

Patients with Brain Metastases from Colorectal Cancer Are Not Condemned

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Abstract. *Background:* Brain metastases (BM) from colorectal cancer are rare (2-3%). They usually occur in advanced stages of the disease and their prognosis is poor. The aim of this study was to assess the impact of surgical resection of BMs from colorectal cancer in terms of overall survival. *Patients and Methods:* A retrospective bi-centric study included all patients with resected BMs from primary colorectal adenocarcinoma from 1998 to 2009. *Results:* Twenty-eight patients [13 males, median: 62 (range: 44-86) years old] were included. Fifteen patients presented with other metastatic sites (lung, liver). BMs were metachronous in 16/28 (57%) of patients [median: 19 months (range: 7-97)]. Median overall survival reached 12 months. Brain recurrences occurred in 32% of patients and were treated by curative intent in 5/9 cases. *Conclusion:* When indicated, an aggressive management based on surgical resection of BMs from colorectal cancer, must be performed, in order to improve overall survival to at least 12 months.

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Colorectal cancer is the third most common cause of death by cancer. Improvement in the efficacy of systemic treatment of colorectal cancer, particularly in advanced colorectal cancer, has allowed for increasing overall survival of patients (1). Widespread use of brain magnetic resonance imaging (MRI) in the radiological workup of these patients has led to an increased detection, and thus incidence (0.74-10.3%), of brain metastases (BM) (2-8).

BMs usually occur in advanced stages of disease, with associated liver (50%) or lung (80%) metastases (9-11). The current curative strategy for the latter types of metastases is well-established (12-13), whereas it is more variable for BMs. Indeed, current treatment options for BMs from colorectal cancer include surgery or stereotactic radiosurgery, with or without whole-brain radiotherapy (WBRT) and, in rare cases, chemotherapy. Surgical treatment of BMs from colorectal cancer has been reported to be associated with a better median overall survival than other modalities, in unique or oligometastatic brain disease (2, 6, 10, 14, 15). Moreover, a combined treatment based on surgery with WBRT is likely to provide a better control of BMs than surgery-alone (4, 9, 15, 16). However, the prognosis of BMs from colorectal cancer remains poor with median survival ranging from two months to fifteen months (10). Patients with BMs from colorectal cancer are often treated in a palliative setting. The aim of the present study was to assess the impact of surgical resection of BMs from colorectal cancer in terms of overall survival.

Patients and Methods

Population. We retrospectively included consecutive patients with resected BMs from primary colorectal adenocarcinoma between 1998 and 2009 in two departments of colorectal surgery (Marseille and Amiens, France). Complete medical files (including hospital charts, operation records, radiography and pathology reports) of all

patients were analyzed. Data about primary colorectal cancer, extracranial metastases and BMs were collected (time from primary diagnosis, clinical presentation, location, number, size and treatment modalities).

Primary colorectal cancer and extracranial metastatic disease. All patients underwent surgical resection of their colorectal cancer. In cases of locally advanced rectal cancer, neoadjuvant chemoradiotherapy [45 or 50 Gy in 25-28 daily fractions, and 5-FU] was performed. In cases of extensive pathological tumor, node or systemic metastases, adjuvant chemotherapy (using 5-FU) was indicated. Liver metastases were treated by surgery (major hepatectomy, *i.e.* more than three resected segments, or minor hepatectomy, *i.e.* from one to three resected segments), chemotherapy/radiofrequency, and lung metastases by surgery and chemotherapy.

Management of BMs. All patients with BMs had post-contrast cerebral MRI or computed tomographic (CT) scan. MP and DH reviewed imaging data. Treatment modality of BMs was conventional craniotomy with surgical resection. Combined stereotactic radiosurgery was performed in oligometastatic brain disease (<4 lesions) including deep-seated and small lesions (<3 cm). Adjuvant WBRT with 30 Gy in 10 fractions was performed after surgery in cases of multiple or bulky BMs (>3 cm). Postoperative follow-up included clinical and radiological assessment every three months during the first postoperative year, then every six months.

Definitions. BMs were termed synchronous when diagnosed within six months after the diagnosis of colorectal cancer and metachronous after six months. Recursive partitioning analysis (RPA), based on age, Karnofsky performance status (KPS), and the extent of extracranial disease, was assessed for each patient. Three prognostic classes of patients were defined: class I included patients aged less than 65 years, with KPS>70 and controlled primary cancer; class III included patients with KPS<70; and class II included all remaining patients. Overall survival was calculated from the date of surgical resection of BMs. Local and distant intracranial recurrence/progression was recorded for all patients.

Statistical analysis. Statistical analysis was performed using Graphpad® (Prism, La Jolla, USA). Qualitative variables, expressed as numbers and percentages, were analyzed with the Chi-square or Fisher's exact test, as appropriate. Quantitative variables, expressed as mean±standard deviation (SD) or median with range, were analyzed with Student *t* or non-parametric Mann-Whitney tests, where appropriate. Statistical significance testing was set at 5%. Survival was estimated by using the Kaplan-Meier method and curves were compared by using the Log-rank test.

Results

Population. Twenty-eight patients out of 150 patients with BMs from colorectal cancer (18%), aged 62 (range: 44-86) years, underwent surgical resection of their BMs. Demographic and colorectal cancer data are summarized in Table I. There was no preferential location of primary cancer. At the time of colorectal cancer resection, disease was locally advanced and extensive in 14% and 43% of cases, respectively. Fifteen patients had lung metastases (n=7), liver

Table I. Clinical and pathological characteristics of the primary tumor and brain metastases (BMs).

	n (%)
Gender M/F, n (%)	13 (46)/15 (54)
Median age, years (range)	62 (44-86)
<65 years, n (%)	15 (54)
>65 years, n (%)	13 (46)
Primary colorectal cancer, n (%)	
Location	
Colon	15 (54)
Rectum	13 (46)
Treatment of primary tumor	
Neoadjuvant radiochemotherapy	2 (7)
Adjuvant chemotherapy	2 (7)
Surgery	
Colectomy	16 (57)
Proctectomy	10 (36)
Abdominoperineal excision	2 (7)
Stage TNM	
I	0 (0)
II	12 (43)
III	4 (14)
IV	12 (43)
Brain metastases, n (%)	
Timing of metastases	
Synchronous	12 (43)
Metachronous	16 (57)
Median interval, months (range)	19 (7-97)
Location	
Supratentorial	20 (71)
Infratentorial	10 (36)
Unilobar	25 (89)
Bilobar	3 (11)
Brain oedema	6 (21)
Number of brain lesions	
Single	23 (82)
Double	5 (18)
Median size, mm (range)	30 (16-44)
Symptomatic	26 (93)
Not symptomatic	2 (7)

metastases (n=5) or both (n=3). Regarding liver metastases, major hepatectomy, minor hepatectomy and radiofrequency ablation were performed in two, two and one patient, respectively. Lung metastases were resected. Patients with liver and lung metastases underwent combined treatment (surgery and chemotherapy) in two cases. None of the patients presented local recurrence before diagnosis of BMs.

Characteristics of BMs. Repartition of RPA stages was as follows: RPA I, n=7 (25%); II, n=9 (32%); and III, n=12 (43%). Characteristics of BMs are summarized in Table I. BMs were more often metachronous (57%). In cases of synchronous BMs, half of the cases (n=6) occurred before diagnosis of colorectal cancer. Five patients presented with

Table II. Univariate analysis for potential predictive factors of better overall survival.

Parameters	Univariate analysis		
	HR	95% CI	p-Value
Age			
<65 years vs. >65 years	2.4	0.4-14.9	0.31
Primary tumor location			
Rectum vs. colon	0.25	0.06-1.0	0.06
RPA stage			
I	I vs. II: 1.2	0.17-9	0.42
II	II vs. III: 1.19	0.16-8.7	0.67
III	I vs. III: 1.6	0.3-8.4	0.65
Time to occurrence			
Synchronous vs. metachronous	0.5	0.1-2.6	0.07
Location of BMs			
Supratentorial vs. infratentorial	0.47	0.1-2	0.3
Adjuvant WBRT			
Yes vs. No	0.74	0.17-3.2	0.68

BMs: Brain Metastases, RPA: recursive partitioning analysis, WBRT: whole-brain radiotherapy, HR: hazard ratio, CI: confidence interval.

double BMs (18%). Location was frequently supratentorial, whether in the frontal (n=11/33, 33%), temporal (n=3/33, 9%), parietal (n = 4/33, 12%) or occipital (n=8/33, 24%) lobes. BM-related symptoms were frequently reported (93%) and consisted of headache (n=10, 36%), nausea or vomiting (n=9, 32%), hemiparesis (n=2, 7%), dysarthria (n=2, 7%), walking instability (n=2, 7%), amnesia (n=1, 3.6%), seizure (n=1, 3.6%) and trouble of visual field (n=1, 3.6%).

Surgical resection of BMs was performed with combined radiotherapy in 10 cases (36%), and without in 18 cases (64%). Combined treatment consisted of WBRT (n=7), stereotactic radiosurgery (n=2) or both (n=1). This combined treatment concerned the tumor bed of resected BMs, except for one case, which was another BM.

Overall and disease-free survival. The median follow-up was approximately 12 months (1-160 months). Median overall survival was 12 months (Figure 1). The 1-year, 2-year and 5-year overall survival rates were 52%, 36% and 18%, respectively. Primary colonic cancer and metachronous BMs tended to be associated with better overall survival (>40 and 39.1 months) than primary rectal cancer or synchronous BMs (30 and 30.5 months, respectively). However, overall survival was not significantly influenced by age, RPA stage, BM location, or combined WBRT (Table II).

Nine patients presented with brain recurrences (32%), at a median time of 8 months (2-64 months). They were treated by surgery in four cases and WBRT in one. Others underwent palliative support because of a poor performance status (n=2); or associated systemic metastases (n=2); liver

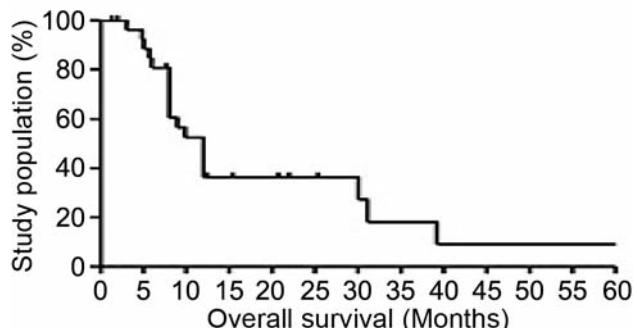


Figure 1. Overall survival (months) for the study population (n=28).

metastasis and carcinomatosis for one, and liver, lung and adrenal gland metastases for the other. Five patients (18%) presented with systemic metastases after the management of BMs, one with carcinomatosis, one in the liver, two in the lung (n=2) and one with bone metastases.

Discussion

We report that surgical resection of BMs from colorectal cancer improved overall survival to 12 months for 50% of patients. Colonic location of primary cancer and metachronous BMs were associated with a better overall survival, although non-significantly.

BMs from colorectal cancer are rare and associated with a universally poor prognosis. Indeed, they occur in approximately 2-3% of all cases at the time of diagnosis of primary colorectal cancer, and 10% during follow-up of the disease, with an overall survival of about five months (2, 4, 5, 7, 8, 9, 17). According to other series (2, 5, 8, 14, 16), most BMs are metachronous, 57% in the current series, at a median occurrence of between 20 and 32 months (10, 14). Surgical resection is indicated in the case of solitary BMs, in patients without important comorbidity or uncontrolled cancer (18, 19, 20). In the current series, the multiple (double) BMs were resected because of uncontrolled neurological symptoms, and systemic disease control. In current literature, surgery of BMs from colorectal cancer is variably assessed from 16% to 100% of the patients (4, 7, 9, 11, 21), due to these restricted indications. Nevertheless, surgical management of BMs from colorectal cancer does increase the median overall survival up to 14 months (21). Combined radiotherapy, based on WBRT, is frequently administered from 29%, as in the current series, to 84% of patients (21). This combined treatment would improve overall survival, from two or five months, in the case of WBRT or surgery alone to 11 months with both ($p<0.05$) (6, 16, 22). We did not observe any significant differences in overall survival with and without combined WBRT. Moreover, we did not identify any previously described predictive factor of good

prognosis, such as age, RPA stage, control of extracerebral disease, tumor number, tumor location and time-to-occurrence of BMs (2, 7, 11, 14, 17, 18, 23). We observed BM recurrence in 32% of patients. This is in accordance with the few data about BM recurrence rate, varying from 7% to 36% (9, 14, 21).

This study is limited by its retrospective nature and the small sample size, which can explain the absence of significant difference for standard predictive factors. Despite this, the current results suggest that in cases of resectable BMs from colorectal cancer, an aggressive management based on surgery and radiotherapy should be indicated to improve overall survival until at least 12 months. BMs from colorectal cancer must not be considered a palliative situation but must be treated based on multidisciplinary-making decisions.

Conclusion

BMs from colorectal cancer are rare and associated with a poor prognosis. When surgery is indicated, it allows for better median overall survival, up to twelve months. If aggressive management by surgical resection is allowed, after multidisciplinary-making decisions, even with other metastatic sites, overall survival can be improved. Curative management of BMs from colorectal cancer should be performed as soon as possible.,

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