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RESEARCH

The METACER national cohort study of brain metastases in gastrointestinal cancers prospectively establishes prognostic factors

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Abstract

Purpose Availability data are scarce and primarily retrospective in patients with brain metastasis (BM) from gastrointestinal (GI) cancers. The objective of this cohort was to determine prognostic factors for survival outcomes in patients with BM from GI cancers.

Methods METACER is a national multicentric prospective cohort study which included patients with BM diagnosis during a histologically proven digestive cancer follow-up between 2010 and 2014. The primary endpoint was overall survival (OS). The secondary endpoints were Progression-Free survival (PFS), prognostic factors, and BM-free survival as time from disease diagnosis to BM diagnosis.

Results METACER included 130 patients, with colorectal cancer (CRC) ($N=105$) and eso-gastric ($N=25$) cancer (EGC). The median OS was 6.6 months: 7.1 months (95%CI: 4.7–9.7) in CRC patients and 5.2 months, (95%CI: 1.9–7.6) in EG patients ($p=0.827$). In multivariate analysis, cerebral BM location (versus cerebellar), BM surgery, performance status (0–1 versus 2), and a unique BM were significantly associated with prolonged OS. BM-free survival were 30.8 months (95%CI:25.2–36.9) in CRC patients and 7.8 months (95%CI:3.8–13.6) in EGC patients ($p<0.001$). In synchronous metastatic disease, BM-free survival were 18.6 months (95%CI:13.1–25.2) in CRC patients and 3.7 months (95%CI:0.03–7.8) in EGC patients ($p<0.001$).

Conclusion BM in GI cancers are of poor prognosis. BM surgery should be considered in case of unique brain lesion. In metastatic settings, EGC patients have shorter BM-free survival than CRC patients.

Keywords Colorectal cancer · Gastric cancer · Esophageal cancer · Metastasis · Brain metastases

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Introduction

Gastrointestinal (GI) cancers are rarely associated with brain metastases (BM) at cancer diagnosis [1–3]. The exact numbers of GI cancer patients with BM are not well-known, and some of them do not include upper GI cancer patients [2–7]. For instance, the Maastricht tumour registry showed a BM incidence between 1986 and 1995 of 8.5% ($n = 720$ CRC) and a cumulative incidence over 5 years of 1.2% in CRC [4]. A prospective enrollment of patients with metastatic CRC between 2010 and 2019 showed a much higher BM incidence in the metastatic setting ($n = 25/171$; 14.9%) in the case of systematic brain imaging [5]. The recent advances in GI cancer management may account for this rare metastatic site increase [6], which might be underdiagnosed in the absence of systematic brain screening as a clinical routine.

Data available on BM from non-CRC GI primary tumours are scarce [8–10]. A review gathered 74 studies from 1980 to 2011, including 2583 GI cancer patients with one or more BM [8]. The primary tumour site was CRC in 79.9% of patients, liver in 9.2%, gastric in 5.8%, oesophageal in 4.6%, and pancreatic in 0.5% of patients. The most extensive series in gastro-esophageal adenocarcinoma retrospectively collected 68 cases between 2008 and 2020 [9]. Median OS after BM diagnosis remains poor in GI cancers, from 2.0 to 8.7 months in the literature [1, 2, 9, 10].

BM management depends on the primary tumour site, the number and size of lesions and localization, and disease prognosis [11]. For lung and breast primary tumours and melanomas, if feasible, the standard of care for resectable BM is surgery followed by radiotherapy or radiosurgery (curative intent radiotherapy alone) [11]. Despite the inclusion of GI cancer patients in BM dedicated trials, BM management is not standardized yet [12] and relies on multidisciplinary treatment based on retrospective series, mainly in CRC [13].

Several groups put efforts at retrospectively stratifying patients using biological [14–17] or clinical features [18–23]. Among them, number of brain lesions [18, 20, 21], performance status [18, 20, 22], surgical treatment [21, 22], or chemotherapy [18, 23] were associated with prolonged OS. The definition of prognostic factors is crucial for treatment decision-making in BM patients, especially for predicting the benefit of radiotherapy or surgery [24, 25]. Large-scale studies must enroll patients over an extensive time period, for instance, 1990–2013, to develop a robust LabBM score [15]. Therefore, there is a critical need for prospective data about GI cancer patients with BM. METACER is a French national cohort aiming to assess OS in patients with BM from GI cancers and identify prognostic factors.

Patients and methods

Patients

METACER is a French multicentric prospective study of BM from CRC and esogastric cancer (EGC) patients. Inclusion criteria were age above 18 years old, diagnosis of metachronous/synchronous BM either histologically proven or without alternative diagnosis on imaging and histologically-proven digestive primary tumours (colorectal, epidermoid esophageal carcinoma, oesogastric, biliopancreatic or vesicular adenocarcinoma, hepatocarcinoma, duodenum, jejunum, small intestine or appendicular adenocarcinoma, or anal canal carcinoma). Given the very few patients enrolled and the data quality, only patients with colorectal and esogastric primary tumours, for whom we complete data were available were included in the analysis.

Clinical data concerning both primary tumour and BM were collected prospectively in the 15 participating French centers. All patients signed informed consent prior to inclusion. The study was approved by the local ethics committee (*Comité de Protection des Personnes sud méditerranée III* en date du 07/04/2010 . N° ICM: 2010/Obs02) and was conducted in accordance with the ethical standard of the Helsinki Declaration.

Outcomes

The main objective was to determine prognostic factors associated with OS of patients with BM from GI cancers. The primary endpoint was overall survival (OS) defined as survival from primary tumour diagnosis to BM diagnosis. Secondary endpoints were OS according to the therapeutic strategy, prognostic factors of BM according to their origin (CRC or OG cancer); progression-free survival (PFS), defined as the time between the date of diagnosis of BM and the first event of progression (local or distant) defined by response evaluation criteria in solid tumours 1.1 (RECIST); BM-free survival defined as the time from cancer diagnosis to BM diagnosis; Stage 4 BM-free survival, defined as the time of from metastatic cancer diagnosis (in brain or any other site) to BM diagnosis; and BM-progression free survival, defined as the time from BM treatment to brain progression defined by RECIST.

Statistical considerations

Qualitative variables were presented for the overall population or by group: number of missing data, number and percentage for each modality of the variable. Quantitative data were presented for the overall population or by group: number of missing data, mean or median, standard deviation,

minimum and maximum. Comparisons between groups were made using the $\chi 2$ test or Fisher's exact test for qualitative variables, and the Student's t-test or Kruskal-Wallis test for quantitative variables.

On the hypothesis of estimating median OS, assuming a difference of one month, power of 90% and two-sided alpha risk of 5%, 127 patients were required. Survival data were estimated by the Kaplan-Meier method, presented as median and rate with their 95% confidence intervals (CI). Follow-up median was calculated using the reverse Kaplan-Meier method with its 95% CI. Event-free patients were censored at the date of the last visit.

Group differences were estimated using the logrank test. Cox regression models, employing a stepwise selection procedure, were applied to study prognostic factors for OS. Hazard ratios (HR) were presented with their 95% CI. Predefined variables included in the multivariate analysis of OS were BM localization (cerebral versus cerebellar), BM surgery, WHO performance status, number of BM sites, brain symptomatic treatment, type of non-brain metastasis, primary tumour location, adrenal gland metastasis.

All statistical tests were two-tailed, and the significance threshold is set at 5% ($p < 0.05$). Statistical analyses were performed on a PC using STATA 13.1 software (Stata Corporation, College Station, TX, USA).

Results

Patients' characteristics

Between 2010 and 2014, 130 patients with synchronous or metachronous brain metastases from gastrointestinal tumours were included in the study, either with CRC (105; 80.8%) or EGC (25; 19.2%) (Table 1). Among them, 84 (64.4%) were women, and the median age was 66.0 (28.0–92.0). A fraction of patients (21/130;16.2%) did not receive any chemotherapy before brain metastases diagnosis. Unfortunately, lines of chemotherapy were not completed enough to establish the number of lines of treatment before BM diagnosis. Most patients (125/130; 96.9%) presented with an adenocarcinoma, with well-differentiated tumours in 45 (37.5%) of cases. Patients had a T3 or T4 tumour status in 84 (87.5%) of cases, a T1 or T2 status in 12 (12.5%), and an unknown T status in 34 (26.2%) of cases; the N status was N0 in 26 patients (27.1%), N1 70 patients (72.9%), and unknown in 34 (26.2%) patients. At primary tumour diagnosis, 56 patients (48.7%) had a non-metastatic disease (M0), and 59 (51.3%) patients were metastatic (M1).

The metastastic localizations (excluding BM) at BM diagnosis were mainly lung (81/130; 68.1%), liver (68/130; 57.1%), and lymph modes (38/130; 31.9%). The other sites were bone (17/130; 14.3%), peritoneum (11/130; 9.2%), and adrenal glands (8/130; 6.7%) (Appendix Table A1). The number of metastatic sites was one in 46 (38.7%) patients, two in 45 (37.8%) patients, and three or more in 28 (23.5%) patients. The median time for non-BM occurrence from cancer diagnosis was 3.3 months (range 0; 107.7). OS was respectively of 12.8, 4.2, and 0.1 months if 1,2 or 3 metastatic sites were involved ($p = 0.147$).

Brain metastases characteristics and management

Neurologic symptoms revealed BM in 120 patients (81.6%) (Table 2). BM diagnosis was confirmed on computed tomography (CTscan) in 100 (77.5%) patients and/or magnetic resonance imaging (MRI) in 80 (62.5%) patients and exceptionally by positron emission tomography (PET-CT) in 6 (4.7%) patients. Histological confirmation was obtained in 11 (8.5%) patients, primarily by surgery (9/130; 81.8%). BM were cerebral in 58.6% of patients, cerebellar in 12.1% and both locations in 29.3% of patients. BM sites were unique in 43.0% of patients, two in 21.1%, and three or more in 35.9%. Brain metastases were in the frontal lobe (29.7%), parietal lobe (23.9%), temporal lobe (21.7%), or occipital lobe (21.0%). They were most often unilateral (63%). Biomarkers were performed: CEA in 77 (81.1%) patients and/or CA19-9 in 17 (17.9%) patients. Markers were above the upper limit in 70 (73.7%) patients (Appendix Table A2).

Most patients (106/130; 84.1%) received a treatment upon BM diagnosis (Table 3). Symptomatic therapy for BM symptoms was given to 106 (84.1%) of patients: corticoids in 100% of cases and Mannitol in 18.4%. A curative treatment was intended in 101 patients (77.7%), either surgery (24/130; 18.9%), among which 22 (95.7%) resections, or radiotherapy (33/130; 25.8%). Most patients treated with radiotherapy received whole-encephalic radiotherapy (70/130; 79.5%). The median dose was 30 Gy (range 8–30). Among treated patients, 39 had a brain progression during follow-up. Brain-progression free survival was 19.6 months, ($_{95}$CI:10.6–26.2) in CRC patients and non-achieved in EG patients ($p = 0.203$).

We further explored the impact of BM location on treatment access comparing patients with cerebral metastases with no cerebellar metastasis ($N = 73$) versus patients with cerebellar metastases ($N = 51$) (Appendix Table A3, $N = 124$ patients as BM location was missing for 6 patients). To increase power, all patients with a cerebellar lesion were included in the latter group, regardless of its association with ($N = 34$) or without ($N = 17$) a cerebral lesion,. The number of brain lesions was significantly higher in patients with cerebellar metastases group ($p = 0.0002$), with a high number of patients with 5 brain lesions or more (2.8% vs. 29.4%). Non-classical BM locations were also more

Table 1 Population and tumour characteristics

	CRC[a] $n=105$	OESO[b] $n=25$	TOTAL $n=130$
Patient Characteristics			
Age at BM[c]diagnosis			
Median (Range)	66.0 (37.0: 92.0)	63.0 (28.0: 83.0)	66.0 (28.0: 92.0)
<65/ ≥ 65[d]	42 (41.6%)/59 (58.4%)	15 (60.0%)/10 (40.0%)	57 (45.2%)/69 (54.8%)
Missing	4	0	4
Gender			
Male/Female	41 (39.0%)/64 (61.0%)	5 (20.0%)/20 (80.0%)	46 (35.4%)/84(64.6%)
Primary Tumour Characteristics			
Grade			
Well-differentiated	38 (38.8%)	7 (31.8%)	45 (37.5%)
Moderate	37 (37.8%)	7 (31.8%)	44 (36.7%)
poor or undifferentiated	6 (6.1%)	5 (20%)	11 (11.0%)
Undetermined	17 (17.3%)	3 (13.6%)	20 (16.7%)
Missing	7	3	10
Histology			
Adenocarcinoma	104 (99.0%)	21 (87.5%)	125 (96.9%)
Squamous cell carcinoma	0 (0.0%)	2 (8.3%)	2 (1.6%)
Undefined Carcinoma	1 (1.0%)	1 (4.2%)	2 (1.6%)
Missing	0	1	1
Primary Tumour Stage			
T1-T2/ T3-T4[e]	11 (12.6%)/76 (87.4%)	1 (11.1%)/8 (88.9%)	12 (12.5%)/84 (87.5%)
Missing	18	16	34
N-/ N+[f]	25 (29.1%)/61(70.9%)	1 (10.0%)/9 (90.0%)	26 (27.1%)/70 (72.9%)
Missing	19	15	34
M0/ M1[g]	50 (53.8%)/43 (46.2%)	6 (27.3%)/16 (72.7%)	56 (48.7%)/59 (51.3%)
Missing	12	3	15
Extra-cerebral Metastases			
No/ Yes	7 (6.7%)/98 (93.3%)	4 (16.0%)/21 (84.0%)	11 (8.5%)/119 (91.5%)
Diagnosis of extra-cerebral disease			
Synchronous/ Metachronous	50 (51.0%)/48 (49.0%)	15 (71.4%)/6 (28.6%)	65 (54.6%)/54 (45.4%)
Number of metastatic sites			
1/2	38 (38.8%)/37 (37.8%)	8 (38.1%)/8 (38.1%)	46 (38.7%)/45 (37.8%)
3 and more	23 (23.5%)	5 (23.8%)	28 (23.5%)

[a]colorectal cancer; [b]oeso-gastric cancer; [c]brain metastases; [d]below or above 65years old. [e]local tumour stage according to American Joint Committee on Cancer (AJCC) 6th Edition. [f]absence or presence of regional invaded lymph nodes. [g]absence or presence of metastases

frequent in those patients (11.3% vs. 56.9%, $p=0.0001$). The neurological symptoms leading to diagnosis (82.2% vs. 84.3%, $p=0.757$) were not increased in patients with cerebellar metastases. Accordingly, there was no difference in administration of symptomatic treatment (81.4% vs. 88.2%, $p=0.309$). There was a non-significant trend of a better WHO performance status (PS 0/1 = 51.5% vs. 40.0% and PS 2–4 = 48.5% vs. 60.0%) in patients with cerebellar metastases. The less frequent BM surgical treatment performed in patients with cerebellar metastases (24.3% vs. 11.8%) was not significant either and there was no difference in radiotherapy.

Survival and prognostic factors

The median overall survival was 6.6 months (95CI:4.5–8.3) (Fig. 1A.) in the whole population, 7.1 months ($_{95}$CI:4.47–9.72) in CRC patients, and 5.2 months ($_{95}$CI:1.97–7.55) in patients with EGC primary tumour (Fig. 1B.). The survival rate at six months, one, and two years were, respectively, 53% ($_{95}$CI:44–61), 30% ($_{95}$CI:22–38) and 13.6% ($_{95}$CI: 08–21; 2 patients).

In univariate analysis (Appendix Table A4 and A5), the Recursive Partitioning Analysis (RPA) prognostic classification, taking into account the patient's age (<65 years), the general status (Karnofsky > 70), and the absence of non-brain metastases, showed a non-significant trend for patients with higher scores, meaning worse condition. In multivariate analysis (Table 3), several prognostic factors were identified. BM location ($p=0.022$; $_{95}$CI:1.09–3.13), BM surgery ($p=0.013$; $_{95}$CI:0.29–0.90), WHO Performance status ($p=0.005$; $_{95}$CI:1.19–2.78), and the BM number ($p=0.021$; $_{95}$CI:0.30–0.90) were significantly correlated with OS. OS was significantly longer in patients with cerebral metastases

Table 2 Brain metastases diagnosis and treatment

	CRC[a] $n=105$	OESO[b] $n=25$	TOTAL $n=130$
Diagnosis			
Neurological Symptoms			
No/Yes	17 (16.2%)/88 (83.8%)	6 (24.0%)/ 19 (76.0%)	23 (17.7%)/ 107 (82.3%)
Histological confirmation			
No/Yes	94 (90.4%)/10 (9.6%)	24 (96.0%)/ 1 (4.0%)	118 (91.5%)/11 (8.5%)
Missing	1	0	1
Biopsy/ Surgery	2 (20.0%)/8 (80.0%)	0 (0.0%)/1 (100.0%)	2 (18.2%)/9 (81.8%)
Brain CT-scan[c]			
No/Yes	22 (21.2%)/82 (78.8%)	7 (28.0%)/18 (72.0%)	29 (22.5%)/100 (77.5%)
Missing	1	0	1
Cerebral MRI[d]			
No/Yes	37 (35.9%)/66 (64.1%)	11 (44.0%)/14 (56.0%)	48 (37.5%)/80 (62.5%)
Missing	2	0	2
PET-scanner[e]			
No/Yes	98 (94.2%)/6 (5.8%)	25 (100.0%)/0 (0.0%)	123 (95.3%)/6 (4.7%)
Missing	1	0	1
Treatment			
Symptomatic treatment			
No/Yes	17 (16.8%)/84 (83.2%)	3 (12.0%)/22 (88.0%)	20 (15.9%)/106 (84.1%)
Missing	4	0	4
-Steroids	84 (100.0%)	22 (100.0%)	106 (100.0%)
-Mannitol	15 (19.0%)	3 (15.8%)	18 (18.4%)
-Others	11 (14.3%)	0 (0.0%)	11 (11.5%0
Curative treatment			
No/Yes	23 (21.9.0%)/82 (78.1%)	6 (24.0%)/19 (76.0%)	29 (22.3%)/101 (77.7%)
Surgery			
No/Yes	79 (77.5%)/23 (22.5%)	24 (96.0%)/1 (4.0%)	103 (81.1%)/24 (18.9%)
Missing	3	0	3
Resection			
R0/R1[f]	21 (95.5%)/1 (4.5%)	1 (100.0%)/0 (0.0%)	22 (95.7%)/1 (4.3%)
Missing	1	0	1
Radiotherapy			
No/Yes	27 (26.2%)/76 (73.8%)	6 (24.0%)/19 (76.0%)	33 (25.8%)/95 (74.2%)
Missing	2	0	2
Stereotactic radiotherapy	20 (29.9%)	2 (12.5%)	22 (26.5%)
Whole-Brain radiotherapy	53 (76.8%)	17 (89.5%)	70 (79.5%)

[a]colorectal cancer; [b]oeso-gastric cancer; [c]computed tomography; [d]magnetic resonance imaging; [e]positron emission tomography; [f] microscopically margin-negative resection/microscopically margin-positive resection

(8.7 months, $_{95}$CI: 5.9–12.3) compared with patients with cerebellar metastases (4.6 months, $_{95}$CI:1.3–7.2) or both (3.7 months, $_{95}$CI:2.4–7.5). Patients who underwent BM surgery had a longer OS, 12.1 months ($_{95}$CI:7.2–18.0) versus 4.6 months ($_{95}$CI:3.6–7.2) in patients who did not undergo surgery for brain metastasis. A WHO performance status of 0 or 1 was associated with longer overall survival (8.4 months, $_{95}$CI:6.6–11.3) than a performance status of 2 (3.3 months, $_{95}$CI:2.4–5.9).

Factors associated with brain metastasis occurence

The median BM-free survival was 25.9 months ($_{95}$CI:21.4–31.2) (Fig. 2A.) in the whole population and 27.6, 19.6, and 26.8 months in patients with 1, 2, and 3 or more metastatic sites, respectively ($p=0.188$). In CRC patients, the BM-free survival was 30.8 months ($_{95}$CI:25.1–36.9). There was no significant difference in the RAS status, which was assessable in 66 patients. In EGC patients, the BM-free survival was 7.8 months ($_{95}$CI: 3.8–13.6).

The Stage 4 BM-free survival (Fig. 2B.) for the whole population was 14.7 months ($_{95}$CI: 7.8–19.6). It was 18.6 months (95CI: 13.1–25.2) in CRC patients and 3.7 months ($_{95}$CI: 0.03–7.8) in EGC patients ($p=0.001$). In univariate analysis, the presence of lung metastases ($p=0.027$ in CRC and $p=0.001$ in EGC), a low number of the non-BM sites involved ($p<0.0001$ in CRC and $p=0.004$ in EGC), surgery of the primary tumour ($p<0.0001$ in CRC, nonsignificant in

Table 3 Multivariate analysis of significant variables in univariate analysis associated with overall survival

	Hazard Ratio	*p*	$_{95}$CI[a]
BM[b] Location			
Cerebral	1	0.022	1.09–3.13
Cerebellar	1.85		
Number of BM site			
1	1	0.021	0.30–0.90
2 and more	0.52		
Adrenal gland metastases			
No	1	0.053	0.99–5.61
Yes	2.36		
Surgery			
No	1	0.021	0.29–0.90
Yes	0.51		
Performance status			
ECOG[c] 0–1	1	0.005	1.20–2.78
ECOG 2	1.83		
Primary Tumour			
CRC[d]	1	0.195	0.35–1.24
OESO[e]	0.66		

[a]Confidence Interval; [b]Brain Metastases; [c]Eastern Cooperative Oncology Group; [d]colorectal cancer; [e]oeso-gastric cancer;

EGC), and well-differentiated tumour ($p=0.016$ in CRC, nonsignificant in EGC) were associated with longer stage 4 BM-free survival.

Discussion

METACER prospectively confirmed a poor OS of 6.6 months for GI-cancer patients with BM. Patients with T3-T4 tumours (65.5%) and lung metastases (68.1%) were over-represented. Cerebral metastases, BM surgery, 0–1 WHO Performance status, and a unique BM were prognostic factors associated with prolonged OS. As cerebral CT scans are not performed systematically in the follow-up of GI-cancer patients, most of the patients had neurologic symptoms at BM diagnosis. Asymptomatic BM are reported as the majority of BM (79%) diagnosed upon screening for clinical trials in metastatic CRC [5].

As for BM management, 22.3% of METACER patients were not considered for treatment, likely due to poor condition. Among those achieving treatment, less than 20% had access to surgery, which, when performed, resulted in R0 resection in more than 95% of cases. Other patients received whole-brain radiotherapy (79.5%) and/or stereotactic radiotherapy (26.5%). The Vienna Registry showed that stereotactic radio-surgery (SRS) had already spread by 2010 [2] and it was reported in a series of patients with BM from CRC in 2011 [13]. However, its use in an adjuvant setting was validated in 2017 [26] which may account for the low rate of SRS in METACER. SRS delivers a higher dose on lesions and allows repeated treatment while maintaining a good quality of life [27]. Nowadays, surgery is frequently combined with SRS, broadening the number of BM locations accessible to treatment. Systematic imaging in late metastatic GI-cancer settings might be considered to improve patient access to multimodal treatment and improve their survival. We expect that the DEMECIA study (NCT03694938), which includes all metastatic CRC patients within six months from the disease diagnosis and performs cerebral MRI yearly, will prospectively evaluate the impact of a systematic cerebral imaging and early BM treatment on quality of life in metastatic CRC patients.

In the European Association of Neuro-Oncology - European Society of Medical Oncology (EANO-ESMO) guidelines [11], prognostic factors are crucial in BM management decision-making. Most prognostic factors are determined based on retrospective studies. METACER confirms good performance status as a significant prognostic factor. As far as the number of BM is concerned, METACER shows that a unique location is of better prognosis, as suggested in a meta-analysis [28]. As the literature is contradictory about the impact of *KRAS* status in retrospective series [7, 22], *KRAS* status was collected in METACER and was not associated with OS in this prospective cohort. BM location appeared as an independent prognostic factor with shorter OS in case of cerebellar lesions. Patients with cerebellar metastases had a non-significant poor WHO performance status and less surgical treatment. Instead, they displayed significantly more numerous brain lesions, and non-classical brain locations, which parameters are therefore more prone to explain the poor prognosis of patients with cerebellar BM. In this study, non-classical brain locations meant non frontal nor parietal, temporal or occipital. Data collection did not allow further description but suggests these atypical locations may be overlapping not only with cerebellum but also brainstem and midline brain lesions, which are hardly accessible to surgical treatment. In contrast to another study in breast cancer [29], no increase in neurological symptoms were observed in patients with cerebellar metastases. However, this BM location remained an independent prognostic factor in the multivariate model, which included also WHO PS and the number of BM locations. This result suggests that the over-representation of non-classical BM locations in patients with cerebellar metastases may explain their poor prognosis. As these are subgroups analyses, these data may be underpowered, therefore, must be interpreted with caution.

This study has several limits. First, the molecular profile of the GI primary tumour was incompletely collected. Especially, HER2 status was not collected whereas it now appears as enriched in EGC cancer patients with BM in the available retrospective studies [10]. This limit is linked to the date this cohort was designed and conducted. However,

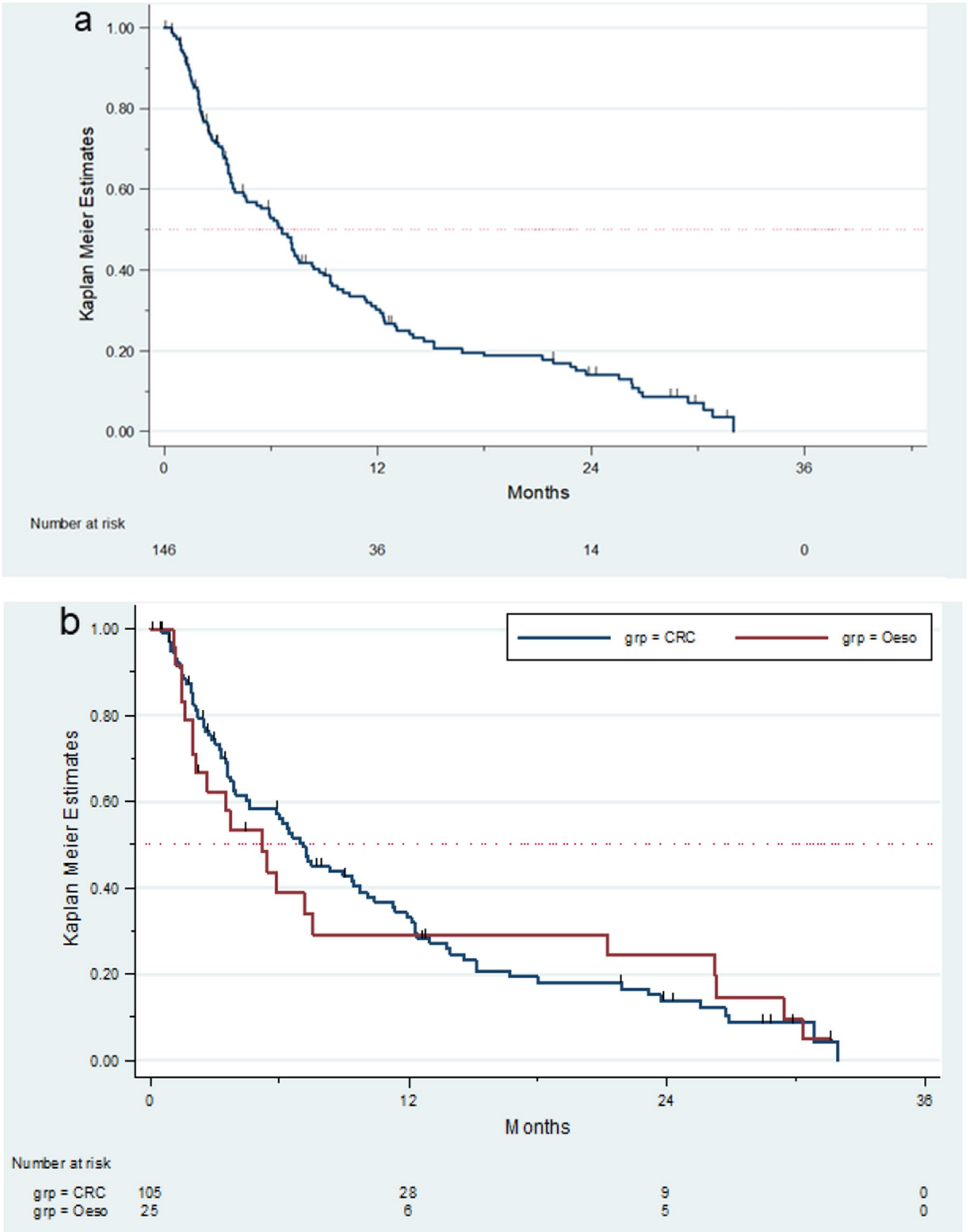
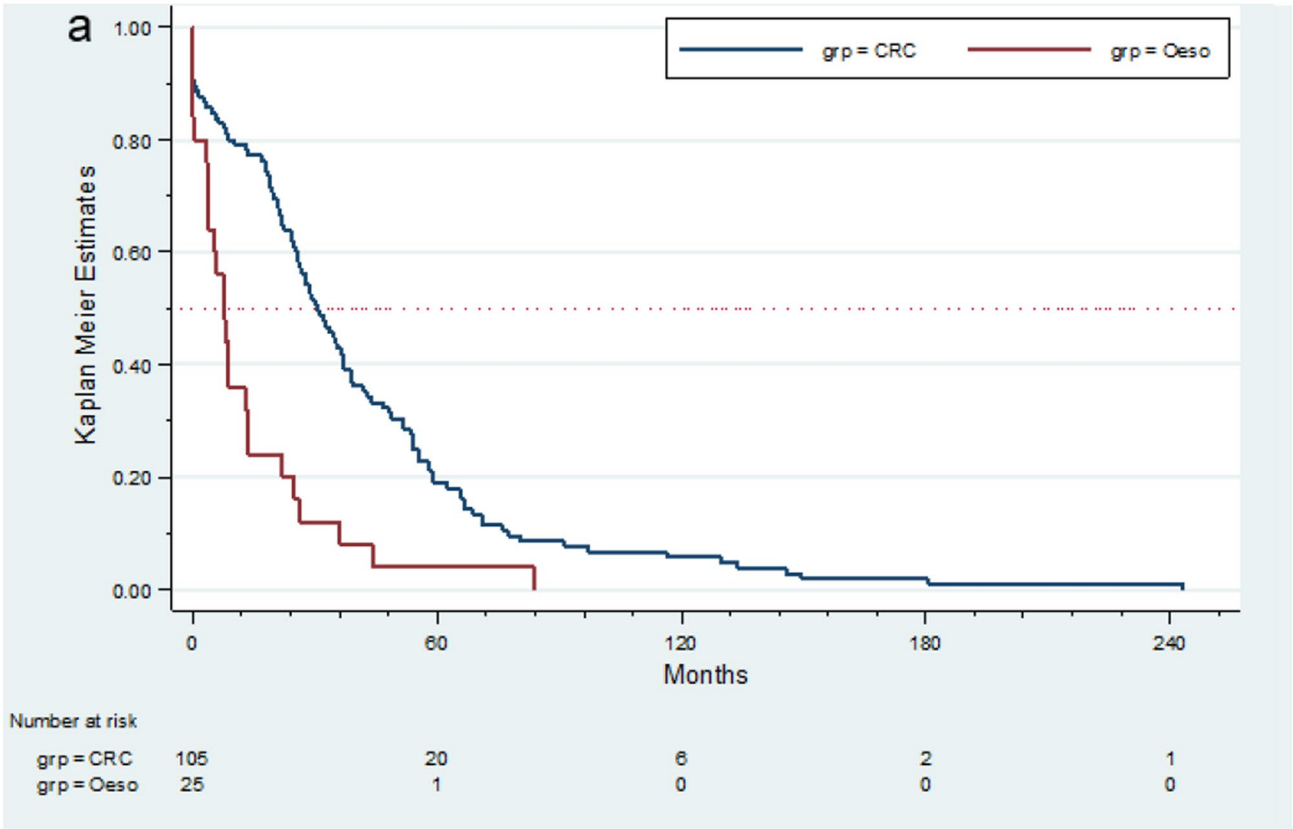


Fig. 1 Overall Survival. **a**. Total cohort **b**. patients with colorectal cancer (CRC) and oesogastric cancer (Oeso)



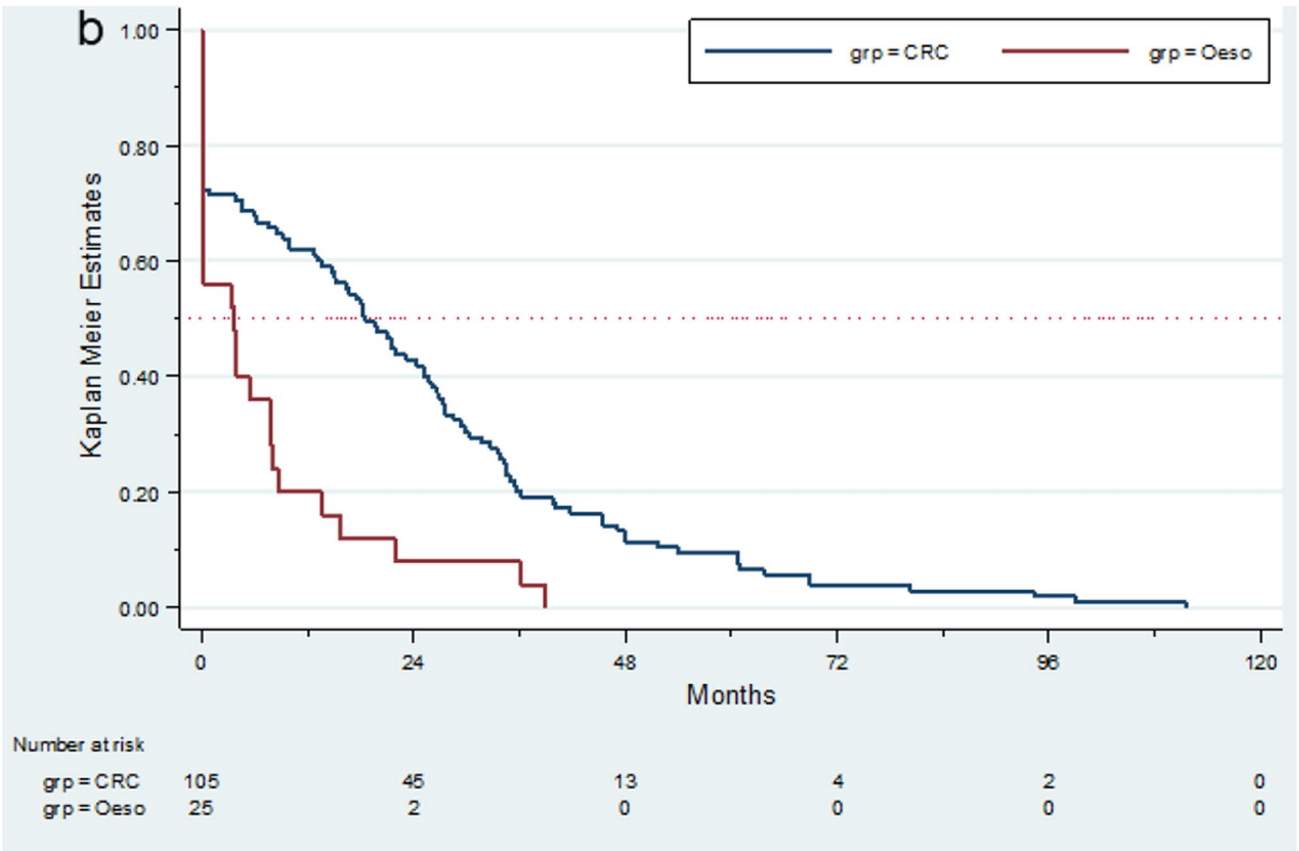


Fig. 2 Brain Metastasis Free Survival curves of patients with colorectal cancer (CRC) and oesogastric cancer (Oeso). **a**. From disease diagnosis **b**. From diagnosis of metastatic disease

the prognosis of GI tumours with brain metastases has not evolved a lot since 2010 and remains lower than 10 months in the literature [1, 2, 9, 10]. This was carefully examined in the Vienna Brain Metastasis Registry [3], in which no significant difference in OS was noted between 1986 and 1999 / 2000/2009 / 2010–2020 with a median OS of four, five, and six months, respectively ($p = 0.091$). Furthermore, CRC data in METACER align with data collected in 351 patients with colon cancer BM from the Vienna Brain Metastasis Registry [3]. Then, patients were enrolled upon BM diagnosis, making the data collection between primary tumour and BM diagnosis primarily retrospective. Therefore, predictive factors of BM in this study remain exploratory. This may account for the result in a univariate analysis showing that lung metastases correlate with longer stage 4-BM free survival in both CRC and EGC, whereas lung metastases were reported as enriched in patients with BM from GI cancers [20, 23]. Its prospective nature conveys METACER's main strength, as prospective data are very scarce in GI cancer patients with BM.

Conclusion

BM occur in GI cancer is associated with a poor prognosis. Some patients have a better survival outcome if they undergo BM surgery. Treatment, including surgery and stereotactic surgery should be discussed in multidisciplinary board, especially in case of good prognostic factors: unique cerebral BM and good performance status.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was conducted in line of the principles of the Declaration of Helsinki. Approval was granted by the local ethics committee (Comité de Protection des Personnes sud méditerranée III en date du 07/04/2010 . N° ICM: 2010/Obs02).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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