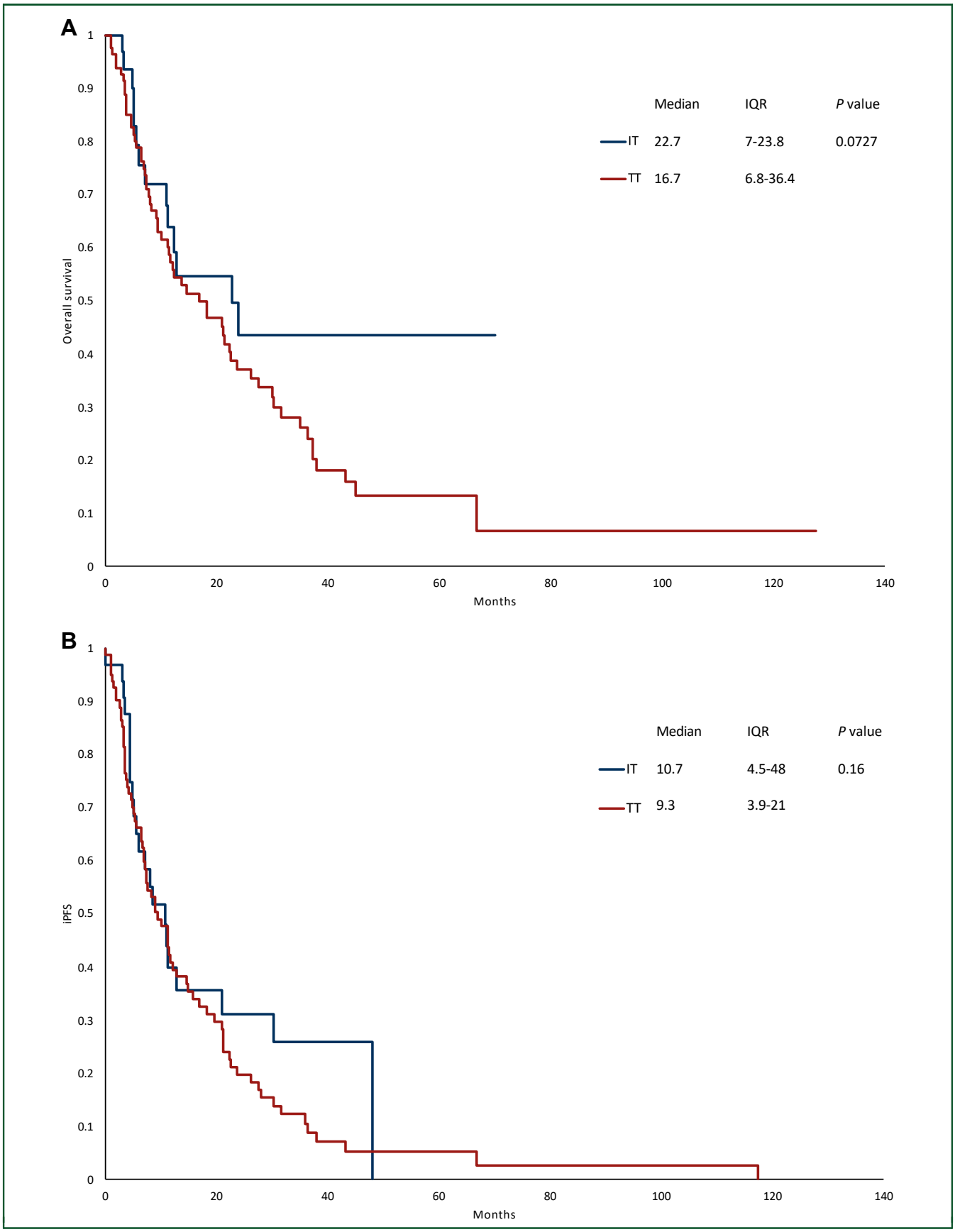

Figure 1. OS (A) and iPFS (B) after BMs diagnosis according to systemic treatment (TT versus IT).
BMs, brain metastases; iPFS, intracranial progression-free survival; IT, immunotherapy; OS, overall survival; TT, targeted therapy.

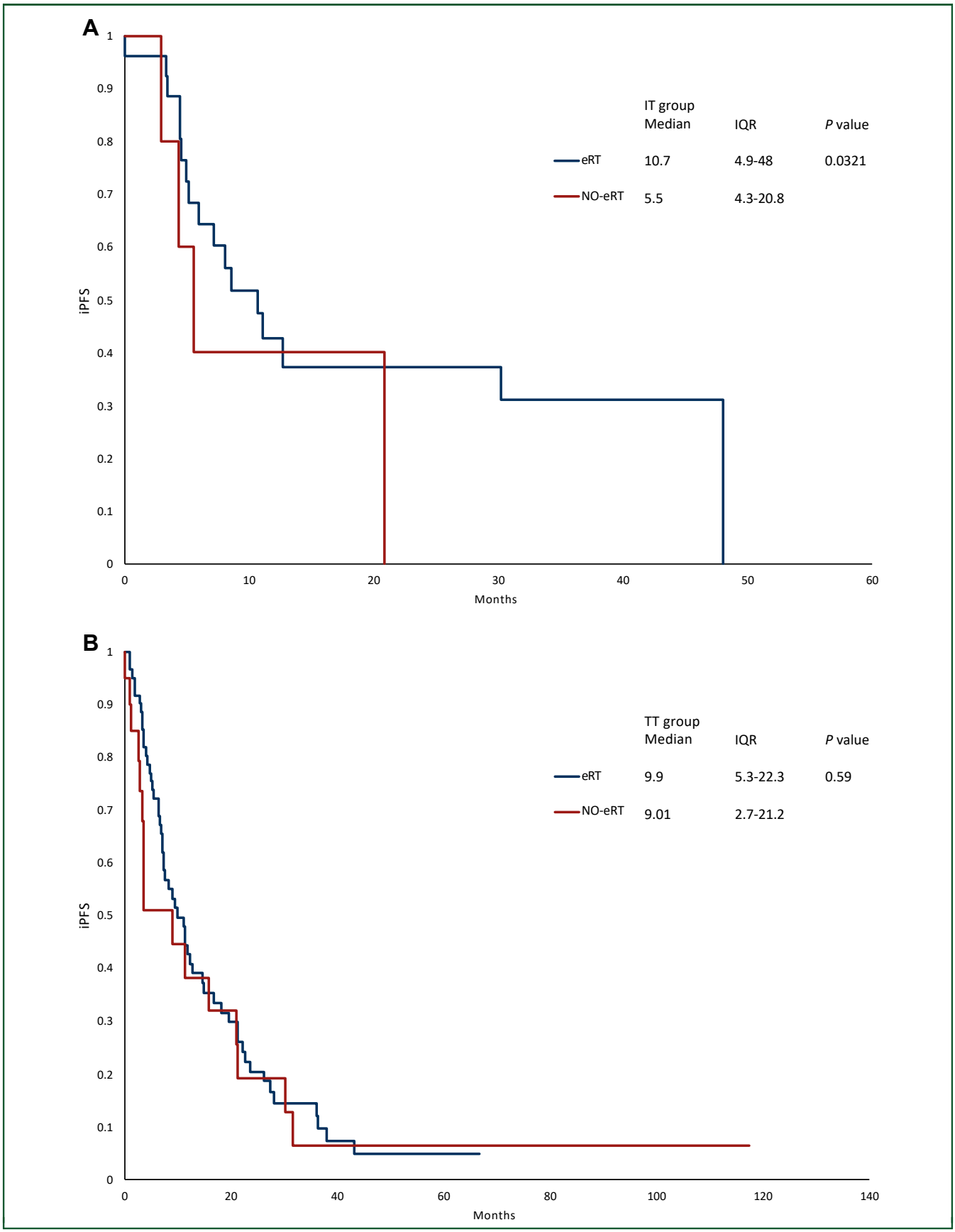

Figure 2. iPFS by eRT and combined IT (A) and TT (B).
eRT, encephalic radiotherapy; iPFS, intracranial progression-free survival; IT, immunotherapy; TT, targeted therapy.

the latter and its metastases.[23] This pre-clinical evidence and clinical data support the use of cytoreductive nephrectomy followed by locoregional therapy (surgery and/or eRT) in patients with solitary BM without extracranial metastases or with a limited burden of extracranial disease.[24] Conversely, for mRCC with multiple distant metastases including one or more BM, cytoreductive nephrectomy should not be proposed as a first-choice option, with systemic treatment in combination with locoregional BM treatment being the usual standard of care.[24] The historical paradigm of using WBRT for multiple intracranial metastases has changed in recent years, with clinical trials demonstrating that SRS alone induces a lower rate of neurocognitive decline without any impairment in the disease control rate [1-year local control rate: 91.8% (95% CI 85.7% to 95.4%); 2-year local control rate: 86.1% (95% CI 77.1% to 91.7%)] and OS [1-year OS: 57.5% (95% CI 40.2% to 71.4%)].[25]

Despite the fact that most randomized registrative trials excluded patients with BM or allowed only patients with previously treated and stable BM, systemic therapies are commonly used to treat mRCC patients with BM. As far as antiangiogenic agents are concerned, their use for the treatment of BM from RCC is mainly supported by retrospective studies, non-interventional prospective studies, or expanded access programs, in which eRT was not mandatory; due to this huge heterogeneity, no clear conclusions can be drawn on the efficacy of antiangiogenics on BM.

The results of a recent meta-analysis conducted on a series of 897 mRCC patients with BM treated with local treatment with or without vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs) confirm that the combined treatment improves OS (HR = 0.60, 95% CI 0.52-0.69, $P < 0.00001$) and BM local control (HR = 0.30, 95% CI 0.11-0.98, $P = 0.05$) without leading to major neurological adverse events.[26] Similarly, data on ICIs for mRCC patients with BM are mostly generated from retrospective studies, *post hoc* subgroup analyses of multicenter trials,[27,28] and non-interventional prospective studies.[29,30] Despite limited data, IT seems manageable in patients with previously treated or asymptomatic BM, but efficacy remains to be demonstrated by ongoing studies.

In our retrospective case series, we observed patients' clinicopathological features and multimodal therapeutic strategies consistent with the literature data and representative of the current diagnostic-therapeutic scenario of BMRCC.[3,5] Most BM were metachronous, located in the supratentorial region, associated with extracranial metastases and half of the patients were symptomatic. The presence of neurological signs/symptoms was not a negative prognostic factor, while a KPS > 70%, non-progressed extracranial metastatic disease, the presence of a single brain metastasis, and the number of lines of systemic therapy after the BM diagnosis proved to be positive independent prognostic factors.

Regarding the treatment received, patients who received eRT (67% of patients, $n = 158/226$) showed only a modest, and not statistically significant, benefit in terms of iPFS compared to those who did not receive eRT (HR = 0.99, 95% CI 0.68-1.47, $P = 0.982$). We suppose that a significant number of patients have never received local cerebral therapy for several reasons: poor general clinical condition and consequent unsuitability for local cerebral therapy, predominant progression of systemic disease (in proportion to the burden of cerebral disease), and non-availability of effective locoregional treatment in the referral clinical institution. Notably enough, systemic therapy after the diagnosis of BM was received by only 55% of the patients ($n = 125/226$), possibly highlighting—at least in part—the negative perception of the prognosis of patients with BM and the unavailability of further effective systemic treatments reimbursed by the Italian National Health System. We hypothesize that a large percentage of patients may not have received an optimal therapeutic strategy because the metastatic site itself, considered 'hopeless', led to a nihilistic medical approach. This finding may be an incentive for physicians to further invest in the therapeutic strategy of patients with BMRCC with experimental drugs or re-irradiation. On the other hand, among treated patients, more than a quarter received up to three lines of systemic therapy, without statistically significant differences in OS between patients receiving TT versus those receiving ICIs; furthermore, the median OS observed is in line with the results of the most recent population. The median iPFS also did not differ significantly when considering the systemic treatments carried out; despite this, patients treated with eRT plus ICIs had a better median iPFS (10.7 months) than those receiving ICIs alone (5.5 months). Instead, a similar iPFS was observed when TTs were used, with or without eRT.

Overall, our data support the use of the eRT—ICI combination in mRCC patients with BM. The biological rationale supporting the combined eRT—ICI approach is that radiation promotes inflammation and stimulates the innate and adaptive immune system, potentially increasing the activity of ICIs.[31,32]

The phase II study GETUG-AFU 26 NIVOREN[27] investigated the efficacy of nivolumab in two cohorts of patients with asymptomatic BMRCC: previously untreated (cohort A, $n = 34$) and treated (cohort B, $n = 34$) with local treatment (surgery and/or radiotherapy) for BM. The intracranial response rate (iRR) was 12% ($n = 4/34$) in patients with a single untreated BM smaller than 10 mm at baseline, while 38% ($n = 13/34$) of patients previously treated for BM had stable intracranial disease as the best response assessed. Median iPFS was 2.7 months (95% CI 2.3-4.6 months) in cohort A and 4.8 months (95% CI 3.0-8.0 months) in cohort B.

In our study, the median iPFS for patients who received eRT in combination with ICI ($n = 25$) was higher (10.7 months) than the literature results detailed above. These conflicting results may be due to the type and duration of first-line treatment. Indeed, the duration of response to first-line anti-VEGFR monotherapy, received by most patients in our study, is an independent predictor for OS in patients treated with anti-programmed cell death protein-1 inhibitors in subsequent lines.[33] Another factor to consider

is the assessment of the intracranial radiological response. RECIST v1.1 criteria are inadequate and misinterpreted for IT-based approaches: an initial increase in the number and size of metastases can be followed by radiographic stabilization or regression. Even in the real-world clinical scenario, we should consider using modified response criteria for IT—eRT combination, such as those recommended in RANO-BM,[34] irRC,[35] iRANO,[36] or iRECIST.[37]

Beyond its retrospective design, this study has several relevant limitations. Firstly, the diagnosis and the selection of locoregional therapy for BM was influenced by the availability/unavailability of advanced diagnostic, surgical and radiotherapeutic procedures and validated therapeutic algorithms at each institution. Secondly, some histological (in particular sarcomatoid differentiation rate), clinical (blood indicators, other diseases, concomitant drugs), and radiological (radiological response of extracranial metastases) information that could have influenced the observed results were not accessible. Thirdly, the large observation period results in a numerical prevalence of systemic anti-angiogenic monotherapy treatments over ICIs or immune-based combinations, the present standard of care for mRCC. In particular, IT was the upfront systemic treatment after the BM diagnosis in only 15% ($n = 35$) of patients. Lastly, the patients received different drugs and therapeutic sequences.

As a whole, our results confirm some key clinical needs to improve BMRCC outcomes: (i) standardization of radiological organ-specific criteria for BM screening and monitoring, to avoid diagnostic delays and inappropriate treatment changes; (ii) specific randomized clinical trials for patients with stable/unstable BM that permit, in case of exclusively encephalic progression, the continuation of systemic treatment with the addition of ablative radiotherapy treatment, in order to evaluate the effective outcomes of multimodal strategies; (iii) implementation of SRS since it is easily applicable to multiple BM, highly effective, and better tolerated than WBRT due to reduced cognitive effects; (iv) integrated multidisciplinary teams to improve the therapeutic management of BM and lead to a reduction in mortality, as demonstrated for other oncological scenarios.

In conclusion, despite the above limitations, our results suggest a potential additive effect in terms of iPFS for eRT combined with IT and encourage a more intensive multimodal therapeutic strategy in a multidisciplinary context to improve survival of BMRCC patients. Our results may be a proof of concept for much needed prospective studies to confirm the suggested therapeutic strategy. Finally, as already happened for patients with bone metastases ,[38] the presence of BM proved not necessarily to be associated with a poor prognosis.

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DATA SHARING

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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