



Clinical features and course of brain metastases in colorectal cancer: an experience from a single institution

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ABSTRACT

Objectives

Brain metastases from colorectal cancer (CRC) are quite rare. Here, we review the characteristics, presentation, and clinical course of such patients at our institution.

Methods

We reviewed the medical records of patients with brain metastases from CRC treated during 2000–2009. Associations between patient, tumour characteristics, treatment modality, and survival were assessed using the Kaplan–Meier method.

Results

We identified 48 patients (25 men, 23 women) who developed brain metastases from CRC. The median age at diagnosis of the brain metastases was 63 years (range: 37–84 years). In 23 of the patients (48%), the primary tumour occurred in the rectum. At diagnosis of brain metastases, 43 patients (90%) also had other systemic metastases (mainly pulmonary and hepatic). The median interval between diagnosis of the primary tumour and of the brain metastases was 24 months. Median survival after a diagnosis of brain metastasis from CRC was 4 months (range: 1–13 months). We observed substantially better survival (13 months, $p < 0.001$) in patients treated with surgery followed by whole-brain radiotherapy (WBRT) than in those treated with radiotherapy or surgery alone. Sex, age, location and number of brain metastases, and timing of diagnosis did not affect survival.

Conclusions

Brain metastases from CRC develop late in the course of the disease, given that most patients already have other secondary lesions. Prognosis in these patients is poor, with those receiving treatment with surgery

and WBRT having the best overall survival. Early detection and treatment of brain metastases with new systemic therapies may improve outcomes.

KEY WORDS

Colorectal cancer, brain metastases, radiation therapy, surgery

1. INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer death in the Western world, accounting for approximately 140,000 new cases and more than 51,000 deaths in 2010 in the United States¹. In Canada, CRC is the fourth most-diagnosed neoplasm, and overall, the second leading cause of death from cancer. In 2010, it was estimated that 22,500 Canadians were diagnosed with CRC, of whom 5900 were residents of the province of Quebec. The 5-year survival rate in 2002–2004 was 61% for men and 62% for women².

Even after complete resection of the colorectal tumour, distant metastases have been noted to develop in 10%–15% of patients. Of all metastases, those to liver are found in 20%–30% of cases, and to lung, in 10%–20%; brain metastases are quite rare^{3,4}. The percentage of CRC patients developing brain metastases during the course of their disease is reported to range from 2% to 12%⁵, but the effect of such metastases on the patient's prognosis is significant. Indeed, patients with brain metastases from CRC have a shorter survival than do those with brain metastases originating from other primary tumours.

With improvements in the management of colorectal tumours, the incidence of metastases at previously uncommon sites is suspected to rise⁶. Previously, the treatment offered for brain metastases was essentially directed at palliating neurologic symptoms. With the advent of new targeted therapies and the resulting improvements in outcome for CRC patients, the management policy for brain metastases has changed. Regardless of the therapy used to

address brain metastases, reported median survival ranges from 2.8 months to 6 months. Whole-brain radiotherapy alone is the most common therapeutic modality administered; however, it is associated with the worst prognosis (the survival rate ranges from 2.2 months to 4 months). Surgical interventions have been shown to improve survival to 6–10 months^{5–7}. Unfortunately, identification of the predictors of survival in the literature is still equivocal. The purpose of the present study was to analyze parameters related to the presentation and outcome of patients with brain metastases from CRC.

2. METHODS

All patients with brain metastases from CRC treated between 2000 and 2009 were identified from SARDO, the databases of the Centre Hospitalier de l'Université de Montréal, and reviewed retrospectively. Patients with any other type of cancer were excluded from the study. For the 48 patients included, we retrieved data pertaining to age at diagnosis, location of the primary tumour, other systemic metastases, interval between CRC diagnosis and identification of brain metastases, number and location of the brain metastases, symptoms at presentation, and treatment modality. A synchronous brain metastasis was defined as a brain metastasis diagnosed within 60 days of the diagnosis of the primary colorectal tumour; otherwise, the brain metastasis was considered metachronous.

Associations between patient and tumour characteristics, treatment modality, and survival were assessed using the Kaplan–Meier method. The log-rank test was used to assess the effect of individual factors on survival.

The study was approved by the chief of medical affairs of the Centre Hospitalier de l'Université de Montréal.

3. RESULTS

Among the 48 patients who were treated for CRC at our institution between 2000 and 2009 and who developed brain metastases, sex was evenly distributed (25 men, 23 women). The median age at diagnosis of brain metastases was 63 years (range: 37–84 years). The median interval between diagnosis of the primary tumour and identification of the brain metastases was 24 months. The primary tumour originated in the rectum in 23 patients (48%), in the sigmoid colon in 6 patients (12%), and in the colon in 19 patients (40%) (Table 1). At diagnosis of brain metastases, 43 patients (90%) also had other systemic metastases, mainly to lung (64%) and liver (50%).

Thirty patients presented with a single brain lesion. Brain metastases from CRC were located in the supratentorial compartment in 26 patients (54%); the infratentorial compartment in 11 (23%); and in both compartments in 11 (23%). The most frequent

presenting symptoms of the brain metastases were neurologic deficit (64%), headache (17%), and confusion or somnolence (19%).

Brain was the unique site of metastasis in 5 patients. In one who presented for headache and vertigo, brain imaging by computed tomography showed a single left cerebellar lesion, and a complete work-up disclosed a rectal mass with no other metastases. In another with a stage III disease who, 1 month after colectomy, presented for headache and blurred vision, a left occipital mass was discovered. This patient underwent surgery but refused postoperative radiation therapy. After a left parieto-occipital recurrence 7 months later, she underwent reoperation and received whole-brain radiation therapy. The remaining patients in this group were known to have CRC, all with stage III disease. Their brain metastases were identified 6 months, 2 years, and 6 years after the initial diagnosis (Table II).

In 11 patients whose brain metastases were diagnosed within 60 days of the primary cancer diagnosis, the metastases were considered to be synchronous. Of those 11 patients, 7 presented first with neurologic symptoms, and the subsequent work-up led to the CRC diagnosis. The remaining 4 patients were known to have CRC when the brain metastases were diagnosed. The origin of the cancer was the rectum in 4 patients and the cecum in the remaining 7.

Median survival after a diagnosis of brain metastases from CRC was 4 months (range: 1–13 months). Of 8 patients who received no treatment for their brain metastases, 7 were not candidates for any treatment because of alteration of general status; they voluntarily declined any treatment. Median survival of those patients was 2 months. In 2 patients who underwent surgery and refused subsequent radiation therapy, median survival was 3 months. Whole-brain radiation therapy was offered to 22 patients; their median survival was 4 months. Compared with patients treated with either radiotherapy or surgery alone, the 16 patients treated with surgery and subsequent whole-brain radiation therapy experienced significantly improved survival (13 months, $p < 0.001$, Figure 1).

The difference in median survival between men and women was not statistically significant (5 months vs. 4 months respectively, $p = 0.6$). Other factors, including age (<70 years vs. ≥ 70 years), location (infratentorial vs. supratentorial vs. both), number of brain metastases (1 vs. 2–3 vs. ≥ 4), and timing of diagnosis (synchronous vs. metachronous), were analyzed, but none were observed to affect survival.

4. DISCUSSION

Brain metastases are a common manifestation of systemic cancers, far outnumbering primary brain tumours⁸. Those originating from a colorectal primary are relatively rare, with a reported incidence ranging from 1% to 4%^{9,10}. A population-based

BRAIN METASTASES IN COLORECTAL CANCER

TABLE I Characteristics of 48 patients diagnosed with brain metastases from colorectal cancer

Characteristic	Patients				
	Overall	No treatment	Surgery	Radiotherapy	Surgery plus radiotherapy
Sex (men/women)	25/23	3/5	0/2	15/7	7/9
Median age (years)	63	63	65	66	61
Primary tumour [n (%)]					
Colon	19 (40)	2	1	11	5
Sigmoid	6 (12)	1	0	3	2
Rectum	23 (48)	5	1	8	9
Brain lesions [n (%)]					
1	30 (63)	3	2	9	16
2–3	8 (16)	2	0	6	0
>3	10 (21)	3	0	7	0
Metachronous	37	6	0	19	12
Synchronous	11	2	2	3	4
Extracranial metastases [n (%)]	43 (90)	7 (87.5)	1 (50)	21 (94.5)	14 (87.5)

TABLE II Clinical characteristics of patients presenting with brain metastases as the unique site of metastasis

Sex	Age (years)	Primary tumour	Symptoms	Metastasis localization	Timing of diagnosis	Treatment	OS after diagnosis (months)
Female	71	Rectum	Vertigo, headache	Cerebellum	Synchronous	Surgery	3
Female	54	Colon	Blurred vision	Occipital lobe	Synchronous	Surgery/WBRT	11
Female	47	Rectum	Headache	Occipital lobe	Metachronous	Surgery/WBRT	4
Male	41	Rectum	Vertigo, headache	Cerebellum	Metachronous	Surgery/WBRT	10
Female	73	Colon	Left hemiparesis	Right frontal lobe	Metachronous	WBRT	2

OS = overall survival; WBRT = whole-brain radiation therapy.

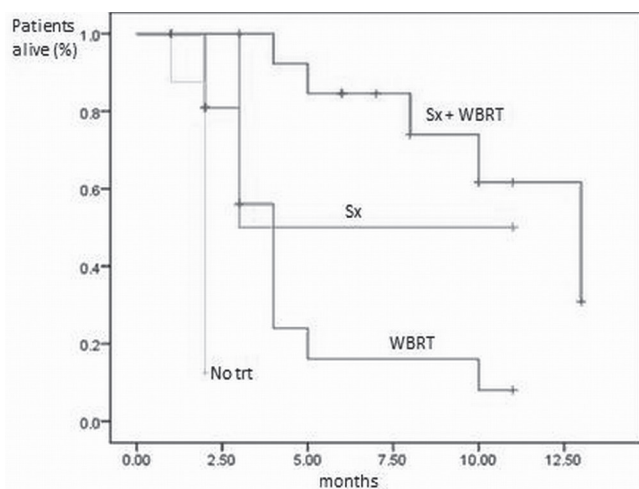


FIGURE 1 Overall survival after a diagnosis of brain metastasis from colorectal cancer in patients treated with surgery (Sx) and whole-brain radiotherapy (WBRT) compared with Sx alone, WBRT alone, and no treatment (No trt).

study showed the 5-year cumulative incidence of brain metastases to be approximately 16%, 10%, 7%, and 5% for patients with lung cancer, renal cell cancer, melanoma, and breast cancer respectively; brain metastases accounted for fewer than 1% of metastases in CRC¹¹.

Although brain metastases from CRC are less common than those from malignant melanoma and lung and breast cancer, their effect on prognosis is equally serious¹². Most brain metastases from solid tumours result from hematogenous spread rather than from dissemination via cerebrospinal fluid. Approximately 80% of lesions are found in the cerebrum, 15% in the cerebellum, and 5% in the brainstem¹³. Posterior fossa metastases originate mainly from pelvic or abdominal primary cancers, possibly through the Batson vertebral venous plexus. Alden *et al.*¹⁰ found that brain metastases from CRC are infrequently the sole site of metastatic disease, and the survival of patients with brain metastases is dismal, at a reported median of less than 3 months¹⁴.

In our series, the median overall survival of patients after a brain metastasis diagnosis was also poor (about 4 months). The primary tumour was more frequently localized in the distal colon—rectum (48%) and sigmoid (12%)—than in the proximal colon (40%), which is consistent with data from other groups^{4,7}. Differences in the vascular anatomy of the proximal and distal parts of the colon probably explain the disparity in metastatic pattern and the higher incidence of brain metastases from rectosigmoid cancer.

Most of our patients had supratentorial brain lesions. Patients with single and multiple brain lesions had comparable survivals, and 90% had concomitant extracerebral metastases upon diagnosis, with lung (64%) and liver (50%) being the most common metastatic sites. That finding may suggest that brain metastases are a late event in CRC, with diagnosed patients already having a high burden of extracranial disease. The poor survival after diagnosis of brain metastases could be explained by the presence of disseminated disease, poor performance status, and patient choice to decline some treatment options rather than by the effects of the brain disease alone.

Current treatment recommendations for brain metastases from CRC do not differ from those for brain primaries⁶. Until recently, the use of chemotherapy to treat central nervous system metastases has been unsatisfactory. In treating brain metastases, the objective is to palliate symptoms and to improve survival and quality of life. Survival of patients treated with steroids alone is about 2 months⁷, which may be extended to 3–6 months with radiotherapy^{7,15}. Patients treated with surgery alone had a survival of 9 months⁷. In our study, neither radiation therapy nor surgery alone improved survival over the survival achieved with corticosteroid treatment. The only survival improvement was seen in patients treated with surgical resection followed by whole-brain radiation therapy, a finding that has been reported by other groups as well^{7,16}. That result may reflect selection bias, because patients that are candidates for the combined treatment modality are those with good performance status, a solitary brain lesion, and controlled systemic disease.

Treatment of metastatic CRC has changed markedly since the incorporation of monoclonal antibodies (bevacizumab, cetuximab, panitumumab) into chemotherapeutic regimens. Those new therapies have led to better and longer patient survival. The incidence of central nervous system metastases is increasing, an observation that may be explained by earlier detection with new imaging techniques and by advances in therapy for metastatic disease.

It is not clear whether patients with advanced CRC, especially those with lung and liver metastases, should undergo earlier brain imaging to diagnose secondary brain lesions. However, given

that brain metastases are not common in CRC, routine brain imaging by computed tomography or magnetic resonance may not cost-effectively change patient survival.

5. CONCLUSIONS

Although brain metastases from CRC are a rare complication, their impact on survival remains serious. Earlier diagnosis followed by an aggressive therapeutic approach may be the best option for long-term disease control.

6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial disclosures to make and no conflicts of interest to report.

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