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Radiological response of leptomeningeal metastases according to revised RANO criteria is associated with overall survival in breast cancer patients

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Abstract

Assessment of treatment response in patients (pts) with leptomeningeal metastases (LM) represents a significant challenge and standardized criteria are needed. In 2017, the RANO LM Working Group proposed a standardized scorecard to evaluate MRI findings (further simplified in 2019). Here, we aim to validate the prognostic impact of response to treatment assessed using this tool in a multicentric cohort of breast cancer (BC) pts. Pts with BC-related LM diagnosed at two institutions between 2005 and 2018 were identified. Baseline and follow-up MRI scans were centrally reviewed and response assessment was evaluated using 2019 revised RANO LM criteria. A total of 142 pts with BC-related LM and available baseline brain MRI imaging were identified; 60 of them had at least one follow-up MRI. In this subgroup, median overall survival (OS) was 15.2 months (95%CI 9.5-21.0). At first re-evaluation, radiological response by RANO criteria was: complete response (CR) in 2 pts (3%), partial response (PR) in 12 (20%), stable disease (SD) in 33 (55%) and progression of disease (PD) in 13 (22%). Median OS was 31.1 months (HR 0.10, 95%CI 0.01-0.78) in pts with CR, 16.1 months (HR 0.41, 95%CI 0.17-0.97) in pts with PR, 17.9 months (HR 0.45, 95%CI 0.22-0.91) in pts with SD and 9.5 months in pts with PD ($P = .029$). A second blinded evaluation showed a moderate interobserver agreement ($K = 0.562$). Radiological response according to 2019 RANO criteria is significantly associated with OS in pts with BC-related LM, thus supporting the use of this evaluation tool both in trials and clinical practice.

Abbreviations: BC, breast cancer; CI, confidence interval; CR, complete response; CSF, cerebrospinal fluid; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hormone receptor; IHC, immunohistochemistry; LM, leptomeningeal metastases; OS, overall survival; PD, progressive disease; PR, partial response; RANO, response assessment in neuro-oncology; SD, stable disease.

Gaia Griguolo and Vittoria Aldegheri contributed equally as first author. Valentina Guarneri and Amelie Darlix contributed equally as last author.

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KEYWORDS

breast cancer, leptomeningeal metastases, radiological assessment, RANO

What's new?

Response assessment in cancer patients with leptomeningeal involvement is challenging and standardized evaluation tools are needed. Here, the authors evaluated the prognostic impact of response to treatment assessed using the 2019 revised Response Assessment in Neuro-oncology (RANO) leptomeningeal metastases criteria in a multi-center cohort of breast cancer patients with leptomeningeal metastases. The findings confirm that evaluation of radiological response using the RANO criteria is feasible in breast cancer patients and that radiological response is associated with overall survival. The study validates the RANO criteria and supports their use in future trials and clinical practice.

1 | INTRODUCTION

Leptomeningeal metastases (LM) represent a severe complication of cancer, diagnosed in approximately 5% to 10% of patients with metastatic disease. Among solid tumors, breast cancer (BC), lung cancer and melanoma represent the most common causes of LM.^{1,2}

The clinical management of patients with LM is challenging. First, the diagnosis of LM may be arduous and current guidelines recommend the combined use of neurological evaluation, neuroimaging with cerebrospinal MRI and cerebrospinal fluid (CSF) analysis for its diagnostic assessment.^{1,2} All of these three techniques have their specific strengths and weaknesses and should be used as complementary in clinical practice. Also, LM is generally associated with a dismal prognosis and limited therapeutic options are available in this setting.³ Generally, a multidisciplinary approach is recommended and potential treatment strategies include systemic therapy, radiotherapy and intrathecal treatment.²

Clinical trials aiming at improving survival of cancer patients diagnosed with LM are needed and nevertheless their conduction is complicated by heterogeneity in patient populations and limited prognosis. Moreover, neuroimaging evaluation and reevaluation of LM presents additional challenges as compared with evaluation of metastatic disease outside the central nervous system (CNS), such as the complex shape of the space being assessed and the dynamic nature of CSF flow. In this context, the availability of a validated tool to assess response to treatment of LM in clinical trials and in daily practice is essential.

To address this issue, the Response Assessment in Neuro-oncology (RANO) LM committee (LANO) first proposed a scorecard to rate MRI findings related to LM.⁴ However, a subsequent study aimed to assess the feasibility and inter-radiologist concordance in the use of this scorecard reported a great degree of discordance and variability. Therefore, a revised and simplified tool was proposed in 2019 and is currently used in clinical trials enrolling solid tumor patients with LM.^{5,6}

However, to date, the prognostic impact of radiological response to treatment evaluated according to these criteria has not been independently assessed in BC patients diagnosed with LM.

Therefore, we designed this study to validate the prognostic impact of radiological response of LM, assessed using the 2019 RANO criteria, in a multicentric cohort of BC patients diagnosed with LM.

2 | MATERIALS AND METHODS**2.1 | Patients**

Consecutive patients with BC-related LM diagnosed at Istituto Oncologico Veneto (Padova, Italy) and Montpellier Regional Cancer Institute (Montpellier, France) from 2005 and 2018 were identified.

Inclusion criteria were: histologically proven invasive BC, age > 18 years at the time of BC diagnosis, diagnosis of BC-related LM based on EANO-ESMO criteria (positive cytology performed on CSF or on the combination of clinical signs and typical neuroimaging findings),² and availability of baseline brain MRI imaging in DICOM format.

Patient demographics, Eastern Cooperative Oncology Group performance status (ECOG PS), primary tumor characteristics, dates of diagnosis of primary BC and LM, presence of extra-CNS and parenchymal BM at time of LM diagnosis, the techniques used for LM diagnosis, treatments received after LM diagnosis and follow-up data were collected from medical charts.

Hormone receptor (HR), estrogen and progesterone receptor, expression were determined by immunohistochemistry (IHC) on primary tumor sample and positivity was defined as IHC staining of at least 1% of tumor cells. HER2 status positivity was defined according to ASCO-CAP guidelines (IHC score 3+ or IHC score 2+ in presence of amplification of the HER2 gene by *in situ* hybridization).⁷

2.2 | MRI evaluation

Anonymized baseline and follow-up MRI scans were centrally reviewed by a dedicated radiologist with 8 years of experience (VA), who was blinded to patients' clinical history (including survival). Data regarding MRI patterns according to EANO-ESMO diagnostic criteria (linear, nodular or both), sites of LM (infratentorial, supratentorial, spinal or a combination of the previous), presence of hydrocephalus and parenchymal brain metastases were collected. Type of LM according to EANO-ESMO diagnostic criteria (Type I defined by positive CSF cytology, type II defined by typical clinical and MRI signs) was also recorded.²

For patients with evaluable follow-up MRI imaging, radiological response assessment on the first re-evaluation MRI after start of treatment for BC-related LM was centrally evaluated using the 2019 revised RANO LM response criteria.⁵ To assess interrater agreement for overall response assessment when applying the 2019 revised RANO LM response criteria, a second radiologist (AP, 8 years of experience), blinded to the first evaluation, reviewed all baseline and follow-up MRI scans for patients who had both available for central review and evaluated radiological response using the same criteria.⁵

2.3 | Statistical analysis

Clinicopathological characteristics were described using standard descriptive statistics. Associations between variables were evaluated using chi-square test, Fisher exact test and t-test.

Overall survival (OS) was calculated from date of baseline MRI and was estimated using the Kaplan-Meier method. Patients alive without event were censored at last follow-up.

For evaluation of prognostic factors, Hazard Ratio (HR) and 95% confidence interval (CI) were calculated using the Cox proportional hazard regression model. All p values were two-sided, with significance level set at $P < .05$.

The Kappa coefficient was used to assess the agreement for overall response assessed using the 2019 revised RANO LM response criteria between the two radiologists.

Statistical analysis was performed using IBM SPSS, version 25.

3 | RESULTS

3.1 | Clinical-radiological characteristics and prognostic factors: overall study cohort

From a comprehensive database of 225 consecutive patients diagnosed with BC-related LM, a total of 142 patients with a baseline brain MRI were identified and included in the present study (flow diagram, Figure 1).

Patient and tumor characteristics of the 142 included patients are summarized in Table 1.

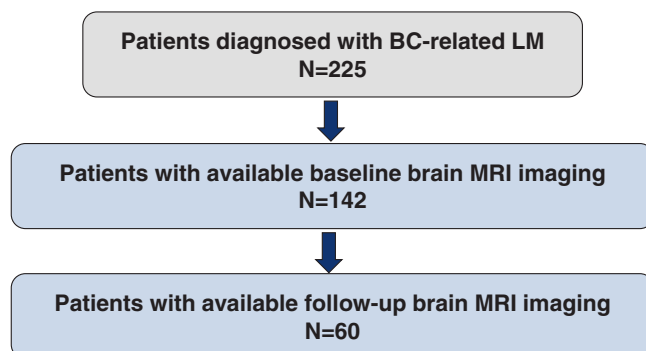


FIGURE 1 Flow diagram of patient selection.

Among the 142 patients included, 78 (54.9%) patients had a positive CSF cytology and were classified as type I LM according to EANO-ESMO classification; for 64 (45.1%) patients, CSF cytology was negative or not performed and leptomeningeal involvement was therefore classified as type II.

Treatment administered for BC-related LM was heterogeneous. The majority of the 142 patients included in the present study received at least one treatment modality, either local, systemic or both, whereas 16 patients (11.3%) were treated with best supportive care alone (of note, data regarding treatment after LM diagnosis were missing for one patient). Systemic treatment was the most frequently used therapeutic strategy, while intrathecal treatment (which included both chemotherapy and, for one patient, trastuzumab) was administered to 85 patients (61.2%). Around a quarter of patients ($N = 36$, 25.5%) received radiation therapy as treatment for LM, which included whole-brain radiotherapy in most cases ($N = 28$).

Radiological findings on baseline brain MRI imaging are described in Table 2. Most patients presented linear meningeal disease at MRI (type A, $N = 69$, 48.6%) or both linear and nodular disease (type C, $N = 60$, 42.2%), while only 13 patients (9.2%) presented a pure nodular disease (type B).

Among the 78 patients with a positive CSF cytology (type I), 41 were classified as type IA (linear), nine as type IB (nodular) and 28 as type IC (linear + nodular). Among patients with negative/not performed CSF cytology (type II), 28 were classified as type IIA (linear), four as type IIB (nodular) and 32 as type IIC (linear + nodular).

At time of LM diagnosis, concomitant brain metastases were identified in 55 patients (38.7%).

Spinal MRI imaging at diagnosis was only performed in a limited number of patients ($N = 28$, 19.7%).

At a median follow-up of 44.2 months (95% CI 31.2-57.1), 134 patients had died. Median OS from baseline MRI was 5.0 months (95% CI 3.4-6.7) and LM was the cause of death in most cases (85 patients among the 109 with available information, 78.0%). HER2 positivity, conserved ECOG performance status, absence of neurologic symptoms at LM diagnosis and absence of infratentorial brain LM were all significantly associated with a prolonged OS at univariate analysis, while the presence/absence of a positive CSF cytology did not impact survival (Table S1).

3.2 | Clinical-radiological characteristics and prognostic factors: patients with follow-up MRI

A total of 60 patients, out of 142 patients (42.3%), had an evaluable follow-up MRI imaging, with drop-off mainly due to deteriorating performance status or death. Clinicopathological characteristics and treatment received after the diagnosis of LM in patients with or without a follow-up MRI are reported in Table 1. The only significant difference between the two subgroups was tumor subtypes distribution, as a significantly higher rate of HER2+ tumors was observed among patients with follow-up MRI.

As might be expected, marked differences were observed between the two subgroups regarding treatments delivered after LM

TABLE 1 Patient and tumor characteristics at time of LM diagnosis in the overall study population, and in patients without and with follow-up MRI, respectively.

	Overall population (n = 142)	Patients with no follow-up MRI (n = 82)	Patients with follow-up MRI (n = 60)	P value*
	n (%)	n (%)	n (%)	
Median age at BC diagnosis (range)	51 (18-78)	51 (18-76)	48 (24-78)	.149
Median age at LM diagnosis (range)	60 (31-84)	61 (31-78)	58 (34-84)	.110
Tumor histology				
Ductal	98 (71.0)	55 (68.8)	43 (74.1)	.708
Lobular	30 (21.7)	18 (22.5)	12 (20.7)	
Other	10 (7.3)	7 (8.8)	3 (5.2)	
Histologic grade				
G1-G2	69 (55.6)	43 (60.6)	26 (49.1)	.212
G3	55 (44.4)	28 (39.4)	27 (50.9)	
Tumor phenotype				
HR+/HER2-	95 (67.4)	60 (74.1)	35 (58.3)	.048
HR-/HER2+	6 (4.2)	1 (1.2)	5 (8.3)	
HR+/HER2+	22 (15.6)	9 (11.1)	13 (21.7)	
TN	18 (12.8)	11 (13.6)	7 (11.7)	
ECOG PS				
0	10 (7.2)	2 (2.5)	8 (13.3)	.110
1	41 (29.5)	23 (28.7)	18 (30.0)	
2	51 (36.7)	30 (37.5)	22 (36.7)	
3	25 (18.0)	16 (20.0)	9 (15.0)	
4	12 (8.6)	9 (11.3)	3 (5.0)	
Symptoms at LM diagnosis				
Yes	122 (86.5)	74 (91.4)	48 (80.0)	.051
No	19 (13.5)	7 (8.6)	12 (20.0)	
CSF cytology				
Positive	78 (54.9)	42 (51.2)	36 (60.0)	.608
Negative	25 (17.6)	16 (19.5)	9 (15.0)	
Not performed	39 (27.5)	24 (29.3)	15 (25.0)	
Extra-CNS disease				
Present	126 (88.7)	72 (87.8)	54 (90.0)	.683
Absent	16 (11.3)	10 (12.2)	6 (10.0)	
Extra-CNS disease status				
Partial or complete response/ not evidence of disease	25 (17.6)	17 (20.7)	8 (13.3)	.132
Stable disease	42 (29.6)	19 (23.2)	23 (38.3)	
Progressive disease	74 (52.1)	45 (54.9)	29 (38.4)	
Missing	1 (0.07)	1 (1.2)	0 (0.0)	
Radiotherapy after LM diagnosis				
Yes	36 (25.5)	13 (16.0)	23 (38.3)	.003
No	105 (74.5)	68 (84.0)	37 (61.7)	
Intrathecal treatment after LM diagnosis				
Yes	85 (61.2)	48 (60.8)	37 (61.7)	.915
No	54 (38.8)	31 (39.2)	23 (38.3)	

TABLE 1 (Continued)

	Overall population (n = 142)	Patients with no follow-up MRI (n = 82)	Patients with follow-up MRI (n = 60)	P value*
	n (%)	n (%)	n (%)	
Systemic treatment after LM diagnosis				
Yes	103 (73.0)	49 (60.5)	54 (90.0)	<.001
No	38 (27.0)	32 (39.5)	6 (10.0)	
Chemotherapy after LM diagnosis				
Yes	79 (56.0)	36 (44.4)	43 (71.7)	.001
No	62 (44.0)	45 (55.6)	17 (28.3)	
Hormone therapy after LM diagnosis				
Yes	43 (30.5)	15 (18.5)	28 (46.7)	<.001
No	98 (69.5)	66 (81.5)	32 (53.3)	
Anti-HER2 therapy after LM diagnosis				
Yes	26 (18.4)	11 (13.6)	15 (25.0)	.084
No	115 (81.6)	70 (86.4)	45 (75.0)	

Note: *Follow-up MRI patient subgroup compared with no follow-up MRI patient subgroup.

Abbreviations: BC, breast cancer; CNS, central nervous system; CSF, cerebrospinal fluid; HR, hormone receptor; HER2, human epidermal growth receptor 2; LM, leptomeningeal metastases; TN, triple negative; ECOG PS, Eastern Cooperative Oncology Group performance status.

diagnosis, with a significantly higher rate of radiotherapy and systemic treatment administration among patients with a follow-up MRI.

Radiological features of LM in patients with or without a follow-up MRI are detailed in Table 2.

As expected, patients with follow-up MRI had a significantly longer OS than patients with no follow-up MRI (median OS 15.2 vs 2.1 months, respectively; $P < .001$, Figure S1), and LM was confirmed as the most frequent cause of death (65% of cases with available information) even in this subgroup of patients.

The associations between clinical features, treatment modalities and OS in the smaller subgroup of patients with follow-up MRI ($N = 60$) are reported in Table 3.

3.3 | Response evaluation

Radiological response to treatment according to 2019 RANO criteria was evaluated on the first available brain MRI re-evaluation ($N = 60$). Median time between baseline MRI imaging and re-evaluation MRI imaging was 2.86 months (IQR 2.07-4.16 months). At time of MRI re-evaluation, extracranial disease was progressing in 22 patients, stable in 28 patients, responding to treatment or absent in seven patients (data missing for three patients).

At time of first disease re-evaluation by brain MRI, radiological response according to RANO 2019 criteria was as follows: complete response (CR) for two patients, partial response (PR) for 12 patients, stable disease (SD) for 33 patients and progressive disease (PD) for 13 patients. Response assessment according to 2019 RANO criteria was significantly associated with OS: median OS was 31.1 months (HR 0.10, 95%CI 0.01-0.78) in patients with CR, 16.1 months (HR 0.41, 95%CI 0.17-0.97) in PR, 17.9 months (HR 0.45, 95%CI

0.22-0.91) in SD and 9.5 months in PD ($P = .029$, Figure 2). A similar prognostic impact of radiological response as evaluated by 2019 RANO criteria was observed after correcting for presence/absence of neurologic symptoms at LM diagnosis (the only clinical factor significantly associated with OS in this subgroup) at multivariate analysis. No significant association was observed between radiological response and main clinicopathological characteristics or treatment modalities (Table S2). Among the 13 patients with radiological progression of LM at first MRI re-evaluation, eight received further treatments including systemic therapies (seven patients) and intrathecal treatments (six patients).

When a second radiologist, blinded to the first evaluation, reviewed baseline and follow-up MRI scans for patients who had both available for central review the agreement for overall response assessment between the two evaluations was moderate (Kappa = 0.562, Table S3). Response assessment (according to 2019 RANO criteria) performed by the second reader showed very similar results in terms of OS observed for each response category (median OS 31.1 months for CR, 15.5 months for PR, 15.3 months for SD and 8.3 months for PD, respectively) and a significant survival trend across response categories was confirmed (log-rank p for linear trend across levels = 0.020). Nevertheless, it should be acknowledged that confidence intervals for OS estimates within the response categories as assessed by the second reader were generally wider and therefore, despite showing similar HRs for the comparison between each response category and the subgroup of patients showing progression of disease at first re-evaluation, only the comparison between the CR subgroup and the PD subgroup reached statistical significance ($P = .042$) (general log-rank p for categorical variable = 0.074; Supplementary Figure 2).

TABLE 2 Baseline brain MRI findings among overall population, patients without and with follow-up MRI, respectively.

	Overall population (n = 142)	Patients with no follow-up MRI (n = 82)	Patients with follow-up MRI (n = 60)	P value*
	n (%)	n (%)	n (%)	
Type of LM				
Linear (type A)	69 (48.6)	48 (58.5)	21 (35.0)	.020
Nodular (type B)	13 (9.2)	6 (7.3)	7 (11.7)	
Both (type C)	60 (42.2)	28 (34.2)	32 (53.3)	
Infratentorial LM				
Yes	73 (51.4)	44 (53.7)	29 (48.3)	.531
No	69 (48.6)	38 (46.3)	31 (51.7)	
Supratentorial LM				
Yes	122 (85.9)	70 (85.4)	52 (86.7)	.826
No	20 (14.1)	12 (14.6)	8 (13.3)	
Cranial nerve enhancement				
Yes	15 (10.6)	8 (9.8)	7 (11.7)	.714
No	127 (89.4)	74 (90.2)	53 (88.3)	
Brain hydrocephalus				
Yes	3 (2.1)	3 (3.7)	0 (0)	.263
No	139 (97.9)	79 (96.3)	60 (100.0)	
Parenchymal brain metastases				
Yes	55 (38.7)	31 (37.8)	24 (40.0)	.791
No	87 (61.3)	51 (62.2)	36 (60.0)	
Spine MRI findings				
Linear	17 (12.0)	10 (12.2)	7 (11.7)	.626
Nodular	0	0	0	
Both	5 (3.5)	3 (3.7)	2 (3.3)	
Negative	6 (4.2)	5 (6.1)	1 (1.7)	
Not performed	114 (80.3)	64 (78.0)	50 (83.3)	

Note: *Follow-up MRI compared with no follow-up MRI.

Abbreviation: LM, leptomeningeal metastases.

4 | DISCUSSION

LM represents one of the most challenging clinical scenarios in metastatic BC, with a generally dismal prognosis and very limited evidence to guide treatment decisions.

However, even in this complex context, significant efforts have been made over the last decades to conduct clinical trials specifically designed for patients diagnosed with BC-related LM^{8,9} and to define and validate neuroimaging response criteria able to accurately assess response to treatment of LM.^{4,5,10}

As recently argued, several points must be addressed before applying with success radiological criteria to LM response assessment, both in daily practice and in clinical trials.¹¹ First, inconsistencies and difficulties in MRI interpretation should be controlled through the implementation and validation of shared criteria, as already reported by the RANO Leptomeningeal Metastasis Group.^{4,5,10} Second, the assessment of radiological response should be clinically useful. Indeed, the clinical utility of radiological assessment remains limited if the

expected survival in a disease is short and OS represents therefore a more easily assessable and reliable endpoint for clinical trials.¹¹ However, we have recently reported that at least a subgroup of patients with BC-related LM can achieve a prolonged survival, exceeding 1 year from LM diagnosis, and might therefore be eligible for more than one line of systemic or local treatment.¹² This is consistent with results observed in recent clinical trials assessing tucatinib-containing regimens for the treatment of HER2-positive BC-related LM.⁸ In this context, accurately identifying responders from non-responders is pivotal, especially in clinical practice, to allow treating physicians to quickly modify treatment to a more effective approach. Last, but not least, the association between radiological response, as defined by validated criteria, and OS should be demonstrated.¹¹ The present study adds to this missing piece of information showing that evaluation of radiological response using the 2019 revised radiological RANO criteria in a multicentric cohort of patients treated for BC-related LM is not only feasible but is also significantly associated with OS. Patients who reached a disease control (CR, PR or SD) presented a longer median

TABLE 3 Prognostic impact of clinical and biological factors on overall survival in the subgroup of patients with a follow-up MRI in univariate analysis.

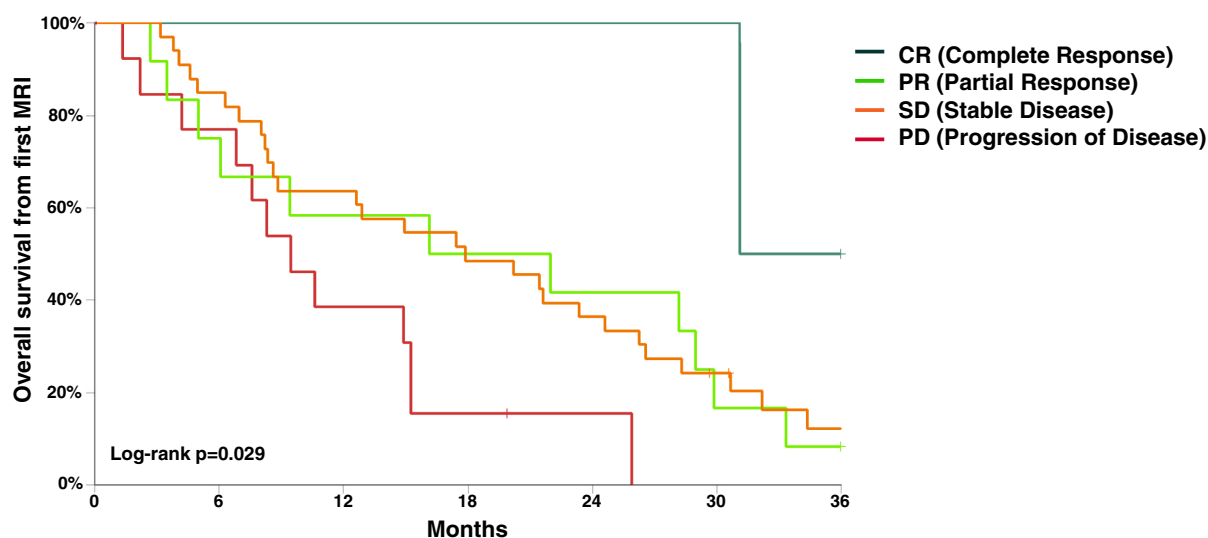
	Median OS, months (95% CI)	Univariate Cox Hazard ratio (95% CI)	P value
Tumor histology			
Ductal	17.9 (10.1-25.7)	0.83 (0.25-2.71)	.161
Lobular	8.6 (0.0-20.3)	1.58 (0.44-5.17)	
Other	14.9 (2.0-27.8)	Ref.	
HR status			
Positive	15.2 (11.9-18.6)	0.84 (0.43-1.63)	.598
Negative	10.6 (4.8-16.4)	Ref.	
HER2 status			
Negative	14.9 (7.3-22.6)	1.40 (0.78-2.5)	.260
Positive	15.2 (8.6-21.9)	Ref.	
ECOG PS			
0	8.3 (0.0-21.1)	0.58 (0.14-2.33)	.829
1	14.9 (4.6-25.2)	0.62 (0.18-2.18)	
2	16.1 (0.0-37.0)	0.76 (0.22-2.57)	
3	7.6 (0.0-15.3)	0.93 (0.25-3.47)	
4	15.2 (0.0-31.6)	Ref.	
Neurologic symptoms at LM diagnosis			
Yes	14.9 (8.7-21.2)	2.43 (1.10-5.36)	.024
No	17.4 (0.0-35.6)	Ref.	
CSF cytology			
Negative	8.6 (7.7-9.5)	0.71 (0.27-1.8)	.294
Positive	14.9 (6.5-23.4)	1.32 (0.71-2.49)	
Not performed	21.6 (12.7-30.5)	Ref.	
Extra-CNS disease			
Absent	9.4 (0.0-37.1)	1.18 (0.47-2.98)	.721
Present	15.2 (9.8-20.7)	Ref.	
Extra-CNS disease status			
Partial or complete response/ not evidence of disease	9.9 (1.1-18.7)	0.99 (0.43-2.28)	.884
Stable disease	15.2 (5.9-24.6)	0.87 (0.49-1.55)	
Progressive disease	14.9 (5.0-24.8)	Ref.	
Radiotherapy			
No	15.2 (9.0-21.5)	1.13 (0.65-1.96)	.652
Yes	14.9 (6.4-23.5)	Ref.	
Intrathecal treatment			
No	17.4 (6.0-28.9)	0.86 (0.50-1.49)	.585
Yes	15.2 (7.4-23.1)	Ref.	
Chemotherapy			
No	8.2 (4.0-12.4)	2.31 (1.28-4.18)	.004
Yes	21.5 (15.8-27.1)	Ref.	
Hormone therapy			
No	9.5 (3.9-15.1)	1.87 (1.07-3.26)	.025
Yes	25.9 (14.7-37.0)	Ref.	

(Continues)

TABLE 3 (Continued)

	Median OS, months (95% CI)	Univariate Cox Hazard ratio (95% CI)	P value
Anti-HER2 therapy			
No	15.2 (9.0-21.5)	1.46 (0.78-2.74)	.237
Yes	16.1 (0.8-31.4)	Ref.	

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; ECOG PS, Eastern Cooperative Oncology Group performance status, HER2, human epidermal growth receptor 2; HR, hormone receptor; LM, leptomeningeal metastases.



RANO LM criteria (2019) radiologic response	N pts	Median OS, months (95% CI)	Univariate Cox HR (95% CI)	p-value	Multivariate Cox HR (95% CI)*
Complete Response	2	31.1 (NE-NE)	0.10 (0.01-0.78)	0.028	0.12 (0.02-1.00)
Partial Response	12	16.1 (0-37.4)	0.41 (0.17-0.97)	0.043	0.48 (0.20-1.16)
Stable Disease	33	17.9 (8.3-27.5)	0.45 (0.22-0.91)	0.026	0.51 (0.25-1.04)
Progression of Disease	13	9.5 (5.9-13.1)	Ref	Ref	Ref

* Corrected by symptoms at LM diagnosis

FIGURE 2 Overall survival from first MRI according to RANO revised response score and Cox models for OS (univariate and multivariate).

OS (more than 1 year), while patients with an early progression at first re-evaluation MRI presented a significantly worse outcome. These results are particularly relevant considering the relative lack of evidence supporting the clinical management of patients affected by BC-related LM.

Moreover, one of the main limitations of the first RANO scorecard that the 2019 revised criteria tried to address was the lack of concordance between raters. To assess interobserver agreement, a second independent evaluation was performed, which confirmed a moderate degree of concordance between the two observers when using the 2019 revised radiological RANO criteria. These results are also in line with a validation study recently published by the RANO and EORTC Brain Tumor Group.¹³ In addition, we also observed that, despite the presence of an only moderate degree of concordance between the two readers, both median OS values and HRs for the

comparison between each response category vs the subgroup of patients showing progression of disease at first re-evaluation showed similar results between the two raters. Even if response assessment as evaluated by the second reader showed only a trend towards statistical significance, as might be expected taking into account the relatively small sample size, the general consistency between the results obtained by the two raters further support that the clinical value of the RANO response criteria is not relevantly affected by interobserver variability.

In addition, we also show that patients with LM represent a heterogeneous population, with various clinical behavior.^{3,13,14} In our study, patients were selected by the presence of a baseline MRI and this potentially led to the selection of a population with a better prognosis than previously reported (median OS 5.0 months). Moreover, patients subsequently selected based on the presence of a follow-up

MRI presented an even longer OS (median OS 15.2 months), thus highlighting the fact that this represents a positively selected subgroup of patients who have a sufficiently good prognosis to allow them to perform the re-evaluation.

In accordance with literature data, we also confirmed the prognostic impact of PS¹⁵⁻¹⁹ and HER2 status,²⁰ while a positive CSF was not confirmed as a negative prognostic factor in our population, despite what recently reported.¹³ In addition, in the selected cohort of patients with a follow-up MRI, the prognostic impact of treatment modalities was also evaluated, and we confirmed the prognostic impact of systemic chemotherapy¹⁷⁻²⁰ and hormone therapy.^{15,21}

The major limitation of the present study is represented by its retrospective nature. For this reason, only radiological data could be accurately collected and assessed, while neurological and CSF assessments were unfortunately not always available. Moreover, spinal MRI was not available for the majority of patients. In addition, it should be pointed out that a large number of patients with BC-related LM were not able to perform a re-evaluation MRI, thus limiting the applicability of our considerations to a relatively selected group of patients. Nevertheless, this study also presents several relevant strengths: a relatively large number of patients, compared with published case series, was included and a centralized revision of MRI imaging, blinded to clinical data, was performed, thus ensuring consistency in the radiological evaluation.

In conclusion, BC-related LM represents a heterogeneous disease and, despite its generally dismal prognosis, a selected subgroup of patients can achieve a prolonged OS. Response assessment in patients with LM is challenging, and standardized tools for its evaluation are needed. In our study, the 2019 RANO revised response score was associated with OS in patients with LM from BC performing a re-evaluation MRI, thus validating these criteria and supporting their use in both future clinical trials and clinical practice.

AUTHOR CONTRIBUTIONS

Study design: Gaia Griguolo, Maria Vittoria Dieci, Amelie Darlix and Valentina Guarneri. Acquisition of clinical data: Gaia Griguolo, Vittoria Aldegheri, Michele Bottosso, Francesca Caumo, Maria Cristina Guarascio, Stéphane Pouderoux, Fabio Busato, Federica Miglietta, William Jacot, Maria Vittoria Dieci, Amelie Darlix, Valentina Guarneri. Image analysis: Vittoria Aldegheri, Francesca Caumo, Alice Pittaro. Data analysis and interpretation: Gaia Griguolo, Maria Vittoria Dieci, Amelie Darlix. Manuscript drafting: Gaia Griguolo, Michele Bottosso. Manuscript revision: Maria Vittoria Dieci, Vittoria Aldegheri, Amelie Darlix, Valentina Guarneri. Final approval of manuscript: all authors. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

Gaia Griguolo reports fees from Eli Lilly, Novartis and Gilead, none related to the present study; Federica Miglietta reports fees from Roche, Gilead, Pfizer, Seagen, Novartis and travel support from Novartis and Gilead, none related to the present study; Maria Vittoria Dieci reports fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, MSD, Novartis, Pfizer, Seagen, none related to the present study; Valentina Guarneri reports fees from Amgen, Exact Sciences, Gilead, GSK, Eli Lilly, Merck Serono, MSD, Novartis, Pfizer, Sanofi, Olema Oncology, AstraZeneca and has a patent licensed to Reveal Genomics (HER2DX), none related to the present study. The remaining authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Anonymized personal data that support the findings of this study are available from the corresponding author upon request, pending on formalization of a Data Transfer Agreement and reinforcing the compliance with the EU privacy law. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The study was approved by the ethics committee of Istituto Oncologico Veneto and Montpellier Regional Cancer Institute and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from participants, where necessary according to local regulation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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