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ORIGINAL RESEARCH

Primary tumor side is associated with prognosis of colorectal cancer patients with brain metastases

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Background: Brain metastases (BM) are a rare complication in colorectal cancer (CRC) patients and associated with an unfavorable survival prognosis. Primary tumor side (PTS) was shown to act as a prognostic and predictive biomarker in several trials including metastatic CRC (mCRC) patients. Here, we aim to investigate whether PTS is also associated with the outcome of CRC patients with BM.

Methods: Patients treated for CRC BM between 1988 and 2017 at an academic care center were included. Right-sided CRC was defined as located in the appendix, cecum and ascending colon and left-sided CRC was defined as located in the descending colon, sigma and rectum.

Results: Two hundred and eighty-one CRC BM patients were available for this analysis with 239/281 patients (85.1%) presenting with a left-sided and 42/281 patients (14.9%) with a right-sided primary CRC. BM-free survival (BMFS) was significantly longer in left-sided compared with right-sided CRC patients (33 versus 20 months, $P = 0.009$). Overall survival from CRC diagnosis as well as from diagnosis of BM was significantly longer in patients with a left-sided primary (42 versus 25 months, $P = 0.002$ and 5 versus 4 months, $P = 0.005$, respectively). In a multivariate analysis including graded prognostic assessment, PTS remained significantly associated with prognosis after BM (hazard ratio 0.65; 95% confidence interval: 0.46-0.92 months, $P = 0.0016$).

Conclusions: PTS was associated with survival times after the rare event of BM development in CRC patients. Therefore, its prognostic value remains significant even thereafter.

Key words: colorectal cancer, brain metastases, primary tumor side, sidedness

INTRODUCTION

Recent data strongly support the biological heterogeneity of colorectal cancer (CRC), arguing that CRCs are actually several different diseases originating at the same location. In addition to molecular biomarkers such as KRAS, NRAS, BRAF, mismatch repair (MMR) deficiency and HER2, primary tumor side (PTS) of CRC has been recently described to act as a prognostic and predictive surrogate parameter in metastatic CRC (mCRC) patients. One-third of colorectal tumors are right-sided and originate from the embryonic midgut, whereas two-thirds are left-sided and derive from the embryonic hindgut.[1,2] Right-sided tumors are associated with a generally worse prognosis compared with left-sided colorectal tumors, as reflected by a higher incidence of mucinous, undifferentiated and signet-ring cell tumors and a usually more advanced stage of disease at initial diagnosis.[3-6] Significant underlying molecular differences could be identified, since right-sided tumors are highly immunogenic characterized by higher rates of MMR deficiency as well as BRAF mutations and exhibit a higher incidence of activated RAS and PIK3CA mutations.[7,8] Moreover, the microbial richness was shown to increase from the proximal to the distal colon.[9] In line with these differences in biological behavior, PTS was only recently incorporated in treatment guidelines as a predictive surrogate parameter for the selection of targeted therapies in the metastatic setting.[10] As observed in several retrospective analyses of phase II and III randomized trials, overall survival (OS) benefit with anti-epidermal growth factor receptor (EGFR) antibodies such as cetuximab and panitumumab was only evident in patients with left-sided RAS wild-type mCRC, whereas patients with right-sided RAS wild-type mCRC may rather benefit from anti-vascular endothelial growth factor receptor (VEGFR) antibodies such as bevacizumab.[11-16] So far, this

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impact might be especially relevant in metastatic disease, since studies of CRC patients with early stages suggested no significant outcome differences with regards to PTS.[17]

Only little is known about differences in metastatic behavior between patients with left-sided and right-sided CRC. Whereas liver and lung metastases are more often observed in left-sided CRC patients, peritoneal metastases may be more common in right-sided CRC. However, the incidence of brain metastases (BM) seems to be comparable, although evidence in this distinct patient population remains scarce due to the rare occurrence of BM in CRC patients.[17] Only 6% of BM patients present with gastrointestinal primaries most frequently located in the rectum and esophagus.[18] Small series so far suggested that BM from CRC are associated with a particularly poor prognosis between 3 and 11 months. Performance status was thereby shown to be significantly worse compared with other entities of primary tumors at BM diagnosis.[19,20]

Within this study, we aim to investigate the influence of PTS on the clinical course and prognosis in a uniquely large cohort of CRC BM patients.

MATERIAL AND METHODS

Patients

Overall, 323 patients treated between 1988 and 2017 for CRC BM at the Medical University of Vienna were identified from the Vienna Brain Metastasis Registry. Seven patients had to be excluded due to incomplete information regarding the clinical course of disease, 10 patients due to incomplete information regarding PTS and 12 patients due to diagnosis of a second primary tumor. Furthermore, 13 patients had to be excluded due to non-exact localization of the primary tumor in the transverse colon and the splenic flexure, respectively, to avoid a potential classification bias in terms of sidedness. Therefore, 281 patients were available for this retrospective analysis (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100168). If leptomeningeal carcinomatosis (LC) was present concomitantly to diagnosis of parenchymal BM, patients were also eligible for inclusion. Information relating to patient demographics, case history and survival were collected by retrospective chart review. This study was conducted in accordance with the Declaration of Helsinki and approval by the institutional review board (IRB) was obtained (ethics committee of the Medical University of Vienna, 1167/2019). All authors had access to the study data and reviewed and approved the final manuscript.

All patients were managed by a dedicated team of CRC BM specialists. Treatment decisions were taken in an interdisciplinary tumor conference. Treatment was carried out according to best clinical evidence and according to current standard of care.

Localization of primary tumor and classification of sidedness

Information about PTS was retrieved according to surgery protocols and histology reports. Patients with primaries in the transverse colon were excluded to avoid a potential classification bias in terms of tumor side allocation. Sidedness of the primary tumor was categorized according to recent international standards[11]: tumors of the appendix, cecum and ascending colon were categorized as right-sided and tumors of the descending colon, sigma and rectum as left-sided tumors (Figure 1).

Statistical analysis

For comparisons patients were grouped in two groups based on the PTS: left-sided and right-sided CRC. OS was defined as the interval from first diagnosis of CRC, diagnosis of mCRC and diagnosis of BM, respectively, until death or last date of follow-up and estimated with the Kaplan–Meier product limit method. To test for differences between two parameters, the chi-square test was used for binary variables and the Mann–Whitney *U* test for differences in mean ranks between two variables. To test for differences between OS curves, the log-rank test was used. BM-free survival (BMFS) was defined as the interval from diagnosis of CRC until diagnosis of BM. Two-tailed *P* values <0.05 were considered to indicate statistical significance. The association of PTS with OS from diagnosis of CRC BM was the main point of interest of the present study.

The graded prognostic assessment (GPA) including Karnofsky performance status (KPS) (<70, 70-89, 90-100), age (<50, 50-59, ≥ 60 years), extracranial metastases (present, absent) and number of BM (1, 2-3, >3) and the recently updated GPA for gastrointestinal cancers (GI-GPA), respectively, including KPS (<80, 80, 90-100), age (<60, ≥ 60 years), extracranial metastases (present, absent) and number of BM (1, 2-3, >3) are the best established prognosticators of outcome in CRC BM patients.[19] Therefore, we predefined *a priori* the inclusion of the PTS together with either the GPA or the GI-GPA into the multivariate model, depending on their significance in the univariate analysis. A multivariate analysis was carried out using the Cox regression model. Due to the exploratory and hypothesis-generating design of the present study, no adjustment for multiple testing was applied and no formal sample-size calculation was conducted.[21] All statistics were calculated using statistical package for the social sciences (SPSS®) 26.0 software (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

A total of 281 patients with CRC BM were available for this analysis. Median age at initial diagnosis of CRC was 61 years (range 33-89 years) and at diagnosis of CRC BM 65 years (range 34-89 years). Some 109/281 patients (38.8%) were female and 172/281 male (61.2%). A total of 92/281 patients (32.7%) had stage IV disease at initial diagnosis of CRC. The primary colorectal tumor was located in the left-sided colon in 239/281 patients (85.1%) including 11/281 patients (3.9%) with a primary in the descending colon, 66/281 patients (23.5%) with a primary in the sigma and 162/

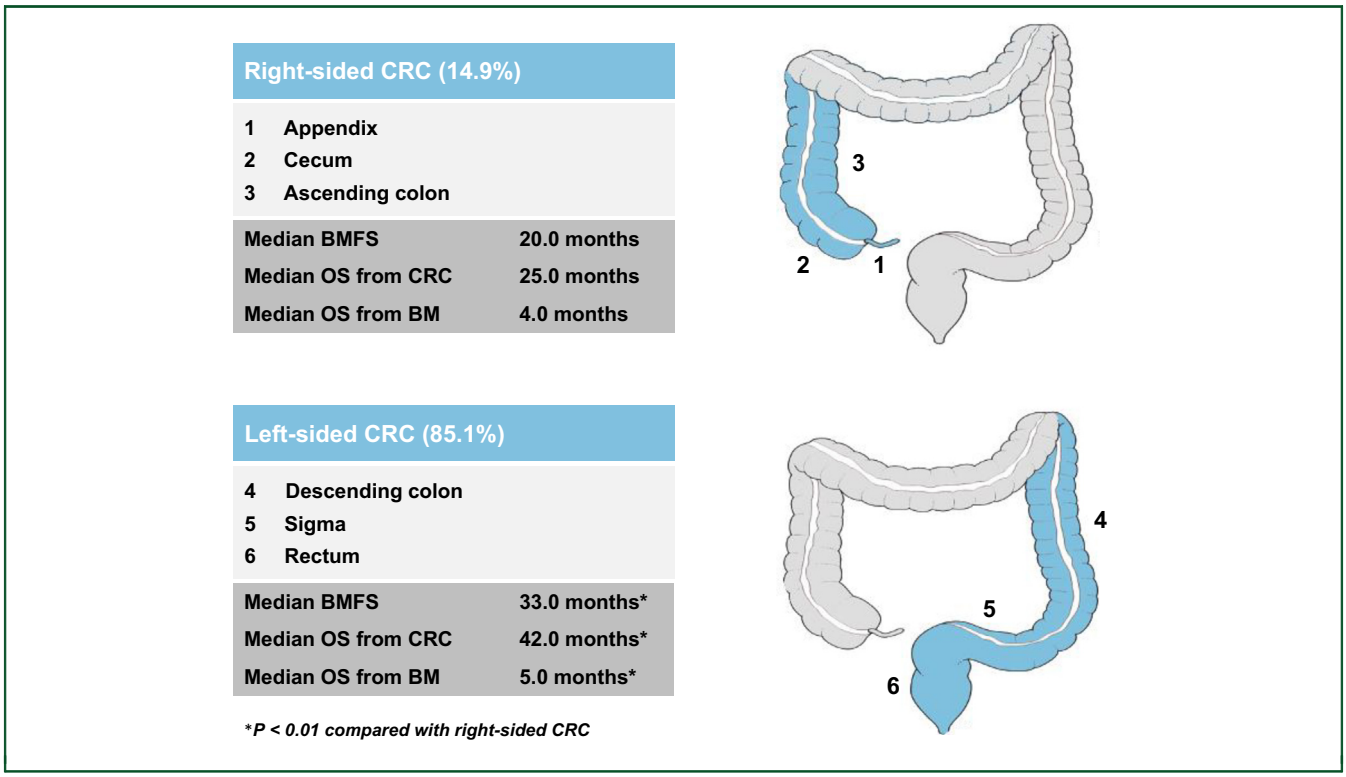

Figure 1. Graphical abstract of the study.
BM, brain metastases; BMFS, brain metastases-free survival; CRC, colorectal cancer; OS, overall survival.

281 patients (57.7%) with a primary in the rectum. A total of 42/281 patients (14.9%) presented with a right-sided tumor including 1/281 patients (0.4%) with a primary of the appendix, 15/281 patients (5.3%) with a primary of the cecum and 26/281 patients (9.3%) with a primary in the ascending colon (Figure 2). Median BMFS was 23 months (range 1-135 months) among the overall population. Median OS from diagnosis of the primary tumor was 40 months (range 0-182 months), from diagnosis of mCRC 22 months (range 0-143 months) and from diagnosis of CRC BM 5 months (range 0-76 months).

Association of PTS with clinical characteristics of CRC BM patients

Baseline characteristics were well balanced between left- and right-sided tumors. Median age at diagnosis of BM and median KPS were not statistically different between right-sided and left-sided CRC patients (64 versus 69 years and 70%; $P > 0.05$; Mann−Whitney U test). At diagnosis of BM, 55.2% with left-sided CRC and 56.8% patients with right-sided CRC presented with progressive extracranial disease ($P > 0.05$; chi-square test). Median number of BM at initial diagnosis of BM was one in left-sided as well as right-sided CRC patients ($P > 0.05$; Mann−Whitney U test). Incidence of concomitant LC diagnosis to solid BM was not significantly different between left- and right-sided CRC patients (2.9% versus 0%, $P > 0.05$; chi-square test) as well as incidence of intracranial recurrence after initial BM therapy (26.5% versus 42.3%, $P > 0.05$; chi-square test). Detailed patient characteristics according to PTS are listed in Table 1.

Association of PTS with survival times in CRC BM patients

Median OS from diagnosis of CRC BM according to the time period of initial CRC diagnosis was not significantly different between patients diagnosed before the year 2000, between 2000 and 2010 and after the year 2010 (5 versus 4 versus 4 months, $P > 0.05$; log-rank test). Median OS from BM diagnosis was numerically, but not significantly different between GI-GPA classes (4 months with class 1 versus 4 months with class 2 versus 5 months with class 3 versus 5 months with class 4, $P > 0.05$; log-rank test) (Figure 3A). Therefore, we also carried out survival analysis according to GPA classes, which was significantly associated with OS from diagnosis of BM (13 months with class 1 versus 13 months with class 2 versus 5 months with class 3 versus 4 months with class 4, $P = 0.004$; log-rank test) (Figure 3B). Patients with left-sided tumors had a significantly longer BMFS compared with patients with right-sided tumors (33 versus 20 months, $P = 0.009$; log-rank test) (Figure 3C). Median OS from first diagnosis of CRC was significantly longer in patients with left-sided tumors compared with right-sided tumors (42 versus 25 months, $P = 0.002$, log-rank test) (Figure 3D). Median OS from diagnosis of mCRC was not statistically different between left- and right-sided tumors (23 versus 21 months, $P > 0.05$; log-rank test) (Figure 3E). Median OS from diagnosis of BM was significantly longer in patients with left-sided tumors compared with right-sided tumors (5 versus 4 months, $P = 0.005$, log-rank test) (Figure 3F).

To evaluate the independent association of sidedness of the primary tumor on prognosis of CRC BM patients, we

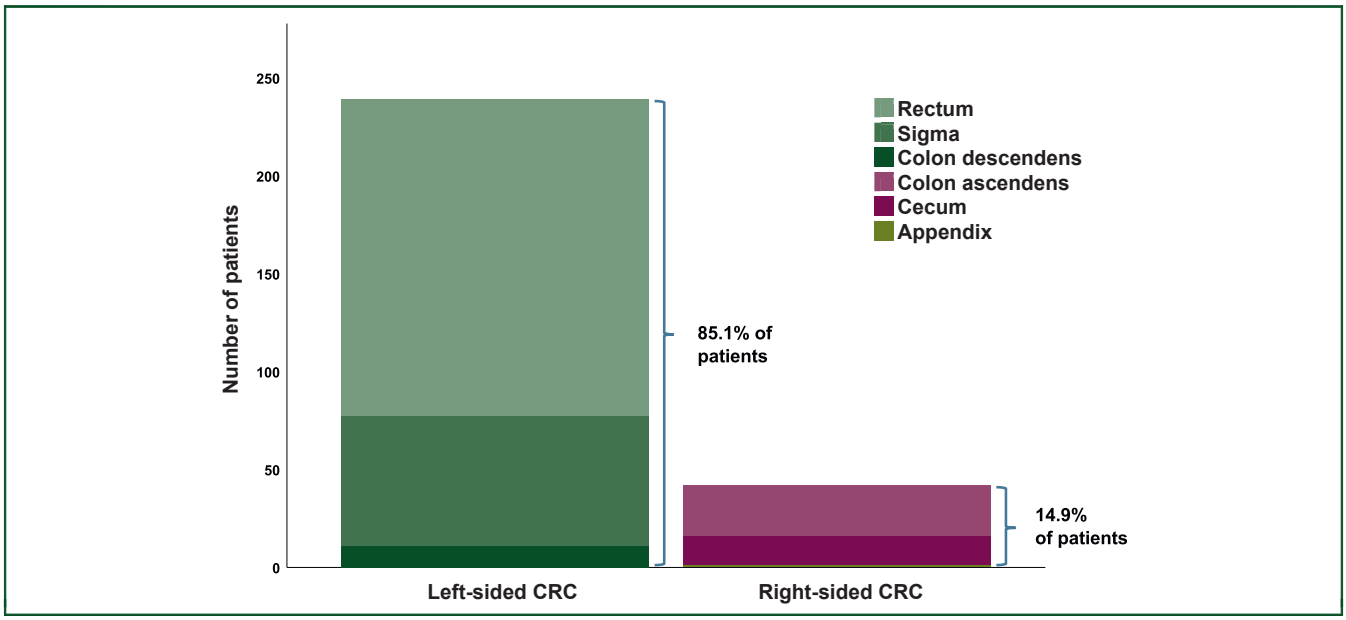

Figure 2. Bar diagram of contribution of patients according to primary tumor side (PTS).
CRC, colorectal cancer.

carried out a multivariate analysis including significantly associated parameters from univariate analyses: PTS and GPA. Within this analysis, GPA [hazard ratio 1.37 (95% confidence interval: 1.12-1.67; $P = 0.002$, Cox proportional hazards model)] as well as PTS [hazard ratio 0.65 (95% confidence interval: 0.46-0.92; $P = 0.016$, Cox proportional hazards model)] were shown to be independent prognosticators of OS (Table 2).

DISCUSSION

Sidedness of the primary tumor was significantly associated with the clinical course in the present series of CRC BM patients. Time from diagnosis of the primary tumor to BM development, as well as survival from BM diagnosis was significantly shorter in patients with a right-sided primary tumor than in patients with a left-sided primary tumor. The present observation suggests that the biological metastatic drivers differing between right- and left-sided CRC might even impact the disease course in the rare event of BM. Therefore, our data further support the theory that CRCs comprise several molecular diverse diseases with differing metastatic behavior originating in the same organ.

In the present cohort of CRC BM patients, left-sided primary was with 85.1% more frequently observed than right-sided primary tumor. This 4 : 1 side distribution is well in line with the one previously observed for mCRC without BM.[12,22,23] Therefore, as previously postulated in rather small series, PTS per se might not influence the development of BM.[24] Survival prognosis of CRC patients in our study was more than 1.5-fold better with a left-sided compared with a right-sided primary. An underlying reason, therefore, might display profound differences in molecular and biological characteristics as well as resulting targeted treatment approaches. Differences in embryological origins lead to distinct gene expression patterns with different methylation and mutation profiles, as well as distinctions in the microbiome of patients.[6,9,25] Recent next generation sequencing studies revealed higher rates of KRAS, NRAS, BRAF, PIK3CA, CTNNBI and SMAD mutations as well as CpG island methylator phenotype (CIMP) and MMR defects in right-sided CRC, whereas left-sided tumors presented more TP53 mutations.[26] Based on that, the consensus molecular subtypes (CMS) of CRC originally described in 2015 by Guinney et al.[27] and defined by gene-expression arrays had been analyzed with regards to prognostic relevance of PTS. Here, CMS2 indicating a rather favorable prognosis was more common in left-sided and CMS1 indicating a rather poor prognosis in right-sided tumors.[27,28] These differences in molecular profiles might impact the brain-specific metastatic behavior, resulting in an easier colonization of right-sided CRC cells in the brain parenchyma. Indeed, RAS mutant CRC was previously shown to present with a significantly higher cumulative incidence of lung, bone and brain metastasis.[29] Further, PIK3CA mutations were postulated to increase the brain metastatic behavior in breast cancer.[30] Preclinical and clinical data further support that PIK3CA inhibitors have clinical efficacy in BM.[31-33] Further, molecular research focusing specifically on molecular drivers could reveal targets for targeted treatment approaches.

Here, we were able to report a unique large cohort of CRC BM patients to gain further insight into the correlation of PTS and prognosis in the specific setting of BM.

Clearly, our study comprises some limitations, which have to be considered. First, due to the retrospective nature, our results need to be interpreted with caution. Second, unfortunately only limited information on the molecular profile of tumors was available, which would have been indeed of great interest to further investigate

Table 1. Patient characteristics according to primary tumor side (PTS)

Patient characteristics	Overall ptx population		ptx with LS CRC		ptx with RS CRC		*P* value
	n	%	*n*	%	*n*	%	
	281	100	239	85.1	42	14.9	
Sex							
Female	109	38.8	90	37.7	19	45.2	n.s.
Male	172	61.2	149	62.3	23	54.8	
Median age at diagnosis of CRC (years)	61		61		66		**0.024**
Range	33-89		33-89		38-79		
Stage IV at diagnosis of CRC							
Yes	92	34.1	76	33.0	16	40.0	n.s.
No	178	65.9	154	67.0	24	60.0	
Unknown			11 (3.9%)				
RAS mutation (KRAS or NRAS)							
Yes	39	79.6	33	76.7	6	100.0	n.s.
No	10	20.4	10	23.3	0	0.0	
Unknown			232 (82.6%)				
Visceral metastases before BM							
Yes	206	78	178	78.4	28	75.7	n.s.
No	58	22	49	21.6	9	24.3	
Unknown			17 (6.0%)				
Liver metastases before BM							
Yes	122	43.4	103	43.1	19	45.2	n.s.
No	142	50.5	125	52.3	17	40.5	
Unknown			17 (6.0%)				
Lung metastases before BM							
Yes	177	66.5	156	68.4	21	55.3	n.s.
No	89	33.5	72	31.6	17	44.7	
Unknown			15 (5.3%)				
Systemic disease at diagnosis of BM							
No evidence of extracranial disease and complete remission	43	16.1	36	15.7	7	18.9	n.s.
Partial remission	6	2.2	4	1.7	2	5.4	
Stable disease	70	26.2	63	27.4	7	18.9	
Progressive disease	126	47.2	110	47.8	16	43.2	
Synchronous diagnosis of CRC and BM	22	8.2	17	7.4	5	13.5	
Unknown			14 (5.0%)				
Progressive systemic disease at diagnosis of BM							
Yes	148	55.4	127	55.2	21	56.8	n.s.
No	119	44.6	103	44.8	16	43.2	
Unknown			14 (5.0%)				
Median age at diagnosis of BM (years)	65		64		69		n.s.
Range	34-89		34-89		39-81		
Median KPS at diagnosis of BM	70		70		70		n.s.
Range	20-100		20-100		40-100		
Median number of BM at initial BM diagnosis	1		1		1		n.s.
Range	1-3		1-8		1-5		
Concomitant LC at diagnosis of BM							
Yes	7	2.5	7	2.9	0	0	n.s.
No	274	97.5	232	97.1	42	100.0	
First line therapy for BM							
WBRT	41	14.9	36	15.5	5	11.9	n.s.
Stereotactic radiosurgery	118	42.9	98	42.1	20	47.6	
Resection	109	39.6	93	39.9	16	38.1	
Best supportive care	7	2.5	6	2.6	1	2.4	
Unknown			6 (2.1%)				
BM recurrence after initial therapy							
Yes	100	40.2	91	42.3	9	26.5	n.s.
No	149	59.8	124	57.7	25	73.5	
Unknown			32 (11.4%)				

BM, brain metastases; CRC, colorectal cancer; KPS, Karnofsky performance status; LC, leptomeningeal carcinomatosis; LS, left-sided; n.s., non-significant; ptx, patients; RS, right-sided; WBRT, whole brain radiotherapy.
Bold value indicates difference in age at diagnosis between right and left-sided CRC.

characteristics of PTS. Since the majority of patients (80%) were diagnosed and treated before the year 2014 when RAS testing was implemented into clinical routine, RAS status only was only available in a small patient subgroup. Despite small sample sizes, the proportion of RAS mutations in left-sided CRC within this study was distinctively pronounced compared with larger randomized trials representing a rather aggressive subgroup population. Nevertheless, right-sided CRC clearly was shown to be a negative prognosticator.

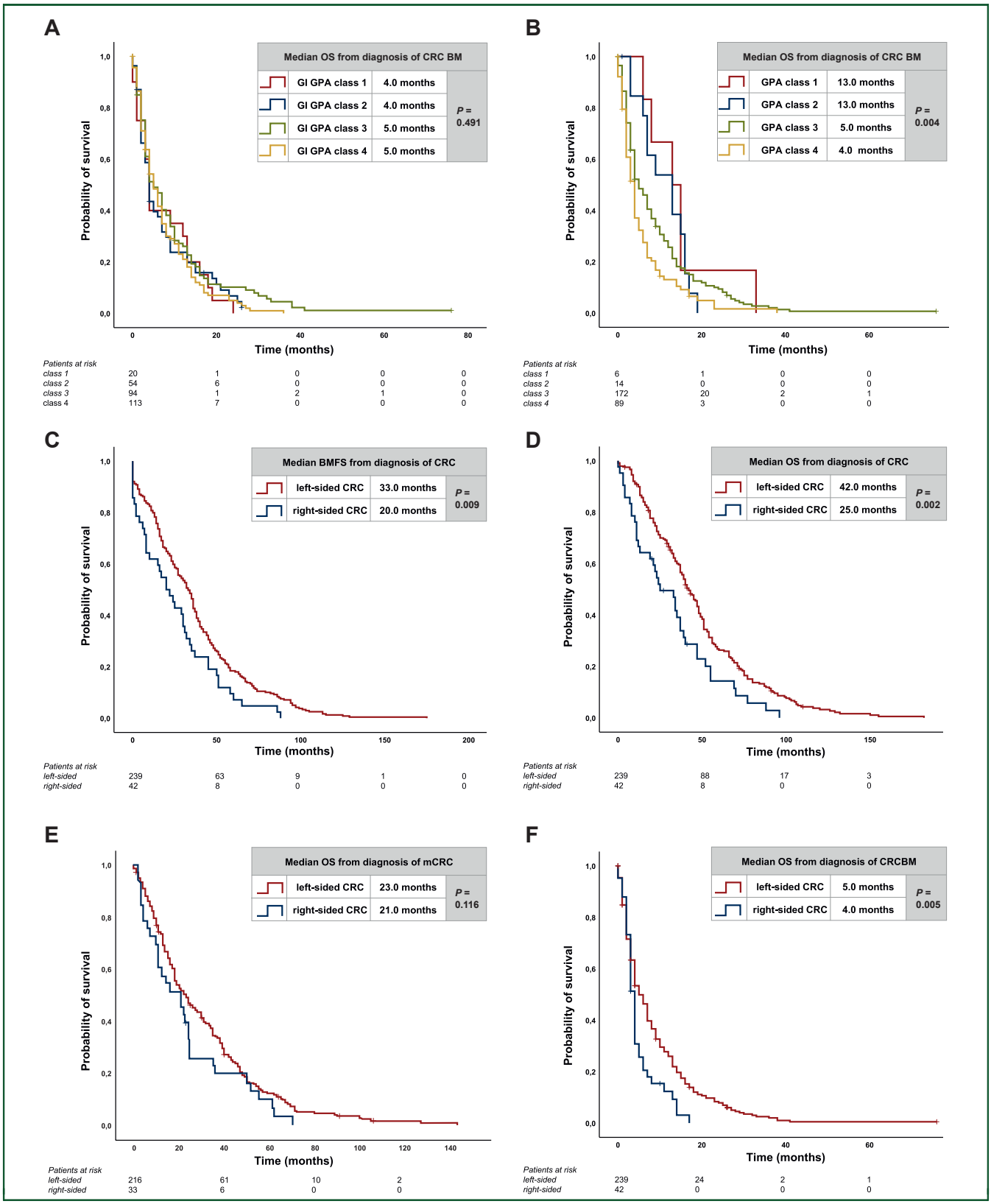

Figure 3. Kaplan–Meier estimates for (A) median OS after diagnosis of BM according to GI-GPA, (B) median OS after diagnosis of BM according to GPA, (C) median BMFS according to primary tumor side (PTS), (D) median OS from diagnosis of CRC according to PTS, (E) median OS from diagnosis of metastatic CRC (mCRC) according to PTS, (F) median OS from diagnosis of BM according to PTS.

BM, brain metastases; BMFS, brain metastases-free survival; CRC, colorectal cancer; GI-GPA, graded prognostic assessment of gastrointestinal cancer; GPA, graded prognostic assessment; OS, overall survival.

Table 2. Influence of primary tumor side (PTS) on overall survival (OS) after diagnosis of brain metastases (BM). Univariable and multivariable Cox proportional hazard models

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
PTS	0.628 (0.444-0.889)	**0.009**	0.651 (0.460-0.923)	**0.016**
GPA	1.389 (1.140-1.693)	**0.001**	1.370 (1.124-1.669)	**0.002**
GI-GPA	1.008 (0.883-1.152)	n.s.	—	—

CI, confidence interval; GI-GPA, graded prognostic assessment of gastrointestinal cancer; GPA, graded prognostic assessment; n.s., non-significant; PTS, primary tumor side.

We applied the standard prognostic assessment scores in our population including GPA as well as the disease-specific form of the GI-GPA. Only the GPA and not the later updated GI-GPA remained significantly associated with OS after BM diagnosis. A potential reason could be that only half of the patients of the validation study for the GI-GPA had a primary within the colon, while the rest presented mainly upper and other gastrointestinal primaries. CRC might therefore display a distinct subgroup of gastrointestinal malignancies. Moreover, the GPA distinguishes more precisely with regards to age and KPS compared with the GI-GPA, which may have allowed for a better discrimination of our patient population.

Conclusion

To our best knowledge, our study represents the largest single-center analysis of CRC BM patients to date. We could determine a clear association between PTS and BMFS as well as OS, since patients with right-sided CRC develop BM significantly earlier and exhibit a significantly impaired prognosis compared with left-sided CR CBM patients. Further investigation of the underlying molecular drivers is warranted to identify potential future treatment targets.

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None declared.

DISCLOSURE

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DATA SHARING

All data generated or analyzed during this study are included in this published article. Data, analytic methods and study materials will not be made available to other researchers. Individual participant data will not be shared.

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