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Prognostic factors of Colorectal Cancer patients with Brain Metastases

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ABSTRACT

Introduction: Brain metastases (BMs) from colorectal cancer (CRC) are rare (≈2%) but are increasing with the improvement of CRC prognosis. The main objective of this study was to evaluate the prognostic factors of BM from CRC.

Materials and Methods: This multicenter retrospective study included all consecutive patients with BM from CRC diagnosed between 2000 and 2017.

Theory/calculation: Prognostic factors of OS were evaluated in univariate (log-rank test) and multivariate analyses (Cox regression model). These prognostic factors could help the management of patients with BM from CRC.

Results: A total of 358 patients were included with a median age of 65.5 years. Primary tumors were mostly located in the rectum (42.4%) or left colon (37.2%) and frequently *KRAS*-mutated (56.9%). The median time from metastatic CRC diagnosis to BM diagnosis was 18.5 ± 2.5 months. BMs were predominantly single (56.9%) and only supratentorial (54.4%). BM resection was performed in 33.0% of the cases and 73.2% of patients had brain radiotherapy alone or after surgery. Median OS was 5.1 ± 0.3 months. In multivariate analysis, age under 65 years, ECOG performance status 0-1, single BM and less than 3 chemotherapy lines before BM diagnosis were associated with better OS. Prognostic scores, i.e. recursive partitioning analysis (RPA), Graded Prognostic Assessment (GPA), Disease Specific-Graded Prognostic Assessment (DS-GPA), Gastro-Intestinal-Graded Prognostic Assessment (GI-GPA) and the nomogram were statistically significantly associated with OS but the most relevant prognosis criteria seemed the ECOG performance status 0-1.

Conclusions: ECOG performance status, number of BM and number of chemotherapy lines are the most relevant factors in the management of patients with BM from CRC.

Keywords:

Colorectal cancer, Brain metastases, Prognostic score, Radiosurgery, Whole brain radiation therapy.

INTRODUCTION

The incidence of brain metastases (BM) from colorectal cancer (CRC) ranges from 0.6 to 3.2% of all CRC and is increasing [1-4]. Improvements in the treatment of metastatic CRC (mCRC) with prolonged survival of more than 30 months probably explain this phenomenon as it corresponds to the mean interval between primary tumor and BM diagnosis [4,5]. Few small series of patients with BM from CRC have identified a specific profile of these patients having predominant primary tumor site in the rectum and sigmoid colon, frequent lung metastases and high rate of *KRAS*-mutated tumors [2,4,6-8].

BMs from CRC are associated with a poor prognosis with a median overall survival (OS) of about 5.0 months but with a high heterogeneity essentially due to extracranial involvement [4,9]. The treatment modalities include local treatments (surgery and radiosurgery), whole brain radiation therapy (WBRT), systemic treatments and best supportive care (BSC). The treatment objectives are local control of the BM, control of the non-tumoral cerebral parenchyma (prevention of other BM) and improving the patient's symptoms and quality of life [10]. Therapeutic strategy is based on patients' characteristics (age and performance status), BM (size and number), extracranial metastases (ECM) and prognosis. Indeed, it is important to identify prognostic factors to help treatment decision-making and prognostic scores could be useful. The most used scores are the Recursive Partitioning Analysis (RPA) classification [11], the Graded Prognostic Assessment (GPA) score [12] and the Diagnosis Specific Graded Prognostic Assessment (DS-GPA) score [13]. The proportion of CRC patients included in the studies developing these scores is unknown. Recently, a Gastro-Intestinal Graded Prognostic Assessment (GI-GPA) was published for all-comers GI cancers. Although tumor site had a major prognostic impact ($p<0.001$), it was not retained in the final model [14]. Indeed, these prognostic scores are not designed specifically for patients with mCRC and are not validated in this specific population. A recent Italian

retrospective study of 119 patients with BM from CRC developed a nomogram to estimate OS [15]. This tool also takes into account the subtentorial or supratentorial location of BM.

The main objective of this study was to identify the clinico-pathological prognostic factors in CRC patients with BM. We also analyzed the distribution of the patients according to the different prognostic scores and evaluated their relevance to predict patient's prognosis.

PATIENTS AND METHODS

Population

This retrospective multicenter study included patients with BM from CRC. Patients were diagnosed between January 2000 and January 2017, in 17 French hospitals using local clinical database. The local Ethics Committee approved the study and, due to the retrospective analysis with a majority of deceased patients, no patient consent was required. The study was performed according to the principles of the Declaration of Helsinki.

Inclusion criteria were age over 18 years old, histologically confirmed CRC and histologically or radiologically confirmed BM by computed tomography-scan (CT-scan) and/or magnetic resonance imaging (MRI). This study did not need an informed consent because of its retrospective nature and most of the patients had died (84.3%). Exclusion criteria were non-adenocarcinoma tumors and leptomeningeal carcinomatosis.

Patient and tumor characteristics

Patients' characteristics were described (age, sex and WHO performance status), as well as characteristics of the primary tumor (site, stage at CRC diagnostic, grade and treatment) and ECM (number, site and treatment). When available, *KRAS/NRAS* (codons 12, 13, 61, 146) and *BRAF* (V600E) mutations and mismatch repair status (MMR) were collected. Characteristics of BM were analyzed, including delay between CRC diagnosis and (supratentorial, subtentorial or both) and treatment (surgery, WBRT, radiosurgery and/or BSC).

Prognostic factors

We tested different scores in predicting the OS of our CRC-derived BM cohort. The RPA and GPA scores are both based on 4 prognostic factors, with 3 factors in common:

Karnofsky index, age, presence of ECM. The RPA also incorporates the control of the primary tumor and the GPA the number of BM. Both scores do not consider primary tumor site and are essentially based on patients with BM from lung and breast cancers and are therefore perhaps not transposable to CRC. The DS-GPA classification for gastrointestinal tumors retains only the Karnofsky index to stratify patients into 4 prognostic classes [13]. Recently, the same team developed the GI-GPA that included Karnofsky index, age, ECM and number of BM [14]. Both of these scores are not specific to CRC. The nomogram is specific to CRC and included Karnofsky index, age, BM site, number of BM as prognostic criteria but excluded patients with a Karnofsky index ≤ 50% [15].

The distribution of patients according to the different prognostic scores RPA, GPA, DS-GPA, GI-GPA and the nomogram was also evaluated to test their relevance [11-15]. OS was also determined according to BM treatment using four groups: BSC alone, focal treatment alone (surgery and/or radiosurgery), WBRT alone and focal treatment plus WBRT.

Statistical analysis

The main objective of the study was to identify prognostic factors of OS. OS was calculated from the date of BM diagnosis to the date of death from any cause. Survival curves were determined using the Kaplan-Meier method. Patients known to be alive were censored at the date of their last follow-up. Prognostic factors of OS were evaluated using the log-rank test for univariate analysis and statistically significant variables with $p<0.10$ and/or clinically relevant variables were included in multivariate analysis using a Cox regression model.

The level of significance was set at a p value of 0.05 (one-sided). Statistical analyses were performed using XLSTAT 2017© software (Addinsoft, USA).

RESULTS

A total of 358 patients with BM from CRC were included. Among them 93.4% had neurologic symptoms that led to the BM diagnosis and 6.6% had non-symptomatic lesions diagnosed on brain imaging. Median age at BM diagnosis was 65.5 years (Table 1). The primary tumors were located in the rectum, left colon and right colon in respectively 42.4%, 37.2% and 20.3% of cases. Tumors were predominantly well or moderately differentiated (89.2%). Most patients had a metastatic disease at diagnosis (58.0%), 26.0% with lung metastases and 37.7% with liver metastases. Most patients had a surgical resection of the primary tumor (82.4%).

KRAS mutations (codons 12-13) were found in 56.9% of cases. Of the 94 wild-type *KRAS* tumors (codons 12-13), 43 had complete *RAS* testing (codons 12, 13, 61 and 146 of *KRAS* and *NRAS*) of which 6 tumors were mutated. Indeed, rate of complete *RAS* mutation were 59.4% (56.0% *KRAS* and 3.4% *NRAS*). *BRAF* mutation was observed in 6.5% and tumors were mostly MMR-proficient (pMMR) (93.7%).

Only 16.2% of patients had synchronous BM and CRC diagnosis. The median time from primary tumor diagnosis to BM diagnosis was 29.2 ± 3.2 months and the median time from ECM diagnosis to BM diagnosis was 18.5 ± 2.5 months. Patients were mostly in good general condition (57.0% ECOG performance status 0-1). The majority of BM was single (56.9%) and only supratentorial (54.4%). At BM diagnosis, 86.1% of patients had ECM, mostly lung (70.1%) or liver (47.0%) metastases. Patients had a median of 2 chemotherapy lines before BM diagnostic (range 0-9).

The median follow-up from BM diagnosis was 44.2 ± 7.4 months and 84.3% of patients had died. Median OS from BM diagnosis was 5.1 ± 0.3 months, ranged from 0.1 to 158.7 months (1-year and 2-year OS were 23.7% and 9.5% respectively) (Supp Figure 1). Median OS from CRC diagnosis was 43.0 ± 1.7 months and median OS from ECM diagnosis

was 31.9 ± 2.9 months.

Prognostic scores RPA, GPA, DS-GPA, GI-GPA, as well as the nomogram, were calculated in the whole population. A significant OS difference between prognostic groups of each score was observed (p<0.0001) (Table 2).

In multivariate analysis, age < 65 years, ECOG performance status 0-1 (p<0.0001), single BM (p<0.0001), and 0 to 2 chemotherapy lines before BM diagnosis (p<0.0001) were associated with better OS (Table 3).

Surgical resection of BM was performed in 33.0% (n=118) of patients, 73.2% (n=262) received radiotherapy alone or after surgery [21.2% radiosurgery (n=76) and 43.6% WBRT (n=156)].

Patients were divided into four groups according to the treatment received (Fig. 1): BSC alone (n=58), focal treatments alone (n=93), WBRT alone (n=114) and focal treatments plus WBRT (n=44). Patients with different or unknown treatment (n=49) were excluded. Patient and tumor characteristics are different according to treatment groups (Supp Table 1). Compared to focal treatments alone and focal treatments plus WBRT groups, BSC alone and WBRT alone groups had more unfit patients who were older, with poor performance status and with more aggressive disease (multiple BM and more frequently ECM).

OS was significantly different depending on the BM treatment. Median OS was 13.0 ±1.0 months in patients with BM surgery compared to 3.4 ± 0.2 months in non-operated patients (p<0.0001). In patients with radiosurgery or WBRT median OS was 5.9 ± 0.3 months compared to 2.1 ± 0.4 months in non-irradiated patients (p=0.0003). Median OS was 12.0 ± 0.7 months in patients with BM surgery alone or with WBRT compared to 8.5 ± 7.3 months in patients with radiosurgery alone or with WBRT (p=0.20).

OS was also different according to the four pre-defined groups: BSC alone (1.3 ± 0.2 months), WBRT alone (3.6 ± 0.2 months), local treatments plus WBRT (9.8 ± 1.4 months)

and local treatments alone (17.1 ± 2.4 months) ($p<0.0001$) (Fig. 2). Patients with BSC alone (1.3 ± 0.2 months) had a shorter OS as compared patients with specific treatments (6.0 ± 0.4 months) (Fig. 3).

Patients in BSC alone and WBRT alone groups were more frequently in the poor prognosis subgroups of each score (RPA, GPA, DS-GPA, GI-GPA and nomogram) compared to local treatments alone and local treatments plus WBRT groups (Supp Table 2). In each subgroup, prognostic scores were correlated with OS, i.e. BSC alone (RPA, GPA, DS-GPA and nomogram), WBRT alone (RPA and DS-GPA), local treatments plus WBRT (RPA, GPA, DS-GPA, GI-GPA and nomogram) and local treatments alone (RPA and GI-GPA) (data not shown).

Concerning prognostic factors, in multivariate analysis, number of previous chemotherapy lines < 3 ($p=0.03$) was associated with better OS in local treatment alone group and age < 65 years ($p=0.01$), female ($p=0.01$), ECOG performance status 0-1 ($p=0.01$) and single BM ($p=0.0008$) were associated with better OS in local treatment plus WBRT group. ECOG performance status 0-1 ($p=0.04$) was associated with better OS in WBRT alone group. *KRAS* WT status ($p=0.03$) and number of previous chemotherapy lines < 3 ($p=0.04$) was associated with better OS in BSC alone group.

DISCUSSION

In this large cohort, prognosis of CRC patients with BM remains poor but with a high heterogeneity of OS ranging from 0 to 159 months. CRC patients with BM had frequently a rectum tumor, lung metastases and a *KRAS*-mutated tumor. The median time from metastatic CRC diagnosis to BM diagnosis was 18 months. We identified age < 65 years, ECOG performance status 0-1, single BM and less than 3 chemotherapy lines before BM diagnosis as good prognostic factors. Among the common prognostic scores available in the literature, the DS-GPA and GI-GPA gave a more homogenous repartition among different subgroups and the closest predictions of OS to the observed OS in our series.

In our study, as already described in other studies, young age, rectal or sigmoid tumor site and lung metastases seemed to be more frequent in mCRC patients with BM compared to all-comers mCRC patients [2,4,8,9,15-17]. Moreover, most of the patients had synchronous metastatic disease at primary tumor diagnosis (58.0%), which probably reflected an "aggressive" disease that would later develop BM, since only ≈25% of patients diagnosed with CRC present synchronous BM. In accordance with the literature, most BMs from CRC were metachronous to CRC diagnostic (≈80%). In addition rate of *KRAS* mutations was high (56.9%) when compared with all-comers mCRC (≈40%) [2,7,18,19]. In our cohort, BM diagnosis occurred with a median time of 30 months after the primary tumor diagnosis and about 20 months after the metastatic disease diagnosis which is in accordance with the literature [4,5]. Due that most patients were at the terminal phase of the disease with both brain and extracranial metastatic sites, we were not able to distinguish whether death was due to BM or ECM. In the same way, most patients died soon after BM diagnosis without further imaging then it is difficult to know if the BM treatment carried out allow a disease control or not beyond analyzing the OS.

Some prognostic scores exist to guide treatment strategies for patients with BM but,

except for the nomogram, they are not designed specifically for mCRC patient's [11,13,14]. The aim of our study was not to develop a new score but to evaluate specifically the already existing scores in the subgroup of CRC. RPA and GPA do not consider primary tumor site and are essentially based on patients with BM from lung and breast cancers. The DS-GPA classification for gastrointestinal tumors retains only the Karnofsky index to stratify patients into 4 prognostic classes with an OS ranging from 3.1 to 13.5 months. The GI-GPA classification for gastrointestinal tumors developed in 2019 is dedicated to GI tumors but the authors did not include the primary tumor site although it was significantly associated with OS ($p<0.001$) [14]. As reported by the authors, median OS ranged from 2 months for gastric cancer to 14 months for anal cancer. Most of the patients in our study were in the "intermediate" or "poor" prognostic groups of RPA, GPA, DS-GPA and GI-GPA scores and few in the category with "good" prognosis. This is probably related to the late diagnosis of BM in CRC. The repartition of patients throughout the four categories seems better for the GI-GPA and DS-GPA scores. RPA and GPA predict worse OS than those observed in our cohort but DS-GPA and GI-GPA were better to predict the observed OS. Although, DS-GPA seems to predict more accurately the observed OS in our cohort, both DS-GPA and GI-GPA scores displayed a balanced repartition of patients throughout the four prognostic groups.

The Nomogram proposed in a recent Italian retrospective study on 227 patients with BM from CRC, treated between 2000 and 2013, excluded patients with a Karnofsky index $\leq 50\%$, which induces a major selection bias [15]. In our cohort, this Nomogram is associated with OS. Nevertheless, the Nomogram estimated a median OS of approximately 9.0 months compared to 5.7 months really observed in our cohort. The Nomogram is difficult to use in routine clinical practice with multiple cut offs for each four prognostic factors. The Nomogram has been also evaluated on a cohort of 64 patients and in 46 patients (72%) the observed survival was shorter than the predicted median (median deviation

of -1.4 months) [20]. Moreover, the Nomogram overestimated OS in patients treated with WBRT by a median of 2.1 months. Our population seemed similar to both studies in terms of primary tumor location with 42% of rectal tumours (34% in the Italian study [15] and 48% in the Norwish study [20]) and in terms of ECM at BM diagnosis with 13.6% of patients without ECM (0% in the Italian study and 27% in the Norwish study). Our cohort was larger than both studies and demonstrated that the Nomogram has some limits to predict OS.

DS-GPA provided the closest estimations of OS to the OS we observed in the three categories. This confirmed that ECOG performance status, which we identified as a prognostic factor, was the most important one. It was included with a bigger weight in the GI-GPA. In our study, age, which had a low weight in the GI-GPA, is an independent prognostic factor but with a p value near 0.05. Our large cohort of 358 patients identified other prognostic factors in multivariate analysis: number of BM and number of previous chemotherapy lines before BM diagnosis. The number of previous chemotherapy lines is not included in any of the existent scores but one study found that patients with BM from CRC receiving ≥ 2 lines of chemotherapy had lower OS compared to other patients [9]. The delay between BM and CRC diagnosis (i.e. synchronous versus metachronous) could be a surrogate marker for the number of previous chemotherapy lines. As confounding factors cannot be considered independent from each other we assumed they could not be included in the same multivariate analysis and we chose to keep delay between BM and CRC diagnosis from the analysis.

Nowadays, the therapeutic management of BM depends on the performance status of the patient, the expected OS, the number, size and location of BM that is to say prognostic factors, rather than tumor location. Identifying the most efficient prognostic factors is of great importance to decide the most adequate BM treatment. In case of a single, large and symptomatic lesion in a patient whose general condition is preserved, surgery is often

preferred in order to improve the quality of life of the patients [21]. Stereotactic radiosurgery can be an alternative treatment option to surgery in case of a single asymptomatic lesion of less than three centimetres, or in case of plurifocal involvement but with a limited volume of parenchyma reached. In other cases with multiple BMs and/or poor performance status (Karnofsky index <70%) and/or poor prognosis (<3 months), WBRT is the best option. Future directions include novel radiation technique such as ultra-high dose rate radiotherapy, which can provide adequate tumor control and spare cognitive decline. The role of systemic therapy in the management of BMs is currently evolving. Most tyrosine kinase inhibitors, e.g. BRAF inhibitors, are able to penetrate the blood-brain barrier. Several studies have demonstrated promising activity of immune checkpoint inhibitors in BMs and trials combining immune checkpoint inhibitors with stereotactic radiosurgery are ongoing [22].

In our study, as in other series, there was a high heterogeneity of BM treatment. Currently, there is no specific consensus on the therapeutic management of BM from CRC. We split the cohort in 4 groups with different treatments (BSC alone, local treatments alone, local treatments plus WBRT and WBRT alone). Consequently, a great difference in term of prognosis was observed with an OS from 1.3 months to 17.1 months according the subgroups. Consistent with the literature, patients with radiation have a better prognosis compared to patients with no radiation (≈6 months versus ≈3 months), as well as patients with local treatments plus WBRT compared to WBRT alone (≈12 months versus ≈3 months) [9,19,23]. In this retrospective study, it is not possible to determine the best treatment option for CRC patients with BM due to the great difference in patients and tumours' characteristics according to treatment subgroups and obvious selection bias. Nevertheless, we analyzed the proposed prognostic factors according to the four treatment subgroups [12,24]. The significant prognostic factors obtained were the previously identified variables, strengthening the relevance to stratify patients with BM derived from CRC. The RPA correlated with OS in

each subgroup of treatment but did not differentiate patients correctly and could not predict OS in our cohort when compared to DS-GPA. It is worth noting that in these subgroups we are not able to differentiate factors identified as prognostic factors and/or predictive factors of treatment efficacy.

Despite its retrospective nature and the prolonged period of patient's inclusion, there are few missing clinical data (≈10%) in our study. Nevertheless, we cannot exclude a selection bias in our population, particularly an over-representation of patients with radiotherapy and/or surgery compared to BSC alone. Another limitation is the heterogeneity of BM treatment but this reflects routine clinical practice. Finally, this is the largest published series so far of CRC patients with BM and, in our opinion, it allows a highly accurate determination of prognostic factors in this subgroup of CRC patients.

In conclusion, we found age < 65 years, ECOG performance status 0 or 1, single BM and less than 3 previous chemotherapy lines clinically relevant good prognostic factors. All these factors can guide treatment decision-making in this particular population of metastatic CRC with BM.

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Conflicts of interest

None.

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Figure captions

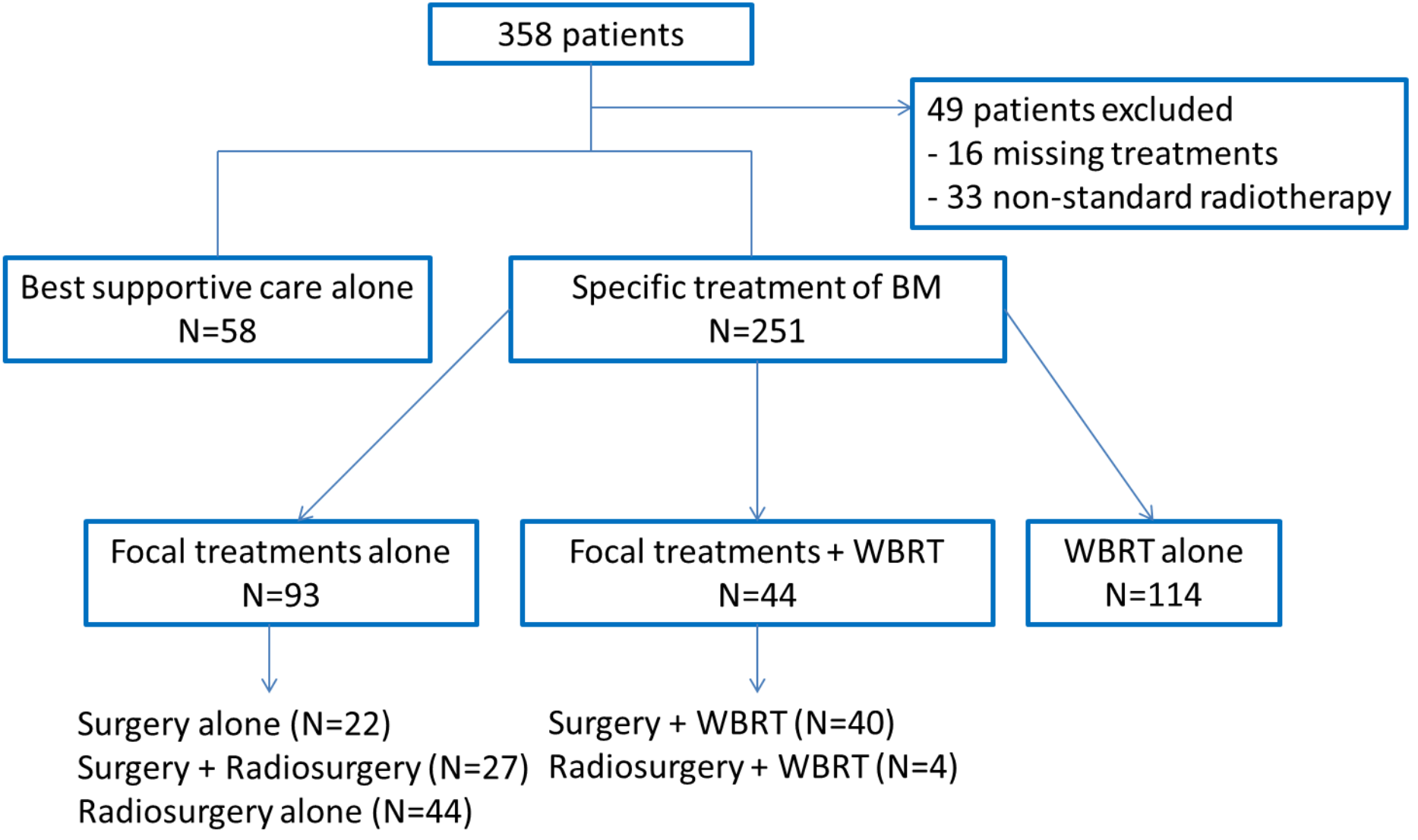
Figure 1. Treatment of brain metastasis(es)

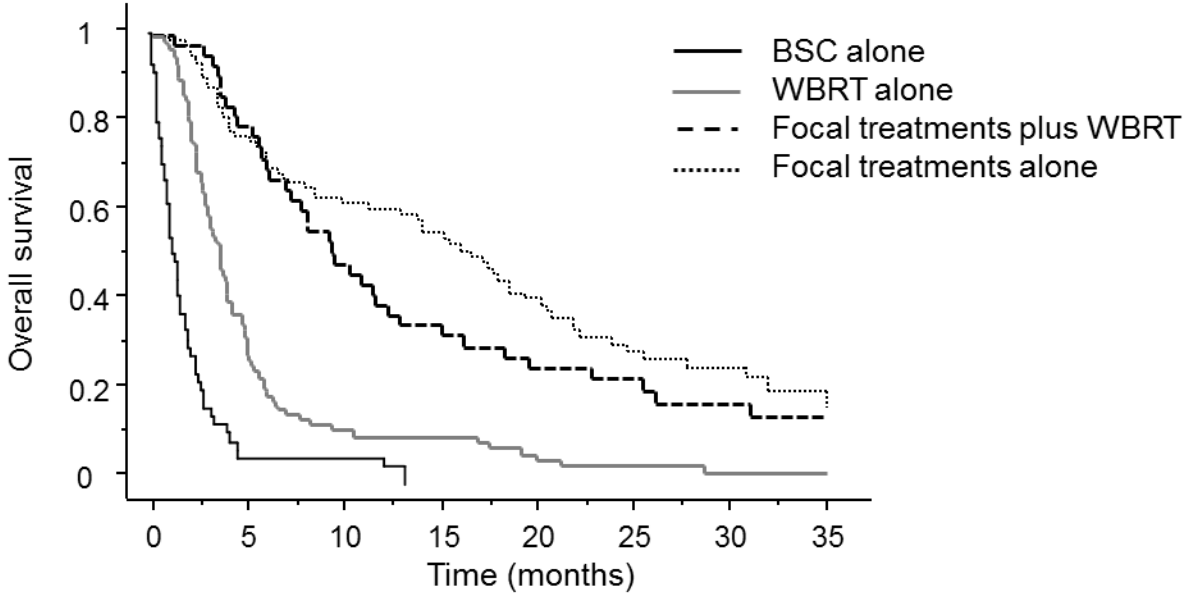
BM: brain metastase(s) ; BSC: best supportive care ; WBRT: whole brain radiation therapy

Figure 2. Overall survival according to treatment groups (n=309)

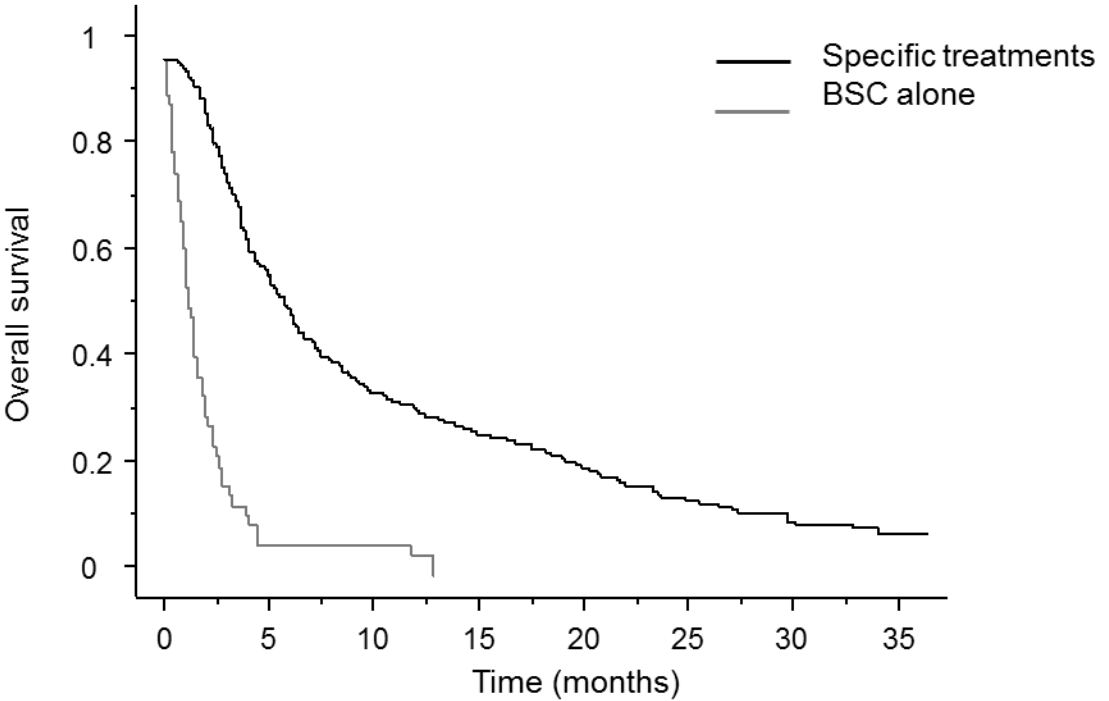
BSC: best supportive care ; WBRT: whole brain radiation therapy

Figure 3. Overall survival with best supportive care (BSC) compared to specific treatments


358 patients
49 patients excluded
- 16 missing treatments
- 33 non-standard radiotherapy
Best supportive care alone
N=58
Specific treatment of BM
N=251
Focal treatments alone
N=93
Focal treatments + WBRT
N=44
WBRT alone
N=114
Surgery alone (N=22)
Surgery + Radiosurgery (N=27)
Radiosurgery alone (N=44)
Surgery + WBRT (N=40)
Radiosurgery + WBRT (N=4)



Patients at risk	309	134	81	59	42	26	17	13
BSC alone	58	3	3	0	0	0	0	0
WBRT alone	114	33	9	7	4	2	1	1
Focal treatments plus WBRT	44	33	20	14	11	8	5	4
Focal treatments alone	93	65	49	38	27	16	11	8



Patients at risk	309	134	81	59	42	26	17	13
BSC alone	58	3	3	0	0	0	0	0
Specific treatments	251	131	78	59	42	26	17	13

Table 1. Patient and tumor characteristics (n=358)

	n (%)
Gender	
Male	205 (57.3)
Female	153 (42.7)
Age at BM diagnosis (median)	65.5 (55.3-71.9)
< 65 years	160 (44.7)
≥ 65 years	198 (55.3)
Tumor site	
Ascending colon	71 (20.3)
Descending colon	130 (37.3)
Rectum	148 (42.4)
Missing	9
Tumor grade	
Well or moderately differentiated	224 (89.2)
Poorly differentiated	27 (10.8)
Missing	107
Stage at CRC diagnostic	
I	19 (5.4)
II	35 (10.0)
III	93 (26.6)
IV	203 (58.0)
Missing	8
Primary tumor resection	
No	63 (17.6)
Yes	295 (82.4)
***KRAS* (codons 12 - 13) status**	
Wild-type	94 (43.1)
Mutated	124 (56.9)
Missing	140
***BRAF* status**	
Wild-type	187 (93.5)
Mutated	13 (6.5)
Missing	158
Delay between BM and CRC diagnosis	
Synchronous	58 (16.2)
Metachronous	300 (83.8)
ECOG performance status at BM diagnosis	
0 or 1	150 (57.3)
2, 3 or 4	112 (42.7)
Missing	96
BM number	
Single	198 (56.9)
Multiple (≥ 2)	151 (43.1)
Missing	8
BM site	
Supratentorial only	185 (54.4)
Subtentorial or both	155 (45.6)
Missing	18
ECM at BM diagnosis	
No	49 (13.9)
Yes	303 (86.1)

BM: brain metastases, CRC: colorectal cancer, ECM: extracranial metastases, ECOG: eastern cooperative oncology group

Table 2. Overall survival according the prognostic scores (n=358)

	n (%)	Median OS observed with the score[§] (months)	Median OS in our cohort (months)	p
RPA classification				<0.0001
Class I	4 (1.5)	7.7	13.3	
Class II	143 (55.2)	4.5	8.0	
Class III	112 (43.2)	2.3	2.9	
Missing	99			
GPA score*				<0.0001
0-1	69 (36.3)	2.6	2.3	
1.5-2.5	103 (56.6)	3.8	7.0	
3	8 (4.4)	6.9	23.2	
3.5-4	6 (2.7)	11.0		
Missing	172			
DS-GPA score**				<0.0001
0-1	114 (43.3)	3.1	2.9	
2-3	103 (39.2)	4.4 and 6.9	7.3	
4	46 (17.5)	13.5	13.8	
Missing	95			<0.0001
GI-GPA score				
0-1	100 (38.6)	3	2.9	
1.5-2	43 (16.6)	7	3.4	
2.5-3	95 (36.7)	11	11.7	
3.5-4	21 (8.1)	17	14.9	
Missing	99			
Nomogram[#]				<0.0001
Number of patients	79	9.0	5.7	
Median of the Nomogram	81.0 ± 8.3			
Missing	279			

* The GPA classification scores 3 and 3.5-4 were grouped together for the OS analysis in view of the small number of patients in each of these groups.
** For the DS-GPA classification, the scores 2 (Karnosfsky at 80) and 3 (Karnosfky at 90) of the classification were grouped together, as they both corresponded to an ECOG performance status at 1.
# For the Nomogram we performed a correlation between the score as continuous variable and OS using a Cox model.
§ Median OS observed in the princeps publication.

DS-GPA: Diagnosis-Specific Graded Prognostic Assessment, GPA: Graded Prognostic Assessment, DS-GI-GPA: Gastro-Intestinal Graded Prognostic Assessment, RPA: Recursive Partitioning Analysis

Table 3. Prognostic factors of overall survival

Prognostic factors	Median OS (months)	Univariate analysis	Multivariate analysis		
		p	HR	CI95%	p
Gender*		0.77			0.16
Female	5.1		1		
Male	5.1		1.22	0.92-1.63	
Age at BM diagnosis*		0.0008			0.048
< 65 years	7.3		1		
≥ 65 years	3.9		1.34	1.00-1.80	
Tumor site		0.20			
Ascending colon	4.6				
Descending colon	5.7				
Rectum	4.4				
Tumor grade		0.68			
Well or moderately differentiated	4.4				
Poorly differentiated	4.6				
Primary tumor resection		0.32			
No	4.0				
Yes	5.2				
***KRAS* (codons 12 - 13) status**		0.77			
Wild-type	4.4				
Mutated	5.4				
***BRAF* status**		0.22			
Wild-type	5.2				
Mutated	3.3				
CEA at BM diagnosis		0.65			
Delay between BM and CRC diagnosis		0.03			
Synchronous	9.7				
Metachronous	4.8				
ECOG performance status*		<0.0001			<0.0001
0 or 1	8.5		1		
2, 3 or 4	2.9		2.45	1.78-3.37	
BM number*		<0.0001			<0.0001
Single	7.5		1		
Multiple (≥ 2)	3.4		2.07	1.53-2.79	
BM site*		0.04			0.38
Supratentorial only	6.1		1		
Subtentorial or both	4.2		1.14	0.85-1.54	
ECM at BM diagnosis*		<0.0001			0.14
No	12.4		1		
Yes	4.3		1.44	0.89-2.34	
ECM site at BM diagnosis		<0.0001			
None	12.4				
Lung	4.2				
Others	5.3				
Number of chemotherapy lines before BM diagnosis*		<0.0001			<0.0001
0-2	6.3		1		
≥ 3	3.2		1.94	1.44-2.63	

* variables included in multviariate analysis (confounding variables were excluded).
BM: brain metastases, CRC: colorectal cancer, ECM: extracranial metastases, ECOG: eastern cooperative oncology group, CEA: carcinoembryonic antigen