Surgery of the Primary Tumour in Stage IV Colorectal Cancer with Unresectable Metastases

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Abstract

Since patients with incurable metastatic colorectal cancer (CRC) only have a relatively limited life expectancy, and resection of the primary tumour is accompanied by both morbidity and mortality, it is under debate whether resection of the primary tumour has an effect on survival or quality of life. The rationale behind the resection strategy is that prophylactic surgery prevents future complications. With current new chemotherapy regimens, a relatively low number of patients with metastatic CRC require surgery for their primary tumour. Many studies concerning the management of incurable stage IV CRC have been performed and most studies suggest a survival benefit for patients undergoing surgical resection of the primary tumour compared with those who received palliative treatment. However, in stage IV CRC with unresectable metastases, the role of a palliative resection of the primary tumour has never been assessed properly. Because randomised clinical trials are lacking, it is difficult to draw conclusions from the present literature.

Keywords

Stage IV colorectal cancer, unresectable metastases, resection of the primary tumour, palliative chemotherapy

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Colorectal cancer (CRC) is one of the two most commonly diagnosed cancers, with approximately 1.2 million new cases each year and more than 600,000 annual deaths estimated to occur worldwide.[1] In addition, roughly one-fifth of patients present with incurable disseminated disease.[2] In the last decade, the development of new chemotherapeutic biological agents has significantly improved overall survival (OS) of these patients.[3–12]

A palliative resection of the primary tumour is frequently performed[13] and there is a clear indication for surgery when patients present with symptoms of the primary tumour. However, if patients present with absent or mild symptoms, the indication for resection is less obvious. Since patients with incurable metastatic CRC (mCRC) only have a relatively limited life expectancy, and resection of the primary tumour is accompanied by both morbidity and mortality,[14–16] it is under debate whether resection of the primary tumour has an effect on survival or quality of life.[17,18] Many studies concerning the management of incurable stage IV CRC have been performed; however, the advantage of a palliative resection of the primary tumour has never been assessed properly.[19] Moreover, most studies do not even report whether a resection of the primary tumour has been performed.[20]

In this article we aim to evaluate the role of surgery of the primary tumour in stage IV CRC with unresectable metastases.

Treatment of Metastatic Colorectal Cancer

At diagnosis of CRC, approximately 20 % of patients present with synchronous mCRC, and the liver is the predilection site in half of these patients.[21,22] The lungs represent the second most common site of metastases from CRC and, according to non-population-based studies, lung metastases are present in 10–15 % of patients with CRC.[23,24]

When metastases are limited, a possible curative treatment can be obtained by surgical resection; however, only 15–20 % of patients are resectable.[25] Median five-year survival for patients undergoing an R0 resection of the metastases is approximately 30 % (range 15–67 %).[26] Despite complete resection and neoadjuvant or adjuvant chemotherapy regimens, recurrences occur in 75 % of the patients.[27]

Extrahepatic disease in combination with liver metastases was generally considered a contraindication for surgery.[28] However, resection of both intrahepatic and extrahepatic colorectal metastases should be considered if resection of all metastatic sites can be complete and the disease is controlled by chemotherapy.[29]

In patients with unresectable metastases, palliative systemic chemotherapy is the treatment of choice. With systemic combination chemotherapy, response rates of 40–70 % have been reported, resulting in a median OS time of approximately 22 months.[30–32] The most frequently used combinations are oxaliplatin or irinotecan plus

Table 1: Study Results on Stage IV Colorectal Cancer and Unresectable Metastases, in which the Non-resection Arm Was Treated with Chemotherapy

Author	Years of Study		Number of Patients	Received Chemotherapy (%)	Secondary Palliative Surgical Intervention	Palliative Resection of Primary Tumour
Scoggins[40]	1985–1997	Resection	66	0	2 (3 %)	-
		Chemo	23	100	2 (9 %)	0
Tebbutt[50]	1990–1999	Resection	280	100	14 (5 %)	-
		Chemo	82	100	8 (10 %)	1 (1 %)
Konyalian[58]	1991–2002	Resection	62	58	#	-
		Chemo	47	60	17 (36 %)	0
Galizia[62]	1995–2005	Resection	42	100	0	-
		Chemo	23	100	6 (26 %)	¶
Ruo[51]	1996–1999	Resection	127	0	6 (5 %)	-
		Chemo	103	83	30 (29 %)	0
Michel[45]	1996–1999	Resection	31	97	0	-
		Chemo	23	100	5 (22 %)	3 (13 %)
Sarela[39]	1997–2000	Resection	-	-	-	-
		Chemo	24	88	6 (25 %)	4 (17 %)
Benoist[44]	1997–2002	Resection	32	94	0	-
		Chemo	27	100	4 (15 %)	3 (11 %)
Karoui[71]	1998–2007	Resection	85	99	27 (32 %)	-
		Chemo	123	100	15 (12 %)	15 (12 %)
Aslam[65]	1998–2007	Resection	366	63	¥	-
		Chemo	281	36	128 (46 %)	0
Bajwa[66]	1999–2005	Resection	-	-	-	-
		Chemo	67	100	27 (40 %)	25 (37 %)
Muratore[43]	2000–2004	Resection	-	-	-	-
		Chemo	35	100	1 (3 %)	0
Poultsides[37]	2000–2006	Resection	-	-	-	-
		Chemo	233	100	16 (7 %)	8 (3 %)
Seo[70]	2001–2008	Resection	144	100	22 (15 %)	-
		Chemo	83	100	4 (5 %)	1 (1 %)

#Konyalian[58] not described; 12 patients with complications, mostly infectious.
¶Galizia[62] not described; 2 colon perforations, 1 intestinal haemorrhage, 1 bowel obstruction, 2 surgery owing to bowel perforation or stent dislocation.
¥Aslam[65] not described; 11 full-thickness wound dehiscence, 11 intra-abdominal collections, 11 anastomotic leak, 7 intra-abdominal sepsis, 5 haemorrhage, 4 post-operative ileus, 1 splenic tear, 1 inter-loop fistula.

capecitabine, or 5-fluorouracil (5-FU) with or without bevacizumab. In case of K-RAS wild-type tumours, anti-epidermal growth factor receptor (EGFR) antibodies, such as panitumumab and cetuximab, are being used.[33]

Resection of the Primary Tumour in Patients with Unresectable Synchronous Metastatic Colorectal Cancer

Traditional surgical teaching promotes resection of the primary tumour in patients with unresectable metastases, even if the primary tumour is asymptomatic. The rationale behind this strategy is that prophylactic surgery prevents future complications of intestinal obstruction, perforation and haemorrhage.[34] However, resection does not provide immediate palliative benefit in case of an asymptomatic primary tumour, and surgery is associated with high mortality (5–13 %) and morbidity (23–48 %) in patients with metastatic disease.[16,34–37] Some studies tried to selectively apply prophylactic surgery in patients with a low metastatic tumour burden, because these patients are presumed to be at risk of obstruction because of long survival. If the metastatic tumour burden is extensive, resection of the primary tumour is unlikely to benefit the patient and is associated with a high risk of post-operative complications. These patients are probably better served by focusing on the disseminated component of their disease and starting with systemic treatment early on in their course, reserving surgery for if and when symptoms from the primary tumour are substantial.[35,38]

Other studies have shown no association between the incidence of complications and the extent of metastatic disease.[39,40] Due to recent advances in systemic chemotherapy, the risks and benefits of immediate or deferred surgical strategies are under debate.

Some clinicians in favour of the surgical approach argue that if the asymptomatic primary cancer is not resected, patients will develop disabling symptoms, such as weight loss and nutritional depletion (secondary to 'near' obstruction), and anaemia, due to bleeding of the primary tumour. Arguments supporting surgery include a lower reported operative mortality for elective surgery in patients with stage IV disease (3–6 %), compared with the more threatening operative mortality rates for non-elective resections in patients with advanced and symptomatic disease (20–40 %).[34,41,42] Another argument supporting this concept is that pre-operative staging is sometimes unclear and that surgery is considered the last and most effective diagnostic tool for the correct staging of abdominal tumours before treatment.[19] In addition, patients are provided with psychological comfort who feel that the 'cancer' has been removed.[35]

Chemotherapy First in Patients with Unresectable Synchronous Metastatic Colorectal Cancer

The advocates of a chemotherapy-first approach prefer to avoid complications, at least in asymptomatic patients. The argument of those who prefer 'elective' surgery, due to higher mortality if

Table 2: Studies Comparing Resection versus Non-resection of the Primary Tumour in Stage IV Colorectal Cancer and Unresectable Metastases

Author	Years of Study		Number of Patients	Overall Survival (months)	p-value	Post-operative Mortality %	p-value
Mäkelä[34]	1974–1983	Resection	66	15	--	5	--
		Non-resection	30	7		17	
Scoggins[40]	1985–1997	Resection	66	14.5	0.59	5	--
		Non-resection	23	16.6		--	
Liu[14]	1986–1991	Resection	57	11	--	9	--
		Non-resection	6	3		17	
Tebbutt[50]	1990–1999	Resection	280	14	0.08	--	--
		Non-resection	82	8.2		--	
Konyalian[58]	1991–2002	Resection	62	13	<0.0001	5	--
		Non-resection	47	5		6	
Beham[59]	1993–2003	Resection	46	18	<0.001	3	--
		Non-resection	21	8		0	
Costi[19]	1994–2003	Resection	83	9	<0.001	8	0.397
		Non-resection	47	4		15	
Yun[60]	1994–2004	Resection	283	15.3	<0.001	3	--
		Non-resection	93	5.3		--	
Stelzner[61]	1995–2001	Resection	128	11.4	<0.0001	12	0.784
		Non-resection	58	4.6		10	
Galizia[62]	1995–2005	Resection	42	15.2	0.03	--	--
		Non-resection	23	12.3		--	
Law[16]	1996–1999	Resection	150	7	<0.001	7	0.01
		Non-resection	30	3		21	
Ruo[51]	1996–1999	Resection	127	16	<0.001	2	--
		Non-resection	103	9		--	
Michel[45]	1996–1999	Resection	31	21	0.718	0	--
		Non-resection	23	14		--	
Mik[63]	1996–2000	Resection	52	21	NS	--	--
		Non-resection	82	14		--	
Benoist[44]	1997–2002	Resection	32	23	--	0	--
		Non-resection	27	22		--	
Kaufman[64]	1998–2003	Resection	115	22	<0.0001	--	--
		Non-resection	69	3		--	
Aslam[65]	1998–2007	Resection	366	14.5	<0.005	8	--
		Non-resection	281	5.83		--	
Bajwa[66]	1999–2005	Resection	32	14	0.005	3	--
		Non-resection	35	6		--	
Evans[67]	1999–2006	Resection	45	11	0.2056	16	--
		Non-resection	57	7		36	
Chan[68]	2000–2002	Resection	286	14	<0.001	--	--
		Non-resection	125	6		--	
Frago[69]	2000–2008	Resection	12	39.1	0.008	8	--
		Non-resection	43	1.0		6	
Seo[70]	2001–2008	Resection	144	22	0.076	0	--
		Non-resection	83	14		--	
Venderbosch[54]	2003–2004	Resection	258	17	0.0001	--	--
		Non-resection	141	11		--	
	2005–2006	Resection	289	21	0.0001	--	--
		Non-resection	159	13		--	

Resection was defined as resection of the primary tumour and non-resection was defined as surgical intervention without resection of the primary tumour. NS = not stated.

emergency surgery is required, was addressed in several studies, where the risk of death was found to be extremely low.[39,43–45] In fact, Poultsides and Paty compared their study population with studies with elective colon resection in the metastatic setting and found that it appears that this deferred approach is associated with at least comparable peri-operative mortality.[46] Another argument for chemotherapy first is that chemotherapy will not only treat the metastases but also the primary tumour; many patients will have improvements of their symptoms, therefore avoiding a possible resection.[37,47] Chau et al. demonstrated that, overall, 86 % of patients had an improvement in symptoms. Of the patients with symptoms, 71 % had diminished pelvic pain/tenesmus, 90 % had improvement in diarrhoea/constipation, 100 % had reduced rectal bleeding and 93 % had weight stabilisation or weight gain.

Advocates of the deferred surgical approach argue that surgery at diagnosis can delay or even preclude systemic chemotherapy, and that most patients will never develop symptoms and these patients

could be spared an unnecessary operation. Additionally, primary CRC surgery may alter the host immune response in such a way that tumour growth is increased in the post-operative period.[48,49] An argument against resection is that patients with unresectable metastasis from CRC who have undergone palliative resection of the primary tumour still face the prospect of further intestinal complications, which may require further surgery (see *Table 1*).[34,50] After resection of the primary tumour, these patients may develop local recurrence or adhesions which can result in obstruction and require subsequent surgery.

A decade ago, when patients were treated with single-agent 5-FU chemotherapy, approximately 20 % of patients with mCRC treated with chemotherapy required palliative surgery for symptoms related to their intact primary CRC.[39,40,46,50,51] In recent years, combinations with modern chemotherapy, such as leucovorin–5-FU–oxaliplatin (FOLFOX), capecitabine–oxaliplatin (XELOX) and leucovorin–5-FU–irinotecan (FOLFIRI), have attained response rates of 50 % and disease control rates of 85 % in prospective clinical trials.[6,52] With these modern chemotherapy regimens, approximately 7 % (range 3–22 %) of patients with mCRC required surgical palliation for their intact primary CRC, as stated in an elegant review by Poultsides.[43–46] These data suggest that, with effective chemotherapy, almost 14 asymptomatic patients need to undergo prophylactic resection of their primary tumour in order to save one patient a subsequent operation for obstruction or perforation.[46] There are indications that this has led to a decrease over time in the percentage of resection of the primary tumour in case of unresectable metastatic colorectal disease.[13]

Survival

Several studies have been performed to analyse OS of patients with stage IV CRC and unresectable metastases, to examine whether to resect the primary tumour or not. Recently, Venderbosch et al. performed a retrospective analysis of two phase III studies (Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer [CAIRO] and CAIRO-2)[8,53] and investigated the prognostic and predictive value of resection of the primary tumour in stage IV mCRC patients.[54] They demonstrated that resection of the primary tumour was a significant prognostic factor for survival in these patients. They also performed a review of the literature and identified 22 non-randomised studies, most of which showed improved survival for mCRC patients who underwent resection of the primary tumour. These results were confirmed in a systemic review by Anwar et al.[48] An overview of these studies is presented in *Table 2*.

However, in all the studies presented a selection bias cannot be excluded. Most studies were not randomised, were performed in single centres and were retrospective in nature. Patients with a good performance status were more likely to undergo surgery, whereas those with extensive disease were more likely to be offered chemotherapy instead. In the absence of randomised controlled trials, the best evidence is obtained from case-matched studies. A case-matched study by Benoist et al. compared 27 patients with asymptomatic CRC and unresectable synchronous liver metastases, who received chemotherapy, with 32 matched patients, who were treated by initial resection of the primary tumour. They found no difference in survival between the operative and the non-operative management.

Prospective studies on this topic are currently planned. Recently a protocol has been developed in the Netherlands for stage IV colon cancer patients with unresectable metastases.[55] In this trial patients will be randomised to either systemic therapy until progression or unacceptable toxicity or to resection of the primary tumour followed by systemic therapy until progression or unacceptable toxicity. The endpoint of the trial is OS and the trial is powered to identify a survival benefit of six months in the surgery group. Also the National Surgical Adjuvant Breast and Bowel Project has started a Phase II trial using 5-FU, leucovorin and oxaliplatin chemotherapy plus bevacizumab for patients with unresectable stage IV colon cancer and synchronous asymptomatic primary tumour.[56] The primary endpoint is the event rate related to the intact primary tumour requiring surgery. In both trials only patients with colon cancer will be randomised and patients with rectal cancer are excluded. Also a trial from Australia/New Zealand (A randomised phase III multicentre trial evaluating the role of palliative surgical resection of the primary tumour in patients with mCRC [SUPER]) is currently running.[57] Patients will be randomised to compare chemotherapy followed by surgery with surgery alone. The primary outcome is to determine whether surgical resection of the primary tumour in patients with stage IV CRC decreases intestinal complications and improves OS and quality of life. For patients with rectal cancer and unresectable systemic disease, a Phase III randomised clinical trial was recently conducted in the Netherlands. In this trial the role of radiotherapy in providing local control will be studied and patients will be randomised to either standard chemotherapy alone or short-course radiotherapy (5 x 5 Gy) on the primary tumour followed by standard-of-care chemotherapy. The primary endpoint is the number of patients requiring an unplanned surgical intervention related to symptoms of the primary rectal tumour.

Summary

In stage IV CRC with unresectable metastases, the role of resection of the primary tumour remains unclear. Because randomised clinical trials are lacking, it is difficult to draw conclusions from the present literature. With current new chemotherapy regimens, including vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) inhibitors, a relatively low number of patients with mCRC require surgery for their primary tumour. Most studies suggest a survival benefit for patients undergoing surgical resection of the primary tumour compared with those who receive palliative treatment. However, these results are likely to be influenced by selection bias, and therefore prospective randomised controlled trials are needed to address this question. ■

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