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## Colorectal cancer: Metastases to a single organ

Sina Vatandoust, Timothy J Price, Christos S Karapetis

Sina Vatandoust, Christos S Karapetis, Department of Medical Oncology, Flinders Medical Centre, Adelaide, SA 5042, Australia

Sina Vatandoust, Christos S Karapetis, Flinders Centre for Innovation in Cancer, Flinders University, Adelaide, SA 5042, Australia

Timothy J Price, Department of Medical Oncology, The Queen Elizabeth Hospital, Adelaide, SA 5011, Australia

Timothy J Price, The University of Adelaide, Adelaide, SA 5000, Australia

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**Correspondence to:** Sina Vatandoust, MD, FRACP, Department of Medical Oncology, Flinders Medical Centre, Bedford Park, Adelaide, SA 5042, Australia. [sina.vatandoust@health.sa.gov.au](mailto:sina.vatandoust@health.sa.gov.au)  
Telephone: +61-8-82048997  
Fax: +61-8-82044997

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### Abstract

Colorectal cancer (CRC) is a common malignancy worldwide. In CRC patients, metastases are the main cause of cancer-related mortality. In a group of metastatic CRC patients, the metastases are limited to a single site (solitary organ); the liver and lungs are the most commonly involved sites. When metastatic disease is limited to the liver and/or lungs, the resectability of the metastatic lesions will dictate the management approach and the outcome. Less commonly, the site of solitary organ CRC metastasis is the peritoneum. In these patients, cytoreduction followed by hyperthermic intraperitoneal chemotherapy may improve the outcome. Rarely, CRC involves other organs, such as the brain, bone, adrenals and spleen, as the only site of metastatic disease. There are limited data to guide clinical practice in these cases. Here, we have reviewed the disease characteristics, management approaches and prognosis based on the metastatic disease site in patients with CRC with metastases to a single organ.

**Key words:** Colorectal cancer; Metastasis; Prognosis; Disease management; Liver metastasis; Lung metastasis; Brain metastasis; Bone metastasis; Peritoneal metastasis

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**Core tip:** Colorectal cancer (CRC) is a common malignancy. In CRC patients, metastases are the main cause of cancer-related mortality. Cancer spread can sometimes be limited to a single organ, representing a malignancy with a distinct biological profile and clinical characteristics. In CRC patients with single site metastases, the resectability of the metastases and the site of metastatic disease affect the clinical characteristics, the optimal management approach and the prognosis.

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## INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies worldwide<sup>[1]</sup> and continues to be one of the leading causes of cancer-related death globally<sup>[2]</sup>. In CRC patients, similar to those with other malignancies, metastases are the main cause of cancer-related mortality. Distant metastatic disease is present in approximately 25% of patients at initial diagnosis, and half of CRC patients will develop metastatic disease<sup>[3]</sup>. Most patients with metastatic CRC have incurable disease. In this group of patients, median survival has improved from less than 10 mo with best supportive care to 14 mo with fluoropyrimidine treatment<sup>[4,5]</sup> and to more than 2 years with a combination of various cytotoxic<sup>[6,7]</sup> and biologic agents<sup>[8,9]</sup>.

The concept of oligometastatic cancer was first proposed two decades ago<sup>[10]</sup>. Cancer spread can sometimes be limited to a single organ, representing a malignancy with a peculiar biological profile and clinical characteristics. In this group of patients, the prognosis differs significantly: some patients with resectable metastases can be offered potentially curative treatments, and occasionally, chemotherapy can be used to render the metastases resectable<sup>[11]</sup>, but the prognosis in others remains grim. Numerous factors are involved in this difference in prognosis. Here, we have reviewed the literature to clarify the prognosis of CRC patients with metastases to a single site (solitary organ) and the prognostic role of the metastatic disease site.

## LIVER

The liver is the most common site of metastasis from CRC; this is thought to be due to the venous drainage of the colon and rectum. Approximately 50% of CRC patients will develop liver metastasis during the course of the disease<sup>[12]</sup>. In patients with metastatic CRC, the liver is the sole organ with metastases in approximately one-third of patients<sup>[13]</sup>. In a retrospective analysis of 780 patients with CRC and liver-only metastases (including both resectable and non-resectable cases), the median overall survival (mOS) was reported as 22.8 mo<sup>[14]</sup>. Depending on the resectability of the metastases, patients with liver metastases from CRC have different prognoses.

## RESECTABLE LIVER METASTASIS

Approximately 20% of patients with hepatic metastases

**Table 1 Hepatic metastasectomy: Large retrospective studies**

Ref.	Patients, <i>n</i>	Median overall survival (mo)	5-yr survival	10-yr survival	20-yr survival
Rees <i>et al</i> <sup>[19]</sup> , 2008	929		36%	23%	
Choti <i>et al</i> <sup>[17]</sup> , 2002	226	46	40%	26%	
Fong <i>et al</i> <sup>[22]</sup> , 1999	1001	42	37%	22%	
Nordlinger <i>et al</i> <sup>[18]</sup> , 1996	1568		28%		
Scheele <i>et al</i> <sup>[20]</sup> , 1995	434	40	33%	20%	17%

present with resectable disease at diagnosis<sup>[15]</sup>. According to one consensus statement, contraindications to resection include the following: unresectable extrahepatic disease, more than 70% liver involvement, liver failure, and being surgically unfit<sup>[16]</sup>. Nevertheless, the selection criteria for hepatic resection are evolving and are beyond the scope of this review. In patients who undergo resection of liver metastases, a 5-year survival of 25% to 58%<sup>[17-25]</sup> and a 10-year survival of 17% to 28%<sup>[17,19-21,26]</sup> have been reported, and one study has reported a 20-year survival of 17%<sup>[20]</sup> (Table 1). A systematic review of the published data showed a 5-year survival of approximately 30%, with the majority of these patients being disease-free<sup>[27]</sup>. Studies have shown that a significant number of 5-year survivors progress to cancer-related death<sup>[21,28]</sup>. However, it appears that patients who survive 10 years are cured<sup>[21,29]</sup>. In patients with resectable liver metastases, perioperative chemotherapy with the FOLFOX regimen has been shown to improve progression-free survival<sup>[30]</sup>. However, this approach has not been shown to improve overall survival<sup>[31]</sup>.

## NON-RESECTABLE LIVER METASTASIS

The majority of patients with liver metastases from primary CRC have non-resectable disease<sup>[32-35]</sup>. Historical data show that without treatment, these patients have a poor prognosis<sup>[36,37]</sup>. Retrospective studies of this population suggest that the amount of liver replaced by the tumor is the most significant indicator of outcome<sup>[38-42]</sup> (Table 2). In a large study by Stangl *et al*<sup>[39]</sup> that included 484 patients, 189 who did not have extrahepatic metastases had a median survival of 9.6 mo. In this group, patients with a lower volume of liver replaced by tumor and grade 1-2 (primary) disease with no extrahepatic and no mesenteric lymph node involvement had the highest median survival (21.3 mo; range, 5-68 mo; 95%CI: 15.6-34.1). According to these studies, the median survival of patients with CRC metastases confined to the liver with a low disease volume is in the range of 11 to 18 mo; with a higher disease volume, the range is 6 to 8 mo. These studies predate the currently available systemic treatments. Nevertheless, even with the improvements in the survival of patients with metastatic CRC using current chemotherapy regimens,

**Table 2** Retrospective studies of patients with unresected liver metastases

Ref.	Patients without extrahepatic metastases, <i>n</i>	The extent of liver involvement	Median overall survival (mo)	Treatments
Yamamura <i>et al</i> <sup>[41]</sup> , 1997 ( <i>n</i> = 73)	67	Metastases in one lobe	13	Chemotherapy (chemotherapy did not significantly affect survival in multivariate analysis)
		Less than four metastases in both lobes	12	
		More than five metastases in both lobes	6	
Stangl <i>et al</i> <sup>[39]</sup> , 1994	189	≤ 25%	11.1	No treatment
		> 25%	6.3	
Chang <i>et al</i> <sup>[38]</sup> , 1989 ( <i>n</i> = 67)	49	< 25%	15.1	Floxuridine (hepatic arterial or intravenously)
		25%-75%	23.8	
		> 75%	14.8	
			7.3	
Arnaud <i>et al</i> <sup>[40]</sup> , 1984 ( <i>n</i> = 56)	(not specified)	One lobe	17	NA
		Both lobes	8.23	
Johnson <i>et al</i> <sup>[42]</sup> , 1981	51	Solitary liver metastasis ( <i>n</i> = 12)	18	NA
		Multiple metastases in one lobe ( <i>n</i> = 6)	7	
		Multiple metastases in both lobes ( <i>n</i> = 33)	8	

mOS: Median overall survival; NA: Not available.

patients with non-resectable liver metastases have a low 5-year survival rate<sup>[43]</sup>.

In some patients, hepatic metastases that are initially deemed non-resectable can be resected after neoadjuvant chemotherapy<sup>[11,44,45]</sup>. Similar 5-year survival rates have been reported in this group compared to patients who initially had resectable disease<sup>[46]</sup>. In some patients with non-resectable liver lesions, radiofrequency ablation is an option that may provide tumor control. In this group of patients, a median survival of 36-59 mo has been reported with local ablation<sup>[47-50]</sup>. Selective intraoperative radiotherapy (SIRT) is another liver-directed treatment strategy that has been shown to control the progression of metastatic colon cancer within the liver. This involves injecting yttrium-labeled microspheres into the liver *via* the hepatic artery<sup>[51]</sup>. Randomized phase III trials that evaluated the addition of SIRT to systemic chemotherapy as part of the treatment of metastatic CRC limited to the liver are underway<sup>[52-54]</sup>. The SIRFLOX study results were presented in the recent Annual Meeting of American Society of Clinical Oncology. In this study addition of SIRT to standard chemotherapy did not improve overall progression free survival but improved liver progression free survival. Overall survival results from this study are not available yet<sup>[52]</sup>.

## LUNG

The lungs are the second most common site of distant metastases from CRC<sup>[55-57]</sup>. Previous studies have shown that 10%-15% of patients with CRC develop lung metastases during the course of the disease<sup>[58,59]</sup>. Compared to colon cancer, patients with rectal cancer are at a higher risk of synchronous and metachronous lung metastases<sup>[57-59]</sup>. This is believed to be due to direct spread of rectal cancer into systemic circulation through the hemorrhoidal veins<sup>[60]</sup>. Isolated lung metastases are thought to be less common: in two

retrospective studies, 2.8%<sup>[58]</sup> and 7.4%<sup>[61]</sup> of patients were reported to have isolated lung metastases. In the multivariate analysis of 5654 CRC patients, those with isolated lung metastases seemed to have a significantly better prognosis compared to those who had another metastatic location in addition to the lungs<sup>[58]</sup>. One retrospective study showed a significantly better prognosis for patients with lung-only disease compared to those with a single organ metastasis to another organ<sup>[14]</sup>.

## RESECTABLE LUNG METASTASIS

In the absence of randomized prospective studies and based on data from retrospective series, it is widely accepted that surgery should be considered for the management of resectable pulmonary metastases from CRC<sup>[62-64]</sup>. Based on the literature, the suitability criteria for the resection of pulmonary metastases include the following: control of the primary tumor; possible complete resection; and adequate pulmonary reserve to tolerate the planned resection<sup>[65]</sup>. Various series have shown mOS of 36.2 mo to 49 mo, 5-year survival rates of 32% to 68%<sup>[66-77]</sup> and 10-year survival rates of 11% to 34%<sup>[75,78-80]</sup> in patients with CRC undergoing lung metastasectomy (Table 3).

A meta-analysis of the published data has suggested that in this group of patients, the absence of thoracic node involvement, prolonged disease-free interval (between primary tumor and metastatic spread), normal pre-thoracotomy carcinoembryonic antigen (CEA), and a single pulmonary lesion are associated with prolonged survival<sup>[63]</sup>; of these criteria, the last three have also been shown to be of prognostic value in a separate analysis<sup>[64]</sup>.

## NON-RESECTABLE LUNG METASTASIS

In the majority of patients with CRC and pulmonary

**Table 3** Retrospective studies including  $\geq 100$  patients with resectable lung metastases from colorectal cancer

Ref.	Year	n	median survival (mo)	5-yr survival rate (%)
Borasio <i>et al</i> <sup>[66]</sup>	2011	137	36.2	55
Hwang <i>et al</i> <sup>[67]</sup>	2010	125	37	48
Riquet <i>et al</i> <sup>[68]</sup>	2010	127	45	41
Watanabe <i>et al</i> <sup>[69]</sup>	2009	113	NA	68
Welter <i>et al</i> <sup>[70]</sup>	2007	169	47.2	39
Yedibela <i>et al</i> <sup>[71]</sup>	2006	153	43	37
Inoue <i>et al</i> <sup>[72]</sup>	2004	128	49	45
Kanemitsu <i>et al</i> <sup>[73]</sup>	2004	313	38	38
Pfannschmidt <i>et al</i> <sup>[74]</sup>	2003	167	40	32
Saito <i>et al</i> <sup>[75]</sup>	2002	165	NA	40
Zink <i>et al</i> <sup>[76]</sup>	2001	110	41	32

NA: Not available.

involvement, the lung metastases are not resectable. In a prospective study of 70 patients with CRC and isolated unresectable lung metastases who were treated with chemotherapy<sup>[81]</sup>, the mOS was 19 mo (95%CI: 12.6-25.4 mo, range: 5-44 mo), with a 2-year OS rate of 38.8%. The first response assessment seemed to be a prognostic factor, with a mOS of 27 mo (95%CI: 23.4-30.6 mo) for patients with a partial response compared with 16 mo (95%CI: 8.3-23.7 mo) and 8 mo (95%CI: 5.2-10.8 mo) in patients with stable disease and disease progression, respectively ( $P < 0.01$ ). Notably, the lung metastases in a small proportion of patients (5.7%) in this study became resectable with chemotherapy<sup>[81]</sup>. In a retrospective study of patients with non-resected lung metastases who underwent palliative chemotherapy, Mitry *et al*<sup>[58]</sup> reported 3-year survival rates of 14.4 and 15.3% for metachronous and synchronous lung metastases, respectively; the 5-year survival rates were reported to be 0 and 8.4%, respectively, for the same cohorts.

## PERITONEUM

In retrospective studies of CRC patients, the rate of peritoneal metastases has been reported to be between 4% and 13%<sup>[82-85]</sup>, with the peritoneum as the only site of metastatic disease in approximately 4% of patients<sup>[82,84]</sup>. The risk factors for peritoneal involvement include right-sided tumor, advanced T-stage, advanced N-stage, poor differentiation grade, mucinous adenocarcinoma and younger age at diagnosis<sup>[86]</sup>. Historically, peritoneal carcinomatosis from CRC has been associated with poor prognosis with a median survival of 6-8 mo<sup>[83,87]</sup>. Intraperitoneal chemotherapy has been suggested to improve outcomes in these patients. In a retrospective analysis of 523 patients with CRC and peritoneal involvement as the sole metastatic site who underwent cytoreductive surgery and intraperitoneal chemotherapy, the overall 1-year, 3-year, and 5-year survival rates were 81%, 41%, and 27%, respectively. In that study, the median

survival was 30.1 mo<sup>[88]</sup>.

A randomized trial by Verwaal *et al*<sup>[89]</sup> showed that in patients with peritoneal metastases of CRC or positive cytology of ascites, in the absence of other distant metastases, cytoreduction followed by hyperthermic intraperitoneal chemotherapy (HIPEC) offers a statistically significant advantage in terms of survival (median disease-specific survival of 22.2 mo in the HIPEC arm vs 12.6 mo in the standard arm) and progression-free survival (12.6 mo in the HIPEC arm vs 7.7 mo in the standard arm). Importantly, in the standard arm of this study, patients received chemotherapy with fluorouracil and leucovorin. In a case-control study, including 48 cases in each arm, patients with resectable peritoneal metastases had a median survival of 24 mo with systemic chemotherapy; in the cytoreduction plus HIPEC group, the median survival reached 62.7 mo, with a 5-year survival rate of 51%<sup>[90]</sup>. In another study of 67 cases and 38 controls, the mOS was significantly prolonged in the HIPEC group (34.7 mo vs 16.8 mo,  $P < 0.001$ )<sup>[91]</sup>. In both of the latter studies, both arms received modern systemic chemotherapy regimens<sup>[90,91]</sup>. This is especially important because in patients with colorectal peritoneal carcinomatosis, modern systemic therapies might be associated with improved outcome (in patients treated systemically alone or with cytoreductive surgery combined with perioperative intraperitoneal chemotherapy)<sup>[92]</sup>.

It appears that in patients with peritoneal metastases from CRC, cytoreductive surgery and intraperitoneal chemotherapy may improve the outcomes, but there is still insufficient evidence in this area<sup>[93]</sup>.

Single organ metastases from CRC are less common in other sites, and below we have reviewed some of these scenarios.

## BRAIN

Compared to liver and lung metastases, cerebral metastases from CRC are uncommon. The incidence of brain metastases in patients with CRC has been reported to be between 0.3% and 6% in different series<sup>[94-97]</sup>. The incidence might be increasing with the recent developments in the treatment of CRC<sup>[98]</sup>. In patients with brain metastases due to CRC, the primary tumor is more frequently located in the distal colon and rectum rather than in the proximal colon<sup>[99,100]</sup>. Brain metastases usually occur later in the course of the disease, and most patients already have metastases in other organs, especially the liver and lung, by the time the brain metastases are diagnosed. The prognosis remains dismal, and the median survival of patients with brain metastases from CRC has been reported to be between 3 and 6 mo<sup>[99,101-104]</sup>, which seems to be worse than the median survival of patients with brain metastasis due to other malignancies<sup>[102]</sup>. In 2%-10% of patients with brain metastasis from CRC, the brain

is the only site of metastatic disease<sup>[99,105,106]</sup>. In these patients, prognostic factors include age, performance status and a controlled primary tumor<sup>[107]</sup>.

The management approach in patients with brain metastases from solid tumors (including CRC) depends on multiple factors, including the following: patient's performance status, the status of the primary cancer, number/location of the brain lesions, and the presence of leptomeningeal disease<sup>[108]</sup>. Local treatments for brain metastases include surgery, whole brain radiotherapy (WBRT) and stereotactic radiosurgery<sup>[109]</sup>. Aggressive local treatments (surgical or radiosurgery in addition to WBRT) improve the outcomes in patients with a good performance status and a limited number of brain metastases<sup>[110,111]</sup>. Retrospective studies have shown that in selected patients with brain metastases from CRC, the mOS may improve (up to 12-15 mo) with aggressive local treatment of the brain lesions<sup>[100,101,106,112-116]</sup>.

## BONE

The incidence of bone metastasis from CRC has been reported to be 10.7% to 23.7% in autopsy series, with signet-ring cell pathology showing a high incidence of bony metastases<sup>[117]</sup>. One retrospective study using bone scans and plain radiography showed that the incidence of skeletal metastasis in patients with CRC was 6.6%; in this study, 83.1% of the patients had other organ metastases, and 16.9% were deemed to have bony metastases only<sup>[118]</sup>. One study used positron emission tomography and/or CT scans in 252 patients with a diagnosis of CRC and found the incidence of bone metastasis to be 5.5%, with a median time from diagnosis to the detection of bone metastasis of 21 mo; in this study, none of the patients had bone-only metastatic disease<sup>[119]</sup>. Different series have shown that the median survival of patients with bone metastases is between 5 to 7 mo after detecting the bone metastases<sup>[120,121]</sup>. There are only a few case reports of patients with solitary bone metastasis from CRC, with a wide range of prognoses<sup>[122-129]</sup>. In some of these cases, the use of radiotherapy<sup>[123]</sup> or surgical resection<sup>[128,129]</sup> of the bone metastases has been reported to achieve favorable results.

## OTHER ORGANS

There are only a few case reports of CRC with isolated metastases to the adrenal glands<sup>[130-132]</sup> and the spleen<sup>[133]</sup>. Surgical resection of the metastatic lesion may play a role in such cases.

## DISCUSSION

In patients with CRC and single-site metastatic disease, the site of the metastatic disease affects both the treatment approach and the prognosis. In patients with oligometastatic disease limited to the liver and/or the

lung (and maybe the peritoneum), the most essential factor that affects the prognosis is the resectability of the metastatic lesion(s). Favorable prognosis in these patients with resectable disease might be due to several factors: in general, such patients have a lower metastatic burden and are in the earlier phases of the disease compared with CRC patients with unresectable metastases, and their performance status is also generally better as they are well enough to tolerate an operation. These confounding factors make it difficult to attribute the improved survival to only one variable; nonetheless, it is likely that the favorable biology of the primary disease plays a role in this complex picture.

In patients with non-resectable oligometastatic disease, those with metastatic disease to the liver or lung have a better prognosis than those with metastases to the peritoneum, brain or bone<sup>[14]</sup>. The relationship between patterns of metastases from tumors and different prognoses can be explained by the "seed and soil" hypothesis, which was first formulated by Paget<sup>[134]</sup>. According to this hypothesis, the cancer cells (the seed) must find a suitable microenvironment in the target organ (the soil) for the metastasis to occur. Metastasis is a highly complex process that requires adaptations in the cancer cells as well as cross-talk between the cancer cells and the microenvironment both in the primary tumor as well as in the target organ<sup>[135-137]</sup>. Previous studies have shown that the involvement of specific organs depends on cancer cell gene expression<sup>[138-140]</sup>. It is conceivable that such differences in the metastasizing cancer cells not only lead to the involvement of various organs but also have an impact on the outcome of the disease. Other factors may also affect the prognosis of patients with different metastatic sites. One is the effect of the target organ on the cancer cells. Studies have shown that cancer cell gene expression, behavior and response to treatment are affected by the target organ microenvironment<sup>[141-144]</sup>.

In patients with metastatic cancer, including patients with single-site metastatic disease, there are several other factors that may also affect survival, including the involvement of vital organs, which plays an important role in the case of brain metastases. The metastatic burden and the disease volume are also important. In conclusion, in patients with CRC and single-site metastasis, the resectability of the metastases and the metastatic disease site affect the clinical characteristics, the optimal management approach and the prognosis.

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