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Patients with colorectal cancer and brain metastasis: The relevance of extracranial metastatic patterns predicting time intervals to first occurrence of intracranial metastasis and survival

Johannes Thurmaier[1] | Volker Heinemann[2,3,4] | Jutta Engel[5,6] | Gabriele Schubert-Fritschle[5,6] | Max Wiedemann[5,6] | Natascha C. Nüssler[7] | Reinhard Ruppert[7] | Jörg Kleeff[8] | Wolfgang Schepp[9] | Florian Löhe[10] | Meinolf Karthaus[11] | Jens Neumann[4,12] | Jörg Kumbrink[4,12] | Francesco Taverna[12] | Arndt Stahler[2,4] | Kathrin Heinrich[2,3,4] | Christoph Benedikt Westphalen[2,3,4] | Julian W. Holch[2,3,4] | Thomas Kirchner[4,12] | Marlies Michl[2,3,4]

[1]Department of General Pediatrics, Ostschweizer Kinderspital, St. Gallen, Switzerland

[2]Department of Medicine III, University Hospital, LMU Munich, Munich, Germany

[3]Comprehensive Cancer Center, University Hospital, LMU Munich, Munich, Germany

[4]German Cancer Consortium (DKTK); German Cancer Research Centre (DKFZ), Heidelberg, Germany

[5]Munich Cancer Registry (MCR), Ludwig-Maximilians-University of Munich, Munich, Germany

[6]Institute of Medical Informatics, Biometry and Epidemiology (IBE), Ludwig-Maximilians-University of Munich, Germany

[7]Department of Surgery, München Klinik Neuperlach, Munich, Germany

[8]Department of Visceral, Vascular and Endocrine Surgery, Martin-Luther-University Halle-Wittenberg, Germany

[9]Department of Gastroenterology, Hepatology and Gastrointestinal Oncology, München Klinik Bogenhausen, Munich, Germany

[10]Department of Surgery, Klinikum Landshut, Landshut, Germany

[11]Department of Hematology, Oncology and Palliative Care, München Klinik Harlaching and Neuperlach, Munich, Germany

[12]Institute of Pathology, Ludwig-Maximilians-University of Munich, Germany

Correspondence
Marlies Michl, Department of Medicine III, Hematology and Medical Oncology, CCC—Comprehensive Cancer Center, University Hospital Grosshadern, Marchioninistr. 15, D 81377 Munich, Germany.
Email: marlies.michl@med.uni-muenchen.de

Abstract

The aim of the study was to investigate the predictive impact of extracranial metastatic patterns on course of disease and survival in patients with colorectal cancer (CRC) and brain metastasis (BM). A total of 228 patients (134 male [59%], 94 female [41%]) with histologically proven CRC and BM were classified into different groups according to extracranial metastatic patterns. Time intervals to metastatic events and survival times from initial CRC diagnosis, extracranial and intracranial metastasis were analyzed. Extracranial organs mostly affected were liver (102 of 228 [44.7%]) and

Abbreviations: BM, brain metastasis; CRC, colorectal cancer; EM, extracranial metastasis; MCR, Munich Cancer Registry; mCRC, metastatic colorectal cancer.

lung (96 of 228 [42.1%]). Liver and lung metastases were detected in 31 patients (13.6%). Calculated over the entire course of disease, patients with lung metastasis showed longer overall survival (OS) than patients with liver metastasis or patients without lung metastasis (43.9 vs 34.6 [P = .002] vs 35.0 months [P = .002]). From the date of initial CRC diagnosis, lung metastasis occurred later in CRC history than liver metastasis (24.3 vs 7.5 months). Once lung metastasis was diagnosed, BM occurred faster than in patients with liver metastasis (15.8 vs 26.0 months; Δ 10.2 months). Accordingly, OS from the diagnosis of liver metastasis was longer than from lung metastasis (27.1 vs 19.6 months [P = .08]). Once BM was present, patients with lung metastasis lived longer than patients with liver metastasis (3.8 vs 1.1 months [P = .028]). Shortest survival times in all survival categories analyzed revealed patients with concurrent liver and lung metastasis. Patients with CRC and BM form a heterogeneous cohort where extracranial metastasis to liver or lungs predicts survival.

KEYWORDS

brain metastasis, extracranial metastatic patterns, metastatic colorectal cancer

1 | INTRODUCTION

Colorectal metastasis to the brain is still a rare but clinically relevant event. In the literature, incidence rates of only 4% to 5% are reported but increasing numbers are witnessed in the last decades.[1,2] Optimized and individualized treatment strategies of the underlying colorectal primary and extracranial metastasis (EM) in the era of systemic-targeted therapies and radical metastatic surgery are cited, inter alia, as explanations for rising patient numbers with colorectal cancer (CRC) and brain metastasis (BM).[3] Accordingly, a detailed debate about this metastatic pattern is justified.

Once colorectal BM is diagnosed, survival ranges between 2 and 4 months apart from few exceptions and is remarkably short compared to other solid malignancies.[4,5] Indeed, neurosurgical and radiotherapeutic treatment approaches can achieve prolonged intracranial tumor control in selected patients.[6-9] However, the absence of routine cerebral imaging standards for mCRC patients at risk means that BM is diagnosed only when symptomatic and, thus, often at a late stage. Therefore, continuous efforts are warranted to identify risk factors for the prediction of BM in CRC.

On average, BM occurs 24 to 32 months after the first diagnosis of CRC,[4,9] but increasing time intervals between first CRC diagnosis and diagnosis of BM are observed also attributing this to constantly improving therapies.[10] The presence of lung metastasis as well as a (K) RAS mutation in the tumor tissue is described as independent predictive factors for BM in CRC patients.[11-14]

The majority of CRC patients develop BM when EM is already present. Thus, BM heralds the final metastatic step of colorectal disease.[4,9] Accordingly, the occurrence of EM following the diagnosis of BM seems to be nonexistent. Patient numbers with solitary BM are small and range in the one-digit percent area.[6,9] Extracranial metastasis appears in about 40% in one organ and in about 45% in two or more organs.[15] Organs most frequently involved are lung and liver.[6,9,16] However, little is known about extracranial metastatic patterns and their impact on survival in patients with CRC and BM.

What's new?

Brain metastases occur in around 5% of patients with colorectal cancer. These are generally not diagnosed until symptoms arise, and usually after other metastases have been found. Here, the authors evaluated patterns of metastases to the liver, lung, or both, looking for an association with survival. Brain metastasis occurs later in patients with lung metastasis than with liver metastasis, and overall survival is longer in patients with lung than with liver metastasis. This is the first analysis of metastasis patterns and survival in CRC patients, and the authors recommend routine cerebral imaging for CRC patients to detect brain metastases.

Thus, the present study aimed to analyze the extracranial metastatic patterns of patients with CRC and BM and intended to define prognostic subgroups for survival depending on the presence of liver or lung metastasis as most affected extracranial organs. To our knowledge, this is one of the largest studies analyzing patients with mCRC and BM up to date.

2 | MATERIALS AND METHODS

2.1 | Patient selection

All patients involved in the present analysis were identified via systematic database search in collaboration with the Munich Cancer

Registry (MCR). The MCR covers an estimated population of approximately 4.9 million inhabitants in southern part of Germany. Search items comprised "colorectal cancer" and "brain metastasis." Patients with a histologically proven diagnosis of CRC and the histological or radiological diagnosis of BM reported to the MCR between 1998 and 2011 were considered. Patients with secondary malignancies and nonadenocarcinoma histology of the colorectum were excluded (Figure 1). Detailed inclusion and exclusion criteria have been reported elsewhere.[4] Available patient and tumor characteristics as well as survival data were collected and form the base of the present analysis.

2.2 | Survival probabilities and statistical analyses

Survival probabilities were estimated using the Kaplan-Meier method, and differences in survival were calculated using the log-rank test on a significance level of 0.05 (two sided). Various overall survival (OS) times were analyzed and defined as OS-1 comprising survival from the time of initial diagnosis of CRC until death from any cause, as OS-2 implying survival from the time of diagnosis of metastatic disease until death from any cause and, as OS-3 encompassing survival from the time of diagnosis of BM until death from any cause.

A univariate analysis Cox proportional hazard model was used to evaluate the effect of independent variables on OS. Therefore, the hazard ratio (HR) and its 95% confidence interval (95% CI) are reported. Pearson's chi-square analysis was applied for comparison of categorical variables. Statistical analyses were performed using statistical software SPSS version 21 for Windows (SPSS Inc, Chicago, IL).

3 | RESULTS

3.1 | Patient and tumor characteristics

Overall, data from 228 patients (134 male [59%], 94 female [41%]) with metastatic CRC (mCRC) and BM were available for the present analysis (Figure 1). Baseline patient demographics and tumor characteristics of the analyzed patient cohort as well as OS times of the entire study population have been reported earlier by our study group.[4] Complementary baseline patients and tumor characteristics regarding extracranial metastatic patterns that form the core of the present publication are summarized in Table 1.

3.2 | Extracranial metastatic patterns in patients with CRC and BM

In 197 patients (86.4%), EM was present when BM occurred and 31 patients (13.6%) presented with solitary BM as the only metastatic site. The extracranial organ most frequently affected was the liver (102 patients out of 228 [44.7%], among them 63 [27.6%] with liver only metastasis), followed by the lung (96 patients out of 228 [42.1%], among them 55 [24.1%] with lung only metastasis) and the peritoneum (20 patients out of 228 [8.8%]). Thirty-one patients [13.6%] presented with liver and lung metastasis, 22 [9.6%] with liver and lung metastasis only (Table 1).

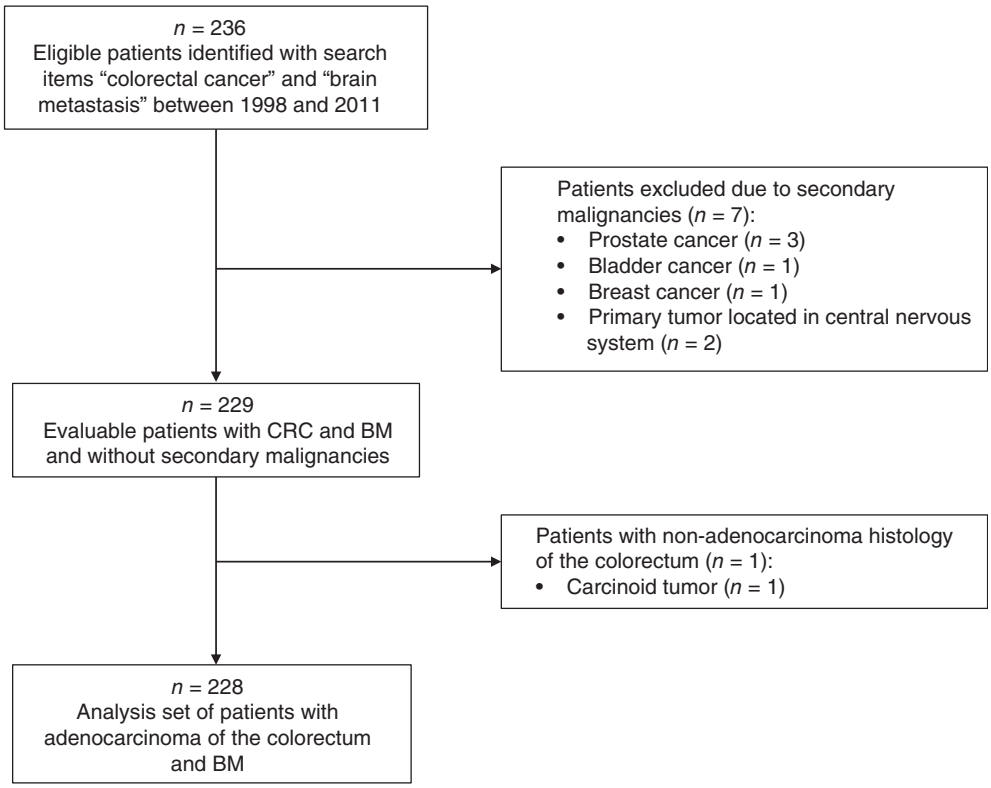

FIGURE 1 Consort diagram of the study population. BM, brain metastasis; CRC, colorectal cancer; N, number

3.3 | Association of extracranial metastatic patterns with primary tumor site and temporal occurrence of EM and BM

Table 2 demonstrates the different extracranial metastatic patterns with focus on patients with (a) liver metastasis, (b) lung metastasis and (c) liver and lung metastasis depending on primary tumor site and temporal occurrence of EM and BM. Primaries from the rectum more often developed lung than liver metastasis (46 [20.2%] vs 34 [14.9%]), whereas primaries from the colon were rather associated with the presence of liver than lung metastases (37 [16.2%] vs 19 [8.3%], global testing $P = .03$). The same number of patients with colon and rectum tumors presented with both liver and lung metastasis (15 [6.6%] and 16 [7.0%]). Patients with colon tumors more often showed synchronous EM, whereas patients with rectum tumors developed metachronous EM ($P = .009$). Regarding the impact of primary colorectal sidedness (left vs right colon) on extracranial metastatic patterns, comparable associations were observed although not reaching the level of significance ($P = .06$ for correlation with extracranial metastatic patterns and $P = .07$ for temporal occurrence of EM, data not shown). Furthermore, a larger number of lung metastasis evolved metachronously, whereas liver metastasis did synchronously ($P < .001$).

3.4 | Impact of extracranial metastatic patterns on survival

Extracranial organ involvement with focus on liver and lung was analyzed for prognostic value on survival and revealed significant effects (Table 3).

3.4.1 | Survival from initial diagnosis of CRC (OS-1)

Patients with lung metastasis showed a longer OS-1 than patients with liver metastasis and patients without lung metastasis (43.9 months vs 34.6 months [$P = .002$], vs 35.0 months [$P = .002$]) (Table 3, Figure 2). Liver metastasis was associated with a shorter OS-1 compared to nonhepatic organ involvement (34.6 months vs 39.8 months, $P = .015$). Among all groups, patients with concurrent liver and lung metastasis revealed the shortest OS-1 (15.4 months, $P < .001$).

3.4.2 | Survival from diagnosis of metastatic disease (OS-2)

From the date of first diagnosis of metastatic disease, patients with liver metastasis showed a longer survival than patients with lung metastasis or patients with nonhepatic metastasis (27.1 months vs 19.6 months [$P = .08$] vs 10.4 months [$P = .002$]) (Table 3; Figure 2). Again, among all groups, patients with concurrent liver and lung metastasis lived the shortest (10.4 months, $P = .015$).

TABLE 1 Baseline patient demographics and tumor characteristics of the analyzed patient cohort

Baseline patient and tumor characteristics (n = 228)	n	%
Primary tumor site		
Colon	102	44.7
Rectum	126	55.3
Right colon	49	21.5
Left colon	173	75.9
Multifocal primary tumor	5	2.2
Unknown	1	0.4
Extracranial metastasis occurrence		
Synchronous (referring to primary diagnosis colorectal cancer)	97	42.5
Metachronous	100	43.9
Brain metastasis occurrence		
Synchronous (referring to primary diagnosis colorectal cancer)	21	9.2
Metachronous	207	90.8
Metastatic pattern		
Extracranial metastasis + brain metastasis	197	86.4
Solitary brain metastasis	31	13.6
Extracranial metastatic sites		
Liver	102	44.7
Only liver	63	27.6
Liver + others[a] (without lung)	8	3.5
Lung	96	42.1
Only lung	55	24.1
Lung + others[b] (without liver)	10	4.4
Liver + lung	31	13.6
Only liver + lung	22	9.6
Liver + lung + others[c]	9	3.9
Peritoneum	20	8.8
Only peritoneum	13	5.7
Only bone	6	2.6
Only lymph node	3	1.3
Others[d]	8	3.5

[a]Others: Lymph node, peritoneum, bone and pancreas.
[b]Others: Lymph node, peritoneum, bone and adrenal gland.
[c]Others: Lymph node, peritoneum, bone, female adnexa and skin.
[d]Others (solitary or in combination): female adnexa, adrenal gland, urinary tract, adrenal cortex, heart, skin and kidney.

3.4.3 | Survival from diagnosis of BM (OS-3)

Once BM was diagnosed, patients with lung metastasis lived longer than patients with liver metastasis (3.8 months vs 1.1 months). Even if global testing did not reach the level of significance ($P = .115$), a head-to-head comparison revealed a significant survival advantage ($P = .028$) (Table 3; Figure 2).

TABLE 2 Extracranial metastatic patterns depending on primary tumor site and temporal occurrence of extracranial metastasis (EM) and brain metastasis (BM)

	Metastatic site								Total		
	Liver		Lung		Liver + lung		Others[a]				χ^2 test
	n	%	n	%	n	%	n	%	n	%	*P* value
Primary tumor site											
Colon	37	16.2	19	8.3	15	6.6	31	13.6	102	44.7	**.030**
Rectum	34	14.9	46	20.2	16	7.0	30	13.2	126	55.3	
Total	71	31.1	65	28.5	31	13.6	61	26.8	228	100.0	

	Synchronous vs metachronous EM[b]				Total		
	Synchronous EM		Metachronous EM				χ^2 test
	n	%	n	%	n	%	*P* value
Primary tumor site							
Colon	53	26.9	36	18.3	89	45.2	**.009**
Rectum	44	22.3	64	32.5	108	54.8	
Total	97	49.2	100	50.8	197	100.0	

	Metastatic site						Total		
	Lung		Liver		Liver + lung				χ^2 test
	n	%	n	%	n	%	n	%	*P* value
Metachronous EM[b]	53	31.7	21	12.6	9	5.4	83	49.7	**<.001**
Synchronous EM	12	7.2	50	29.9	22	13.2	84	50.3	
Total	65	38.9	71	42.5	31	18.6	167	100.0	

	Metastatic site						Total		
	Lung		Liver		Liver + lung				χ^2 test
	n	%	n	%	n	%	n	%	*P* value
Synchronous BM[b]	2	1.2	5	3.0	8	4.8	15	9.0	**.001**
Metachronous BM	63	37.7	66	39.5	23	13.8	152	91.0	
Total	65	38.9	71	42.5	31	18.6	167	100.0	

Note: The *P* values < .05 in bold.

Abbreviations: EM, extracranial metastasis; BM, brain metastasis; χ^2, Pearson's chi-squared test; n, number.

[a]Others: solitary brain metastasis (n = 31), lymph node, peritoneum, bone, female adnexa, skin, pancreas, kidney, adrenal gland, adrenal cortex, urinary tract and heart.

[b]Referring to primary diagnosis colorectal cancer.

3.5 | Temporal occurrence of extracranial metastasis

Based on the results depicted earlier, Figure 3 provides a graphical overview of the chronological occurrence of liver and lung metastasis in patients with mCRC and BM. On a visualized time scale, lung metastasis occurs 24.3 months after first CRC diagnosis (Figure 3) and thereby much later in CRC history than liver metastasis (7.5 months after primary diagnosis). Contrarily, the time interval between the diagnosis of EM and the occurrence of BM was shorter in patients with existent lung metastasis than in patients with existent liver metastasis (15.8 months vs 26.0 months). Nevertheless, counted from the date of first CRC diagnosis, BM appears later in patients with lung metastasis compared to patients with liver metastasis (40.1 months vs 33.5 months).

4 | DISCUSSION

Patients with CRC and BM constitute an unfathomed cohort. Here, we present a detailed description of extracranial metastatic patterns and temporal occurrence of EM in this selected patient group. Ultimately, we show that patients with CRC and BM form a heterogeneous cohort where EM to liver or lung can predict survival. For our analyses, we refer to one of the largest databases ever published containing 228 patients with CRC and BM that was set by our study group.[4]

Earlier we showed that in more than 85% of all CRC patients, EM is present when BM occurs and that no patient develops EM after the diagnosis of BM.[4] Several authors confirm these findings quoting percentages in the range of 77% to 95% for the presence of EM.[9,15,17] Thus, it might be fair to assume that apart from rare cases the majority

TABLE 3 Univariate cox proportional hazards modeling OS times for OS-1, OS-2 and OS-3 according to extracranial metastatic patterns

		OS-1			OS-2			OS-3		
Metastatic patterns	**N**	**Months (Δ)**	**HR (95% CI)**	**P**	**Months (Δ)**	**HR (95% CI)**	**P**	**Months (Δ)**	**HR (95% CI)**	**P**
Extracranial metastatic site										
Metastatic site (1)				**<.001**			**.002**			.115
Lung (reference)	65	43.9	– (–)	–	19.6	– (–)	–	3.8	– (–)	–
Liver	71	34.6 (9.3)	1.74 (1.23-2.47)	**.002**	27.1 (–7.5)	0.74 (0.53-1.04)	.08	1.1 (2.7)	1.46 (1.04-2.06)	**.028**
Liver + lung	31	15.4 (28.5)	2.87 (1.86-4.44)	**<.001**	10.4 (9.2)	1.71 (1.11-2.63)	**.015**	2.2 (1.6)	1.47 (0.95-2.26)	.083
No lung	132	35.0 (8.9)	1.62 (1.20-2.20)	**.002**	17.1 (2.5)	0.97 (0.72-1.31)	.849	1.5 (2.3)	1.35 (1.00-1.82)	.052
Metastatic site (2)				**<.001**			**<.001**			.082
Liver (reference)	71	34.6	– (–)	–	27.1	– (–)	–	1.1	– (–)	–
Liver + lung	31	15.4 (19.2)	1.65 (1.08-2.52)	**.021**	10.4 (16.7)	2.20 (1.43-3.38)	**<.001**	2.2 (–1.1)	1.01 (0.66-1.54)	.970
No liver	126	39.8 (–5.2)	0.69 (0.51-0.93)	**.015**	10.4 (16.7)	1.60 (1.19-2.14)	**.002**	2.6 (–1.5)	0.74 (0.55-0.99)	**.045**

Note: The *P* values < .05 are in bold. First indicated variable corresponds as reference. Time in median months.

Abbreviations: CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; N, number; OS, overall survival; OS-1, overall survival from time of first diagnosis of CRC; OS-2, overall survival from time of diagnosis of metastatic disease; OS-3, overall survival from time of diagnosis of brain metastasis; Δ, time difference between every categorial variable and reference variable in median months.

of CRC patients develops BM as last metastatic step in colorectal history.

Analyses on the temporal occurrence of lung and liver metastasis and their impact on survival formed the core of our investigations. We clearly demonstrate that in patients with CRC and BM lung metastasis develops considerably later in CRC history than in liver metastasis. However, once lung metastasis is present, BM occurs significantly faster than in patients with liver metastasis. Time interval from lung metastasis to BM was only 15.8 months and thus 10.2 months shorter than from liver to BM (Figure 3). Accordingly, OS from the diagnosis of lung metastasis was shorter than from the diagnosis of liver metastasis (19.6 months vs 27.1 months, Table 3, Figure 2).

In parallel, Chyun et al describe comparable results from 18 patients analyzed with CRC and BM where time intervals between lung and BM were also shorter than between liver metastasis and BM.[18] These results strengthen the assumption that lung metastasis compared to liver metastasis is a late event in CRC history with BM. Nevertheless, considering the entire course of the disease patients with lung metastasis still shows a longer OS calculated from the date of initial CRC diagnosis compared to patients with liver metastasis or patients without lung metastasis (43.9 months vs 34.6 months [*P* = .002] vs 35.0 months [*P* = .002]) (Table 3, Figure 2). Whether this effect results from extensive surgery and local treatment of metastasis or whether distinct underlying tumor biology determines disparate metastatic patterns remains unclear.

In a meta-analysis of 19 trials with more than 3800 mCRC patients, Koehne et al demonstrate a positive correlation between the presence of lung metastasis and survival, however, without special references to patients with BM.[19] Consequently, our analysis is the first to support the presence of lung metastasis as a negative predictive factor for the development of BM and as a positive prognostic factor for survival counted from initial CRC diagnosis in the selected group of patients with colorectal BM.

Once BM is present, survival times are concerningly short in all subgroups ranging from 1.1 months in patients with liver metastasis to 3.8 months in those with lung metastasis. Findings are in line with data from numerous other authors that report strikingly short survival times for patients with colorectal BM.[5,9,16] Finally, it may not seem surprising that patients with concurrent liver and lung metastasis show the shortest survival times in all survival categories from all groups analyzed.

The present study also revealed a significant correlation between primary tumor site and temporal occurrence of EM in the selected cohort of patients with CRC with BM. Primaries located in the rectum typically metastasized later (metachronously), whereas tumors from the colon more often set synchronous metastasis (*P* = .009). Furthermore, rectal primaries more frequently developed lung metastasis, whereas colon tumors commonly presented with liver metastasis (*P* = .03). In summary, lung metastases, compared to liver metastasis, occur more often in rectal tumors than in colon tumors and are associated with a metachronous metastatic pattern (*P* < .001). Accordingly, previous studies also depicted a higher incident rate of lung metastasis in rectal cancers.[12,20]

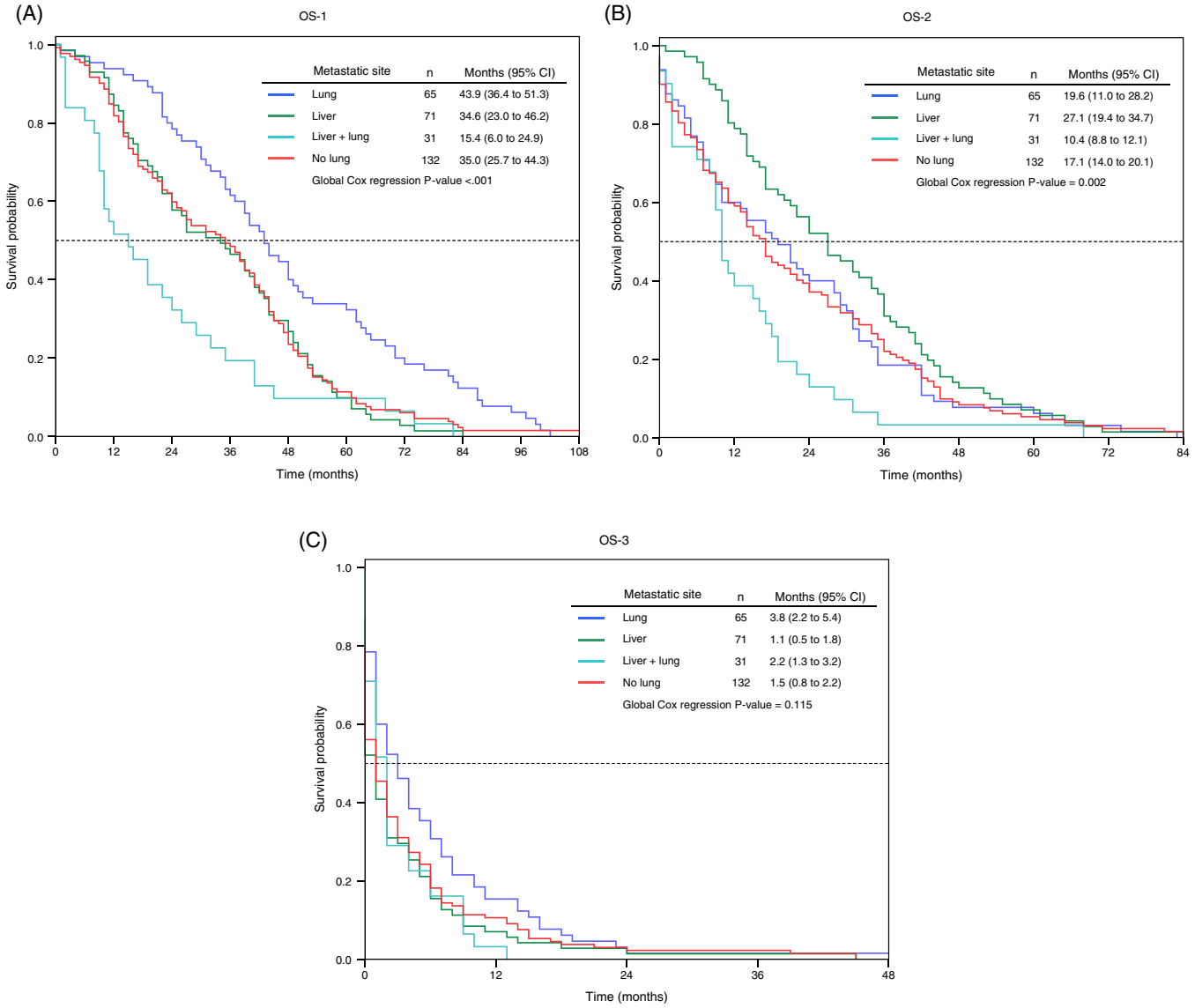

FIGURE 2 Kaplan-Meier survival curves for OS-1 (survival from initial diagnosis of CRC), OS-2 (survival from diagnosis of metastatic disease) and OS-3 (survival from diagnosis of BM) according to extracranial metastatic patterns. Definition of subgroups and patient numbers: "Lung" consists of "lung only" (n = 55) and "lung+others (without liver)" (n = 10); "Liver" consists of "liver only" (n = 63) and "liver+others (without lung)" (n = 8); "Liver+lung" consists of "liver+lung only" (n = 22) and "liver+lung+others" (n = 9); "no lung" consists of all metastatic localizations except lung metastasis. Definition of "others": lymph node, peritoneum, bone, female adnexa, skin, pancreas, kidney, adrenal gland, adrenal cortex, urinary tract, heart [Color figure can be viewed at wileyonlinelibrary.com]

In the study cohort, 42.1% and 44.7% of all patients presented with lung and liver metastasis, respectively, and thus at similar proportions. This finding is not necessarily in contrast to published data from other authors that report a higher incidence of lung metastasis when BM is diagnosed later on.[15,16,21] Our data originate from a cancer registry and the present study design is retrospective in nature, whereas other authors refer to epidemiologic longitudinal studies.[12,13] Indeed, the presence of lung metastasis is a known independent risk factor for the development of BM in CRC and does not contradict our data.[12,13]

The present analysis is certainly limited by several factors. The study design was explorative and data acquisition was carried out by interrogating a cancer registry between 1998 and 2011. As a consequence, collected data do not cover the current standard of care in mCRC patients. However, due to the rare occurrence of BM in CRC, prospective trials investigating such questions have not been conducted in the past and will presumably not be initiated in the future. Thus, only cancer registries or population-based epidemiological studies can and will further serve as data sources for such analyses. As an advantage of the investigated data set, patients were not highly selected based on specific interventions (eg, the ability to receive local treatment of BM) and hence should be representative for the entire cohort of patients with CRC and BM.

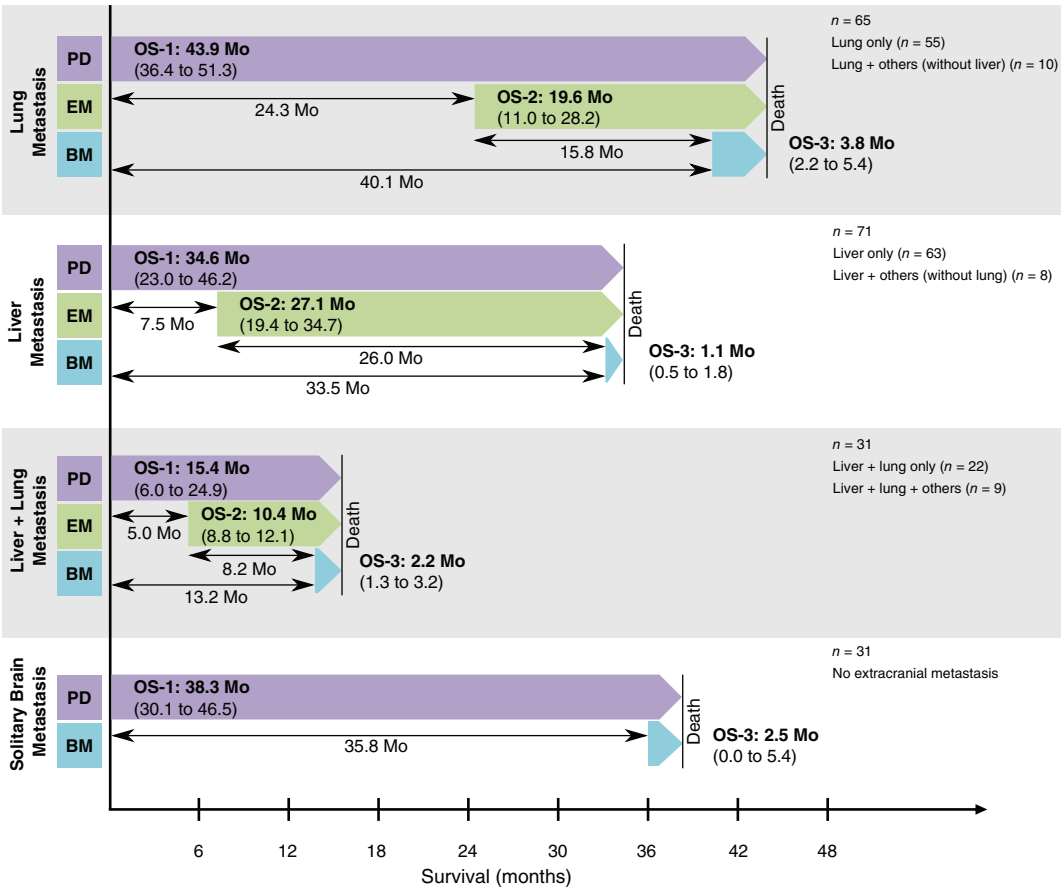

FIGURE 3 Chronological occurrence of extracranial metastasis of the analyzed patient cohort. BM, brain metastasis; EM, extracranial metastasis; OS, overall survival; OS-1, overall survival from time of first diagnosis of CRC; OS-2, overall survival from time of diagnosis of metastatic disease; OS-3, from time of diagnosis of brain metastasis; PD, primary tumor diagnosis. Mo, months; median 95% confidence interval of overall survival is indicated in () [Color figure can be viewed at wileyonlinelibrary.com]

With regard to clinical practice and based on the data presented here (Figure 3), we would like to initiate a debate on the establishment of cerebral imaging guidelines for CRC patients at risk. In concrete, performance of brain imaging on a 3-monthly basis in CRC patients with the diagnosis of (a) lung metastasis before 12 months and (b) liver metastasis before 24 months as well as for patients with (c) liver and lung metastasis could be a feasible way. Surely, this proposal for cerebral imaging guidelines has certain weaknesses. First, provided we follow this approach, BM occurring early in the course of the disease would be missed. Second, the majority of CRC patients presents with liver metastasis, and in this cohort, median OS exceeded 24 months in the latest randomized phase III trials. Thus, one point of criticism would be that a large number of mCRC patients with liver metastases would receive cerebral imaging, potentially overburdening imaging pathways in clinical practice. Third, it is still unknown whether early detection of colorectal BM followed by specific treatment changes prognosis. This should become a matter of further investigation in clinical trials, also including, for example, the question of the patient number needed to screen.

Nevertheless, a new approach to this topic is definitely justified and, the presented work is to initiate a long overdue discussion on if and when to screen mCRC patients for BM.

5 | CONCLUSION

To our knowledge, this is the first analysis that exclusively and elaborately explores the impact of extracranial metastatic patterns on survival in patients with CRC and BM focusing on involvement of the two pivotal organs lung and liver. Results originate from source data consisting of one of the largest patient populations with CRC and BM that was ever assembled. Time intervals before and survival times after the diagnosis of lung or liver metastasis differ significantly between groups and predict survival. Routine cerebral imaging should be integrated in CRC patients' care in compliance to their individual risk for BM according to EM. Further effort is desired to gain a deeper understanding why some mCRC patients develop BM and others do not.

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CONFLICTS OF INTEREST

JT, JE, GSF, MW, NCN, RR, JK, WS, FL, MK, JN, FT, KH and TK declare no conflict of interest. VH received honoria for talks, advisory boards and travel expensens by Merck, Amgen, Roche, Takeda, Servier, Pierre Fabre, Taiho, Lilly Oncology, Servier, Sanofi and Bayer Pharmaceuticals. AS received honoria for talks by Roche and reimbursement for travel by Roche, Amgen and MSD Sharp & Dohme. CBW received personal and speakers' fees, reimbursement for travel and accommodation and honoraria for participance in advisory boards from Bayer, Celgene, Ipsen, Rafael Pharmaceuticals, RedHill, Roche, Servier, Shire/Baxalta and Taiho and grant support by Roche. JK received honoraria and reimbursement for travel and accommodation for participance in advisory boards and from speaker's bureau from AstraZeneca, Novartis, Quality Initiative in Pathology (QuIP) and Roche. JWH served on advisory board for Roche, has received honoraria from Roche and travel support from Novartis. MM received honoraria for talks by SIRTeX, Roche and MSD and travel expenses by SIRTeX, Amgen and Merck.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study is available from the corresponding author, [MM], upon reasonable request.

ETHICS STATEMENT

The study was approved by the local ethical review committee (approval number 505-11) and was conducted according to the Declaration of Helsinki. Patients gave informed consent before acquisition of their data by the Munich Cancer Registry.

ORCID

Julian W. Holch https://orcid.org/0000-0002-4755-0179
Marlies Michl https://orcid.org/0000-0002-4198-3627

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