

# Surgery of the primary in stage IV colorectal cancer with unresectable metastases

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## Abstract

Surgery plays an important role in the treatment of patients with limited metastatic disease of colorectal cancer (CRC). Long term survival and cure is reported in 20–50% of highly selected patients with oligometastatic disease who underwent surgery. This paper describes the role of surgery of the primary tumour in patients with unresectable stage IV colorectal cancer. Owing to the increased efficacy of chemotherapeutic regimens in stage IV colorectal cancer, complications from unresected primary tumours are relatively infrequent. The risk of emergency surgical intervention is less than 15% in patients with synchronous metastatic disease who are treated with chemotherapy. Therefore, there is a tendency among surgeons not to resect the primary tumour in case of unresectable metastases. However, it is suggested that resection of the primary tumour in case of unresectable metastatic disease might influence overall survival. All studies described in the literature (n=24) are non-randomised and the majority is single-centre and retrospective of nature. Most studies are in favour of resection of the primary tumour in patients with symptomatic lesions. In asymptomatic patients the results are less clear, although median overall survival seems to be improved in resected patients in the majority of studies. The major drawback of all these studies is that primarily patients with a better performance status and better prognosis (less metastatic sites involved) are being operated on. Another limitation of these studies is that few if any data on the use of systemic therapy are presented, which makes it difficult to assess the relative contribution of resection on outcome. Prospective studies on this topic are warranted, and are currently being planned. *Conclusion:* Surgery of the primary tumour in patients with synchronous

metastasised CRC is controversial, although data from the literature suggest that resection might be a positive prognostic factor for survival. Therefore prospective studies on the value of resection in this setting are required.

## Introduction

For the majority of patients with metastatic colorectal cancer (mCRC) there are no curative options, but a significant benefit in median overall survival (OS) can be achieved with palliative systemic treatment [1]. This treatment currently consists of cytotoxic chemotherapy and targeted therapy. The 5-year OS of patients who are diagnosed with distant metastases ranges from 10% to 20% [2–4]. The median OS is improved when patients are being exposed to all available cytotoxic drugs during the course of their disease [5].

Possible screening programmes and public awareness regarding symptoms of colorectal cancer might lead to detection of early stage CRC. In that line, it is expected that there will be a decreasing percentage of patients presenting with synchronous mCRC. Recent studies have shown that this is not the case, and there is an ongoing increase in patients with synchronous mCRC, now in up to 20–25% of cases [6].

mCRC patients with synchronous metastases may present with a variable degree of symptoms of their primary tumour, and a palliative resection of the primary tumour prior to the initiation of systemic treatment is frequently performed [7]. The indication for surgery is obviously present in patients with symptoms of the primary tumour. However, in patients with few or absent symptoms the indication for resection is under debate, and its effect on survival and quality of life is uncertain [8–10]. The possible influence of a palliative resection of the primary tumour on

survival has never been assessed properly [11] and most randomised studies in mCRC do not even report whether a resection of the primary tumour has been performed [12].

In this paper we evaluate the role of surgery in controlling local complications of the primary tumour and the possible influence of resection of the primary tumour on survival.

### **Treatment of metastatic colorectal cancer (mCRC)**

Colorectal cancer (CRC) is one of the leading causes of cancer death, affecting 11,000 patients each year in the Netherlands [13]. In approximately 20% of patients distant metastases are already present at time of diagnosis [6]. The liver is the most common metastatic site. Other frequent sites of disease involvement include the lungs, regional lymph nodes and peritoneum [14]. Approximately 50% of CRC patients with early-stage disease will eventually develop liver metastases. When metastases of CRC patients are restricted to the liver, possible curative treatment can be obtained by surgical resection of the metastases. Patients with oligo-metastases restricted to the lungs may also be candidates for surgical resection. Complete surgical resection of metastatic lesions substantially improves survival rates to around 35–60% in selected patients [15–19]. Even extra-hepatic disease is no longer a contra-indication for surgery in selected patients [20]. In case of peritoneal carcinomatosis, hyperthermic intraperitoneal chemotherapy (HIPEC) is a promising treatment in selected patients with limited peritoneal carcinomatosis, and long term survival can be achieved [21]. In all other cases, CRC patients with unresectable liver and/or unresectable extrahepatic metastases are treated with systemic combination chemotherapy. Most common combinations are oxaliplatin or irinotecan plus 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 panitumumab and cetuximab are being used. These systemic chemotherapeutic combinations have response rates of 40–70% resulting in a median overall survival (OS) rate of approximately 22 months [22–24].

### **Resection of the primary tumour with “unresectable” synchronous mCRC**

#### *Local control of the primary*

Resection of the colorectal primary tumour in case of metastatic disease has been proposed traditionally.

This was performed to prevent complaints and complications because of growth of the primary tumour, such as obstruction, perforation or bleeding. Emergency surgery was associated with high morbidity and even mortality. With recent advances in systemic chemotherapy the risks and benefits of immediate or deferred surgical strategy have changed. In contrast to the response rates of 5-FU and leucovorin of approximately 15%, combinations with modern chemotherapy like infusional fluorouracil/leucovorin with oxaliplatin or irinotecan have yielded response rates of 50% and disease control rates of 85% in prospective clinical trials [25,26]. Furthermore, the addition of the antiangiogenic agent bevacizumab and/or cetuximab to the above combinations has provided clinically significant improvement in response rates. Several studies have shown that in the era of effective chemotherapy there is a relative infrequency of complications from unresected primary tumours. Several studies reported about the need for surgical intervention in case of an intact primary in case of stage IV disease. In the era of modern systemic therapy, it is noticed that less than 15% of the patients required surgical and/or other primary related interventions [27–31]. In other words, more than 85% of the patients do not need resection of their primary. This will probably reduce costs and hospital admission days. Other investigators have recognised that patients with metastatic colorectal cancer who have undergone palliative resection of the primary tumour still face the prospect of further intestinal complications, which may require further surgery [28,32]. In general practice, this has led to a decrease over time in percentage of resection of the primary tumour in case of unresectable metastases [7]. 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; therefore, patients should be spared unnecessary operations. Even in selected patients with resectable metastatic disease, the liver first approach is advocated, to prevent unnecessary colorectal surgery, which has in general more complications than straightforward liver surgery [19,33,34].

No data from prospective randomised trials are available to compare chemotherapy or resection of the primary tumour in stage IV patients with low or absent symptoms of their primary tumour. All data on this topic are derived from retrospective analyses, which do not provide reliable information on the symptoms of the primary tumour at diagnosis and/or on the indication to perform or to refrain from resection of the primary tumour. In view of this, the

National Surgical Adjuvant Breast and Bowel Project (NSABP) has started a phase II trial: “A Phase II Trial of 5-Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) Chemotherapy Plus Bevacizumab for Patients with Unresectable Stage IV Colon Cancer and a Synchronous Asymptomatic Primary Tumor” [35]. This prospective trial will deal only with colon cancer and not with rectal cancer. The primary end point is the event rate related to the intact primary tumour requiring surgery – that is, the rate of haemorrhage, perforation, fistula formation, and obstruction.

Another protocol has been developed in the Netherlands; “The role of radiotherapy in providing local control in patients with stage IV rectal cancer and unresectable systemic disease: A comparative phase III randomised clinical superiority trial, with internal pilot” (P.I.: dr C Verhoef and dr JWA Burger). In this multicentre randomised controlled trial, patients with stage IV rectal cancer with unresectable systemic disease will be randomised to either short course radiotherapy (5×5 Gy) on the primary tumour, followed by standard of care chemotherapy, or standard of care chemotherapy alone. The primary endpoint is the number of patients requiring an unplanned surgical intervention related to symptoms of the primary rectal tumour. Secondary endpoints are survival, quality of life, cost–benefit analyses and non-surgical interventions. The first patients are to be included early in 2012.

### *Survival*

Circumstantial evidence comes from data that show an increased growth rate of liver metastases upon resection of the primary tumour, as determined by an increased vascular density, proliferation rate, and metabolic growth rate [36–38]. These data suggest that the outgrowth of metastatic disease may at least partly be controlled by the primary tumour. Clinical data to support this concept are lacking. Studies in which this latter observation has been correlated with clinical outcome have not been performed. However, several retrospective studies have been done to analyse the survival in patients with “unresectable” metastatic disease between resection of the primary versus no resection of the primary. Venderbosch and colleagues recently performed a retrospective analysis of two phase III studies (CAIRO and CAIRO2) investigating the prognostic and predictive value of resection of the primary tumour in patients with synchronous mCRC treated with systemic therapy [39]. They identified resection of the primary tumour as a prognostic factor for overall survival. A major limitation of their study

is that the decision to resect the primary tumour was made prior to study entry, and that they provide no information about the reasons for non-resection, such as nonresectability of the primary tumour, poor condition of the patient, symptomatic metastases requiring priority for systemic treatment, or absence of symptoms of the primary tumour. Obviously, patients who were and who were not operated on may well represent very different patient populations. However, when these variables were included in a multivariate analysis, resection of the primary tumour remained a significant prognostic factor in the CAIRO2 study and in the subgroup of patients with one metastatic site in the CAIRO study.

Venderbosch [39] also performed a review of the literature regarding this subject (Table 1). All studies that were identified were of non-randomised design, performed in a single centre, and retrospective of nature with only one exception. The median OS was improved in resected patients in the majority of studies. An important limitation of these studies is that few if any data on the use of systemic therapy were presented, which makes it difficult to assess the relative contribution of resection on outcome.

In all studies presented to date a selection bias is likely. Therefore, prospective studies on this topic are warranted, and these are currently being planned. A protocol has been developed in the Netherlands; “The role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of coloncancer, a randomised phase III study” (P.I.: Prof dr JHW de Wilt and dr M Koopman). This prospective trial will deal only with colon cancer and in contrast to the NSABP trial mentioned earlier [35], the primary end point of this trial is overall survival. In this multicentre randomised controlled trial, patients with stage IV colon cancer with unresectable systemic disease will be randomised to either systemic therapy until progression or unacceptable toxicity, or surgery followed by systemic therapy until progression or unacceptable toxicity. The primary endpoint is overall survival. Secondary endpoints are progression-free survival, quality of life, cost–benefit analyses and (non-)surgical interventions. The first patients are to be included early in 2012.

### **Conclusion**

In stage IV colorectal cancer with unresectable metastatic disease, the role of resection of the primary tumour remains unclear. With regard to survival, most retrospective studies favour resection of the primary,

Table 1  
Median survival (months) in patients with unresectable metastatic colorectal disease; resection of the primary cancer versus no resection of the primary cancer

Author	Study period	Resection/ No resection	No. of patients	OS (mo)	<i>p</i> value
Makela [32]	1974–1983	Resection	66	15	–
		No resection	30	7	
Liu [40]	1986–1991	resection	57	11	–
		No resection	6	3	
Konyalian [41]	1991–2002	Resection	62	13	<0.0001
		No resection	47	5	
Beham [42]	1993–2003	Resection	46	18	<0.001
		No resection	21	8	
Costi [11]	1994–2003	Resection	83	9	<0.001
		No resection	47	4	
Law [43]	1996–1999	Resection	150	7	<0.001
		No resection	30	3	
Mik [44]	1996–2000	Resection	52	21	NS
		No resection	82	14	
Stelzner [45]	1995–2001	Resection	128	11.4	<0.0001
		No resection	58	4.6	
Yun [46]	1994–2004	Resection	283	15.3	<0.001
		No resection	93	5.3	
Frago [47]	2000–2008	Resection	12	23.7	0.008
		No resection	43	4.4	
Aslam [48]	1998–2007	Resection	366	14.5	<0.005
		No resection	281	5.83	
Ruo [49]	1996–1999	Resection	127	16	<0.001
		No resection	103	9	
Kaufman [50]	1998–2003	Resection	115	22	<0.0001
		No resection	69	3	
Scoggins [29]	1985–1997	Resection	66	14.5	0.59
		No resection	23	16.6	
Tebbutt [28]	1990–1999	Resection	280	14	0.08
		No resection	82	8.2	
Michel [51]	1996–1999	Resection	31	21	0.718
		No resection	23	14	
Benoist [52]	1997–2002	Resection	32	23	–
		No resection	27	22	
Galizia [53]	1995–2005	Resection	42	15.2	0.03
		No resection	23	12.3	
Bajwa [54]	1999–2005	Resection	32	14	0.005
		No resection	35	6	
Chan [55]	2000–2002	Resection	286	14	<0.001
		No resection	125	6	
Evans [56]	1999–2006	Resection	45	11	<0.0001
		No resection	57	2	
Seo [57]	2001–2008	Resection	144	22	0.076
		No resection	83	14	
Koopman [39,58]	2003–2004	Resection	297	18	0.0001
		No resection	169	12	
Tol [39,59]	2005–2006	Resection	329	21	0.0001
		No resection	149	13	

but results are likely to be influenced by selection bias. When the primary tumour is not resected and the patient has started with palliative chemotherapy, the rate of unplanned or emergency surgery is relatively low and therefore does not warrant surgery of the primary in future patients. Only retrospective studies are available and prospective randomised controlled trials are currently being initiated to address this subject.

### Conflict of interest statement

The authors have no conflict of interest to declare.

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