SYNCHRONOUS COLORECTAL LIVER METASTASES

Anne E.M. van der Pool

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"We can't solve problems
by using the same kind of thinking
we used when we created them."

Albert Einstein

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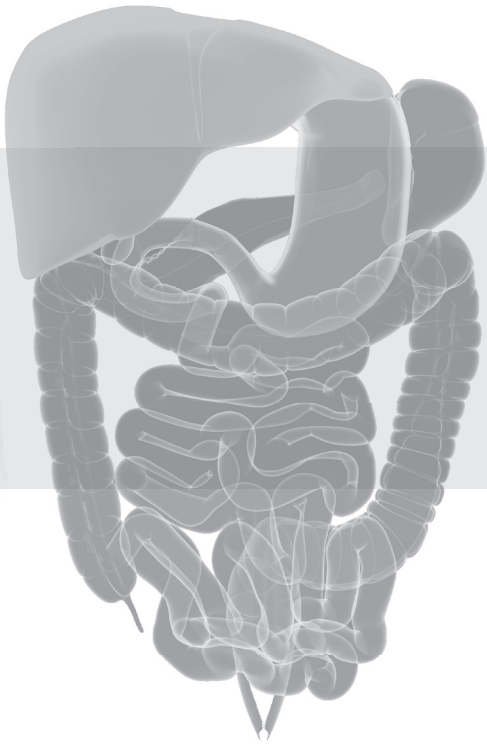
INTRODUCTION AND OUTLINE OF THE THESIS



HISTORY

Colorectal cancer is one of the most common malignancies worldwide and ranks second in cancer-related deaths in many parts of the Western world. Once in the lymph or blood vessels, colorectal cancer can quickly spread and the liver is known to be a favourable site for metastases. The presence of colorectal liver metastasis (CLM) is associated with a poor outcome.

In last centuries new developments in techniques and anatomical knowledge have improved the outcome for this group of patients. Kousnetzoff and Pensky (1896) suggested the use of haemostasis by electrocautery, tourniquet, and suturing with flexible needles for controlling bleeding.[1] The Pringle manoeuvre (1908), a technical advance which established the vascular control of the liver by compressing the portal triad, was a major step in surgery.[2] Different techniques to reduce bleeding followed, including ligation, vascular and aortic clamping.

Topographic liver anatomy generally describes the liver in terms of four lobes: right, left, quadrate, and caudate. However, the veins, arteries, and bile ducts of the liver do not conform to this anatomic division. Healey (1953)[3] used the hepatic arteries and bile ducts as the basis of division and Couinaud (1957)[4] the portal and hepatic veins. In 1999 Couinaud described that the portal and hepatic vein segmentation has to be preferred over the arteriobiliary segmentation.[5] Throughout the world, liver surgeons used different terms. In 2000, a group of international liver surgeons proposed a standardized Nomenclature. The use of Brisbane 2000 terminology of hepatic anatomy and resection has led to better communication among surgeons.[6]

Many technical tools in the last 20-30 years further refined hepatic surgery: the concept of routine intraoperative ultrasonography for liver surgery, vena portal embolization (VPE) and the introduction of the ultrasonic dissector for division of the hepatic parenchyma.[7-9] The introduction of low central venous pressure anaesthesia and vascular inflow and outflow control were essential to minimize blood loss during hepatectomy.[10] Today, resection for liver metastasis provides favourable outcomes compared with the natural history.[11]

SYNCHRONOUS COLORECTAL LIVER METASTASES

About 25% of patients who underwent a resection for colorectal cancer have liver metastases identified either preoperatively or during laparotomy, i.e. synchronous liver metastases. Synchronous presentation of CLM has been associated with poor outcome and indicates a more aggressive behaviour of the primary tumour. Many risk scores used synchronicity as a risk factor, found to be predictive of survival.[12-14]

Careful evaluation of all patients in a multidisciplinary setting allows for better identification of those patients most likely to benefit from surgical resection as opposed to those who would benefit more from nonoperative therapies, given their more aggressive disease.

Surgical management of this group of patients is a challenge. There is an ongoing discussion on the timing of chemotherapy administration in relation to resection of synchronous colorectal liver metastases (SCLM). Patients are selected for a staged or simultaneous operative approach. Potential benefits of simultaneous resection include avoidance of a second laparotomy and decreased time to initiation of adjuvant chemotherapy. At the other hand, a simultaneous resection can cause complications related to the magnitude and complexity of the combined operation. In case of a staged approach, the timing of resection is still a controversial debate. Should the primary tumour or the liver metastases be resected first?

In this thesis we will discuss the developments in the treatment of colorectal liver metastases, differences between synchronous and metachronous disease and the influence of chemotherapy. We focussed on patients with (colo)rectal cancer and synchronous liver metastases.

The incidence of colorectal cancer in the Netherlands counts 12.000 patients a year. The liver is the most common site of metastases, with 20% of patients presenting with liver metastases at diagnosis; an additional 25-30% develop liver metastases in follow-up. For patients who present with synchronous colorectal liver metastases, resection of the primary tumour is not curative unless it is performed with resection of all metastatic disease. For patients who only receive supportive care, median survival rates are poor and do not exceed 5-6 months.[15-16] Due to new effective chemotherapeutic agents the outcome has improved for these patients. Despite the gains made with chemotherapy, surgical resection of all metastatic disease offers the best chance of long-term survival. Improved imaging modalities have probably leaded to higher number of patients with liver metastases. Better surgical techniques and tools and improvements in per-operative management increase the safety of liver resection.[17] In a population based study we investigated whether all these improvements have resulted in more candidates eligible for curative hepatic resection with an increase of survival. We determined the trends in incidence of synchronous liver metastases, resection of the primary colorectal tumour, use of chemotherapy, hepatic surgery and survival in patients diagnosed in the South western part of the Netherlands with colorectal cancer and synchronous liver metastases from 1995-2007 *(chapter 2)*.

The traditional approach for SCLM has changed from palliative treatment toward an aggressive multimodality approach. General improvements in operative and anaesthetic techniques have resulted in an increase of patients eligible for surgery. The advent of more effective chemotherapeutic agents including irinotecan and oxaliplatin shows higher response rates. Ancillary procedures such as VPE and radiofrequency ablation (RFA) make it possible to treat patients with bi-lobar liver metastases who have been contraindicated previously for liver surgery. To compare all the above mentioned factors that changed the treatment policy in patients with synchronous liver metastases we studied in *chapter 3* the outcome of patients who underwent surgery for SCLM in a single centre treated before and after 2000.

In the past, stage IV disease (i.e. colorectal cancer and synchronous metastases) was a contra-indication for resection. Nowadays, the indication for liver resection has been expanded and liver surgery is the current standard in the treatment of SCLM. Little is known about the difference in characteristics between synchronous and metachronous liver metastases. Several investigators have reported that synchronicity is a poor prognostic factor in the outcome.[12-14, 18-22] It has been stated that the seemingly more aggressive tumour biology of synchronous metastases is responsible for this observation. None of these studies evaluated the outcome in the era of new effective chemotherapeutic agents. For these reasons, clinicopathological data and outcome in patients with synchronous and metachronous colorectal liver metastases, treated with primary resection first followed by partial liver resection in a second stage, were analyzed in *chapter 4*.

The treatment of rectal cancer is a challenge for a colorectal surgeon. Disease-free and overall survival depends on stage and adequate resection, in particular in terms of the circumferential resection margins.[23] The standard treatment for early stage rectal cancer is pre-operative radiotherapy (25Gy) followed by surgery.[24] Patients with locally advanced disease (clinically large T3 on colonoscopy or T4 on MRI and/or positive lymph nodes, i.e. ≥8 mm on CT or MRI) have a higher recurrence rate and will therefore more benefit from the downstaging effect of the neo-adjuvant therapy. For this reason, long pelvic irradiation (50Gy) has been applied in these patients with or without the combination of chemotherapy.[25-26] Radiotherapy may lead to high morbidity and treatment of the rectal tumour is only curative if resection of all metastatic disease is possible. Currently, patients with rectal cancer are treated with a staged (resection of the rectal primary followed by treatment of the liver metastases) or a simultaneous resection. Combined resection of hepatic metastases and the primary tumour seem appropriate. It has the appeal of a single operation, which may be beneficial in terms of quality of life and costs. In patients with a locally advanced rectal tumour morbidity is considerably higher than "regular" colorectal surgery. Combining this with partial liver resection may increase morbidity and mortality and it is generally accepted that locally advanced rectal cancer is a contra-indication for simultaneous resections.[27] It is also known, that the morbidity of extensive pelvic surgery after neoadjuvant radiation therapy is considerable.[28-29] In case of anastomotic leakage, low-pelvic abscess or persistent perineal wound infections, start of treatment of the hepatic metastases could be extended beyond 3 to 6 months or even more. Liver metastases rather than the primary tumour determine survival. A treatment strategy is needed to select those patients most likely benefit from surgical resection of both the disease as opposed to patients in whom needless surgery could be avoided and who would benefit more from nonoperative therapies. Because the liver metastases define the prognosis of the patient, it seems reasonable, to treat the hepatic metastases first. Therefore we started with the "liver first approach" in patients with locally advanced rectal cancer and synchronous liver metastases *(chapter 5 and 6)*. In the last decade, as a result of improved chemotherapy regimens for colorectal liver metastases, a rising number of patients with unresectable and resectable disease are treated with systemic chemotherapy (CTx). The theoretical advantages for patients with resectable disease include the treatment of undetected distant micro-metastases, both in the future remnant liver as well as in extra-hepatic sites, thus reducing the risk of disease recurrence after resection. It may also be useful to determine chemo-responsiveness of the tumour to select the optimal adjuvant therapy and it has the ability to identify patients with progressive intra- or extra-hepatic disease under chemotherapy in whom surgery would be inappropriate. Furthermore, preoperative CTx is being increasingly used to downsize colorectal liver metastases and appear to convert 13% of initially deemed unresectable disease to resectable disease.[30-31] Neoadjuvant chemotherapy may

also allow for a smaller resection (the potential to preserve hepatic parenchyma) and to increase the probability to achieve margin-negative resection. Furthermore, the EORTC 40983 trial[32] showed an absolute increase in rate of progression-free survival at 3 years of 7% in patients who received per-operative oxaliplatin-based CTx but no difference in overall survival was found. The rising use of chemotherapy combinations for CLM raises concerns about the potential hepatotoxicities induced by systemic drugs and the effects of these drugs on per- and postoperative outcome. In this review (*chapter 7*), the hepatic injury and per- and postoperative outcome is evaluated for the use of 5-FU/leucovorin, oxaliplatin, irinotecan and the monoclonal agents bevacizumab and cetuximab.

The presence of liver injury can result in increased postoperative complications following a liver resection, especially after a high number of cycles. An important risk factor for postoperative complications in patients undergoing a liver resection is hepatic steatosis.[33] Patients with an increasing amount of steatosis are encountered more frequently in the Western world, and the incidence is expected to rise in the near future due to the current obesity epidemic.[34] While mild steatosis (5-33%) is relatively harmless, the presence of moderate (33-66%) and severe (>66%) steatosis should be taken into consideration before performing an extended liver resection. In an era where neo-adjuvant chemotherapy is being applied more frequently and steatosis is being encountered more often, it is becoming of greater importance to screen pre-operatively patients for the presence of a marked steatosis degree (>33%). In *chapter 8* we evaluated the accuracy of CT or MRI for the detection of steatosis in patients after neo-adjuvant chemotherapy.

Fluoropyrimidines with oxaliplatin is a commonly applied combination of CTx used since 2000 in patients with CLM. It yields clinical response rates of 55% and median survival of 22 months.[35-36] However, several studies have demonstrated that oxaliplatin-based CTx can cause injury (sinusoidal dilatation) in the nontumour-bearing liver, which may influence the surgical outcome.[37-38] Nowadays, even higher clinical and pathological response rates can be achieved by combining cytotoxic agents with bevacizumab, a molecular-targeted therapy.[39-40] Adding bevacizumab to oxaliplatin-based CTx might have detrimental consequences on outcomes after resection of CLM.[41-42] Questions also remain about the optimal timing and safety of surgery in patients receiving bevacizumab. In *chapter 9* we assessed the influence of bevacizumab added to oxaliplatin-based CTx on liver injury and postoperative complications.

Despite the curative intent of hepatic resection in patients with colorectal liver metastases, more than 60% will suffer from recurrence after liver resection, the liver being the most common location.[43] Since liver resection has become safer through improvements in surgical techniques and per-operative management, repeat hepatic resection is being more frequently performed in patients with hepatic recurrences. Recent technologic advances have also made local ablative treatments (radiofrequency ablation) and external

beam radiotherapy (stereotactic body radiation therapy) for liver tumours accessible. In *chapter 10* we outlined our experience in a single centre with local treatment for recurrent liver disease.

Unfortunately, most of the patients with a recurrence are not eligible for surgery because of unfavourable tumour factors, less remnant liver after the first operation or due to a patients' general condition. Other local treatment techniques, of which radiofrequency ablation is the most widely used, offer a high local control rate in patients with liver metastases who are inoperable.[44-45] However, RFA is preferably performed in metastases <3 cm, not localized in the proximity of major blood vessels, the main biliary tract or gallbladder, or just beneath the diaphragm.[44] Therefore we studied the role of stereotactic body radiation therapy, a non-invasive technique that delivers biologically very large doses of irradiation in a few fractions *(chapter 11)*.

This thesis is concluded with a discussion in English and summary in Dutch.

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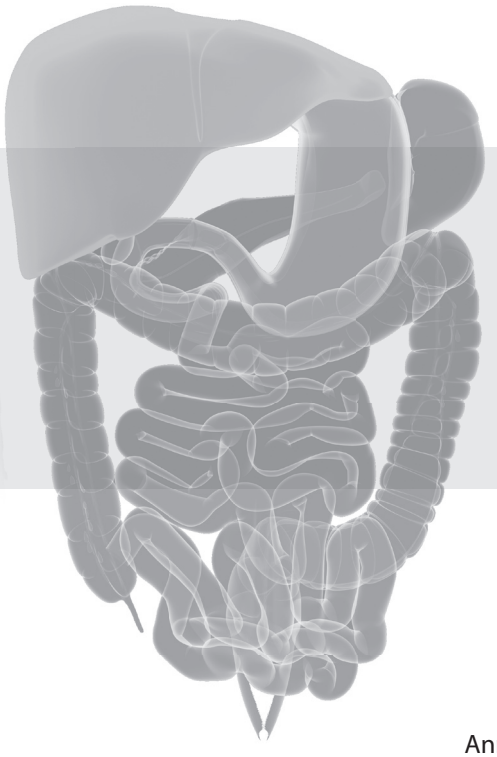
PART I

SYNCHRONOUS COLORECTAL LIVER METASTASES: TRENDS IN TREATMENT

2

TRENDS IN TREATMENT AND SURVIVAL FOR PATIENTS WITH STAGE IV COLORECTAL CANCER; A POPULATION BASED SERIES



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ABSTRACT

Aim To determine the incidence, patterns of care and survival for patients who present with stage IV colorectal cancer (CRC) in a population-based series.

Method Computer records for patients diagnosed with stage IV CRC diagnosed between 1995 through 2007 were retrieved from the Rotterdam Cancer Registry. Surgical resection of the primary tumour, chemotherapy use, hepatic surgery and survival were evaluated according to year of diagnosis, age, gender and primary tumour site.

Results In the South western part of the Netherlands 19.014 new patients with colorectal cancer were diagnosed and synchronous metastatic disease was found in 3.482 patients (18%). This proportion increased during the study period from 16% to 21%. Surgical resection of the primary tumour was performed in approximately 50% of the patients and did not change over time. Postoperative 30-day mortality was 8%. Chemotherapy use increased from 18% in the first period to 56% in the latest period. Liver surgery increased from 4% in the first period to 10% in the latest period. Median survival increased from 7 months to 12 months and two-year survival from 14% to 28%. Two-year survival declined with increasing age and was significantly worse for right-sided tumours (14%).

Conclusion Survival for patients with stage IV colorectal cancer has improved over time which is probably due to the increased use of chemotherapy and the increased rate of patients who underwent hepatic surgery.

INTRODUCTION

Colorectal cancer is the second leading cause of cancer related death, accounting for over 4500 deaths in the Netherlands in 2005 (www.ikcnet.nl). Approximately 15-25% will have liver metastases at the time of primary diagnosis.[1] For patients who present with stage IV disease, resection of the primary tumour is not curative unless it is performed with resection of all metastatic disease. Unfortunately, most patients are not considered eligible to undergo curative resection and palliative resection of the primary tumour might be required in case of obstruction, perforation or bleeding. For patients who only receive supportive care, median survival rates are poor and do not exceed 5-6 months.[2,3] Introduction of novel chemotherapeutic regimens such as oxaliplatin and irinotecan has improved the outcome for these patients.[4,5] More recently, randomized controlled trials and a population-based series reported median survival rates of 16 to 23 months by using poly-chemotherapy or combining modern chemotherapy (CTx) with targeted therapy. [3, 6-8] However, hepatic resection remains the only chance of long-term survival with reported 5-year survival rates of 45-58%.[9-11]

The purpose of this study was to determine the incidence, patterns of care and survival for patients who present with stage IV colorectal cancer in the South western part of the Netherlands. Trends in the incidence of metastases, surgery of the primary tumour, chemotherapy use, hepatic surgery and survival were studied according to period of diagnosis, age, gender and location of the primary tumour.

MATERIALS AND METHODS

Computer records for patients with colorectal cancer stage IV disease, diagnosed from 1995 to 2007, were retrieved from the Rotterdam Cancer Registry. This registry covers the South western part of the Netherlands (about 14% of the Netherlands), a region with 2.3 million inhabitants, 15 general hospitals and 1 university hospital. Newly diagnosed cancer patients are notified to the registry through notes from pathology departments and hospital discharge diagnoses. After notification, trained registration clerks collect data from the clinical records, including gender and age, date of diagnosis, tumour site, TNM stage and type of treatment. Due to privacy regulations death certificates cannot be used as an additional source of notification of cancer cases in the Netherlands. Despite the lack of this notification source, the cancer registry in the Netherlands knows a high completeness (96,2%) due to the infrastructure of the Netherlands health care and the notification procedure.[12] For the current study, information on liver surgery was checked against the Liver Surgery Database of the university hospital. Annual follow-up

information was obtained from the Municipal Personal Records Database. It includes the general personal details and contains information on vital status for all Dutch citizens.

Per-operative mortality was defined as death within 30 days from the date of resection. Year of diagnosis was recoded into three periods: from 1995-1999 (group 1, systemic treatment applied was mainly 5-FU and leucovorin), from 2000-2004 (group 2, new effective chemotherapeutic agents were already available but not generally used) and from 2004-2007 (group 3, combination chemotherapy more generally used, partly due to the Cairo trial[13]). Primary site had been coded according to the ICD-O 3 regulations but was recoded as rectum, left colon (including spleen flexure and sigmoid) and right colon. Chemotherapy was defined as an application of chemotherapy in neoadjuvant or palliative setting that was part of the primary treatment plan. Unfortunately, type of chemotherapy had not been coded in a standard manner. Surgical resection of the primary tumour was defined as any type of colorectal resection. Liver surgery implied partial hepatectomy, RFA was not registered as a specific procedure.

Tabulations were initially evaluated with chi-square statistics. Due to the large number of patients involved, even small differences proved statistically significant ($p<0.01$), reason for us to refrain from reporting p-values. Survival probabilities were determined using actuarial survival analysis from date of diagnosis until date of death or censured at 31-12-2008. Differences in survival between subgroups were tested for significance with the log-rank test. For the evaluation of survival in patients who underwent hepatectomy, survival analysis was performed from date of hepatic surgery.

Multivariate evaluation of survival was performed using Cox proportional hazard analysis. A full model was fitted comprising the variables age, gender, sub site and period. The largest category was assigned as the reference group. Hazard ratios (HR) were calculated and presented with 95% confidence intervals. A separate model was fitted after inclusion of treatment variables. The remaining impact of period was tested using the log-likelihood ratio. Due to confounding by indication and the obligatory calculation of survival from day of diagnosis, the hazard ratios for the treatment variables cannot be readily interpreted. Treatment coefficients are certainly biased because treated patients experience an upfront survival benefit, just by being alive at the start of treatment.

RESULTS

From 1995 through 2007, 19.014 new patients with colorectal cancer were diagnosed in the south-western part of the Netherlands and synchronous metastatic disease was found in 3.482 patients (18%). This proportion increased during the study period from 16% to 21% ($p<0.001$) (Table 1-1).

Table 1-1 Trends in incidence, treatment and survival in patients with stage IV disease

	N	M1	Colorectal Surgery	Chemotherapy	Hepatic surgery	Survival	
						Median (months)	2-Year
1995-1999	6680	1098 (16%)	576 (52%)	203 (18%)	41 (4%)	7.1	14%
2000-2004	7309	1348 (18%)	671 (50%)	548 (41%)	52 (4%)	8.4	19%
2005-2007	5023	1036 (21%)	517 (50%)	583 (56%)	98 (10%)	11.6	28%

Resection of the primary tumour

From the total study group, 1759 patients (51%) underwent resection of the primary tumour and this proportion remained stable over time. Patients aged 80 years or older and patients with the primary tumour located in the rectum underwent less often resection of the primary tumour (Table 1-2). Postoperative mortality (30-day) was 8%.

Table 1-2 Factors associated with resection of the primary tumour, chemotherapy receipt and hepatic surgery among stage IV colorectal cancer diagnosed in 1995-2007

	Colorectal Surgery	Chemotherapy	Hepatic surgery	Survival	
				Median (months)	2-Year
Age					
20-49	143 (57%)	174 (70%)	26 (10%)	13.4	26%
50-59	331 (54%)	369 (60%)	55 (9%)	12.5	27%
60-69	505 (53%)	454 (48%)	66 (7%)	10.4	24%
70-79	537 (50%)	296 (27%)	40 (4%)	7.3	17%
80+	248 (41%)	41 (7%)	4 (1%)	3.9	7%
Gender					
Male	987 (52%)	774 (41%)	119 (6%)	9.2	20%
Female	777 (49%)	560 (36%)	72 (5%)	8.0	17%
Site of the primary tumour					
Right	658 (56%)	431 (37%)	31 (3%)	7.1	14%
Left	831 (57%)	582 (40%)	102 (7%)	9.9	23%
Rectum	257 (36%)	282 (40%)	57 (8%)	10.3	22%

Chemotherapy

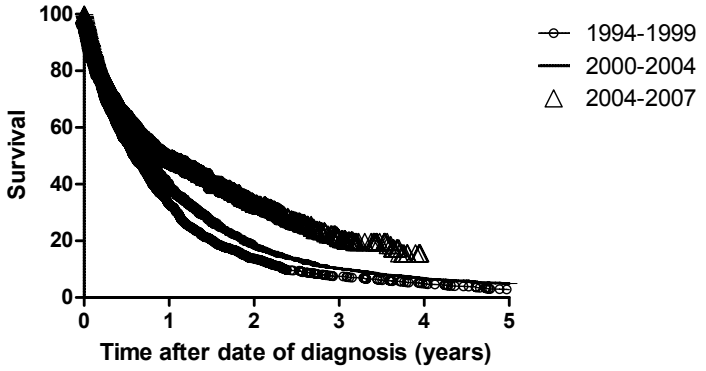
From the total study population, 1334 patients (38%) received chemotherapy in neoadjuvant or palliative setting. Chemotherapy use increased significantly over time (18% vs. 56%) and decreased with increasing age.

Hepatic surgery

In the total study group, 191 patients (5%) underwent hepatic surgery. Over time, an increase in patients who underwent hepatic surgery was reported from 4% in 1995-1999 to 10% in 2004-2007. Younger patients and patients with the primary tumour located in the left colon or rectum underwent more hepatic surgery.

Survival

Median survival increased over time from 7.1 months in the first period tot 11.6 months in the last period. Similarly, 2-year survival increased from 14% to 28% (p<0.001) (Fig. 1-1). Patients who underwent resection of the primary tumour had a significantly better 2-year survival (30% versus 9%, $p < 0.001$). Survival was less favourable for elderly patients and patients with cancer of the right colon. For patients treated with hepatic surgery, 2-year survival increased from 62% in the first period to 84% in the second period and 71% in the third period (NS). The primary multivariate analysis suggested a prognostic impact of age and subsite and an improvement of survival in more recent years (Table 1-3). This period effect lost its statistical significance ($p = 0.55$) after inclusion of information on colorectal surgery (HR=0.49), chemotherapy (HR=0.51) and liver surgery (HR=0.24).



Patients at risk

1994-1999	1098	364	153	83	55	32
2000-2004	1348	530	250	143	93	48
2004-2007	1036	514	173	50	-	-

Fig 1-1 Survival of patients with stage IV colorectal cancer diagnosed in 1995-2007

Table 1-3 Multivariable survival analysis for stage IV colorectal cancer diagnosed in 1995-2007

	Model without treatment		Model including treatment	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Age				
20-49	0.71	0.61-0.82 0.66-0.81	1.05	0.90-1.22
50-59	0.73	0.75-0.90	0.95	0.85-1.05
60-69	0.82		0.96	0.88-1.06
70-79	1 (ref)	1.37-1.69	1	
80+	1.52		1.29	1.16-1.43
Gender				
Male	1 (ref)		1	
Female	1.00	0.93-1.07	0.95	0.88-1.02
Site of the primary tumour				
Right	1.22	1.12-1.32	1.11	1.03-1.21
Left	1 (ref)		1	
Rectum	1.01	0.92-1.12	0.84	0.77-0.93
Period				
95-99	1.17	1.08-1.27	1.00	0.92-1.09
00-04	1 (ref)		1	
05-07	0.80	0.73-0.88	0.95	0.87-1.04
Treatment				
Colorectal surgery			0.49	0.46-0.53
Chemotherapy			0.51	0.47-0.56
Liver surgery			0.24	0.20-0.30

DISCUSSION

The proportion of colorectal cancer patients diagnosed with stage IV disease in the South western part of the Netherlands slightly increased over the specified period. Chemotherapy use and the rate of patients who underwent hepatic surgery increased over time and resulted in a significantly increased survival rate which is comparable with the data found by Kopetz *et al*.[14] The results of this two-centre study has some limitations: they excluded patients who did not receive any treatment because of poor performance status or preference. Although they included only patients undergoing primary therapy in these two institutions, a referral bias likely remains.

In the population-based study by Lemmens *et al*.[15] from the Eindhoven Cancer Registry (one of the eight comprehensive cancer centres in the Netherlands) resection of the primary tumour and use of chemotherapy was analyzed in the different periods of diagnosis (1975-2006) according to age for stage IV colon and rectal cancer. Palliative chemotherapy was increasingly administered in patients with stage IV colon and rectal disease in their study which is comparable to our results. As a result two-year survival

rates increased over time. Resection rates of the primary tumour remained high except for patients with stage IV disease, showing a decrease since 2000.

Traditionally, the standard treatment for stage IV colorectal cancer was to perform a palliative resection of the primary tumour in order to prevent the risk of intestinal obstruction, perforation or intractable bleeding. However, prophylactic resection of the primary tumour in patients with distant metastases is associated with high mortality (6-10%) and morbidity (20-25%).[16,17] Poor nutritional status and a deteriorated overall condition are held responsible for this phenomenon. Several investigators compared outcomes for patients who presented with incurable stage IV colorectal cancer depending on whether they underwent resection of the primary tumour.[18-23] The majority of these studies did not observe a benefit after resection of the primary tumour and questioned the merit of initial surgery for preventing symptoms of obstruction.[18-20, 23] Two studies observed a significant survival advantage for patients who underwent surgical resection and thus advocated for elective resection of asymptomatic primary colorectal tumours.[21,22] In these studies, however, the groups were not properly matched. There were distinct advantages in demographics of patients selected for surgical resection and this imbalance in prognostic factors may have caused the survival difference. In the present study, 2-year survival was significantly better in patients who underwent resection of the primary tumour, but the comparison was obviously biased by other prognostic factors.

Benoist et al[23] performed a matched case-control study and suggested that systemic chemotherapy without resection of the bowel cancer should be the primary treatment of choice because it would reduce costs and avoid unnecessary surgery. In our experience and others, minor symptoms of patients with rectal cancer, such as mild obstruction, pain, bleeding and mucus discharge, reduced after the first or second cycle of chemotherapy.[24,25] Moreover, it has been suggested that the majority of patients with incurable stage IV colorectal cancer who present with only minimal symptoms of the primary tumour may die of progressive systemic disease before the development of major complications related to the primary tumour.[18] This approach is supported by Poultsides et al[26] who showed that from 233 patients who received up-front combination palliative chemotherapy for metastatic colorectal disease only 16 patients (7%) required a surgical intervention with a median time-interval from initiation of CTx to surgical intervention of 7 (range, 1-27) months. Surprisingly, the resection rate of the primary tumour in the current study did not change over time. For rectal lesions, surgery of the primary tumour was performed less often. This may be due to awareness of greater morbidity and mortality associated with pelvic surgery or fear for a permanent colostomy.[27]

Policy for the treatment of stage IV colorectal cancer has changed in recent years. Novel chemotherapy regimes result in higher clinical response rates of the liver metastases. Furthermore, it may downsize the primary tumour, reducing the complication risk and enabling a high number of R0 resections. In our series chemotherapy in palliative

and neoadjuvant setting increased as did the number of patients who underwent hepatic surgery. Probably as a result, 2-year survival increased from 14% (1995-99) to 28% (2004-07). According to multivariate analysis, this period effect was independent of age, gender and sub site but lost its statistical significance after inclusion of treatment variables, suggesting that the change in treatment was associated with the more favourable outcome.

The detection rate of stage IV colorectal disease increased over time and could be due to differences in registration or incidence, but is probably due to increased and improved imaging modalities. The percentage of hepatic resections more than doubled during the study period. Due to the better resolution of new imaging techniques, smaller metastases can be detected for which hepatic resection may offer cure. Detection of smaller metastases can be considered as a type of lead-time bias and may accomplish an improvement of survival. Besides the higher detection rate, a more aggressive treatment approach has resulted in an increased resectability rate. Reports on reduced morbidity and mortality following major hepatic resections for CRC liver metastases have changed our conservative policy toward a more aggressive approach.[28-31] Multiple metastases, bi-lobar disease, margins less than 1 cm, and limited extra hepatic disease are no longer considered contra-indications for resection which enlarges the number of patients eligible for resection.[31-34] It is well established that repeat, and even sequential hepatectomy for recurrent colorectal liver metastases is feasible with survival and morbidity rates similar to those reported after initial hepatectomy.[35,36] Also, the combination of conventional resection with local techniques such as radiofrequency ablation can allow more patients to undergo curative treatment.[9] In addition, introduction of the ultrasonic dissector (CUSA, Tyco healthcare, Mansfield, MA, USA) has enabled more refined and precise surgery. The use of chemotherapy treatment rates increased considerably during the study period. Chemotherapy has become more effective in recent years with the introduction of new agents such as irinotecan, oxaliplatin, bevacizumab and cetuximab. These novel drugs achieve higher clinical remission rates of metastases which will lead to higher hepatectomy rates.[4,5,37] Despite the optimistic reports on new developments for the treatment of stage IV CRC, median survival is still less than a year at population level.

Resection of the primary tumour and hepatic metastases was less often performed in patients over 80 years of age. This may reflect the perceived morbidity of these procedures in an elderly population. A review by the Colorectal Cancer Collaborative Group found that elderly patients had an increased prevalence of co morbidity and were more likely to present with late-stage disease and to undergo emergency procedures.[38]

In conclusion, survival for patients with stage IV colorectal cancer has improved over time which is probably due to the increased use of chemotherapy and the increased rate of patients who underwent hepatic surgery. The timing of surgical resection of the primary tumour is a controversial issue and should be subject to prospective investigations.

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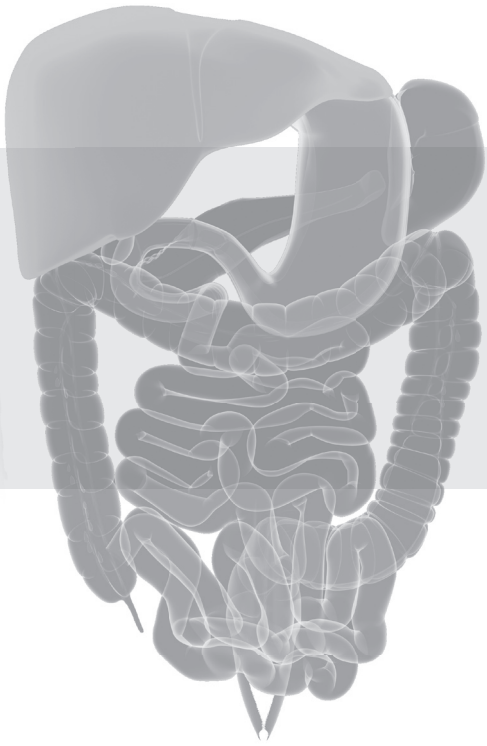
3

TRENDS IN TREATMENT FOR COLORECTAL SYNCHRONOUS LIVER METASTASES; DIFFERENCES IN OUTCOME BEFORE AND AFTER 2000



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ABSTRACT

Background The traditional treatment for stage IV colorectal cancer has changed from palliative chemotherapy toward an aggressive multimodality approach. In the current study outcome in patients who underwent surgery for synchronous colorectal liver metastases (CLM) in a single centre was evaluated.

Methods From January 1991 to May 2008 all consecutive patients with synchronous CLM who underwent curative resection of both primary and metastatic disease were included. Date of resection was divided into two groups: date of hepatic resection before and after the year 2000.

Results Fifty patients (26%) with synchronous CML were resected before 2000 and 142 patients (74%) underwent resection after 2000. The estimated 5-year disease-free survival before and after 2000 was 9% and 27%, respectively (P =0.379). More patients who underwent resection after 2000 were treated with local therapy or underwent resection for intra-hepatic recurrence (62% vs. 28%, P = 0.033). The estimated 5-year survival before and after 2000 was 26% and 44%, respectively (P = 0.001).

Conclusion Survival rates in patients with synchronous CLM have been increased in the past decade. The introduction of new chemotherapeutic drugs and a more aggressive treatment approach in patients with liver recurrence were probably major factors in this progress.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related death in Europe.[1] At the time of diagnosis, approximately 25% of the patients already have manifest liver metastases.[2] Only a selected group (15–20%) of patients with synchronous colorectal liver metastases (CLM) are candidates for resection with the intent to cure.[3] The traditional approach for stage IV CRC has changed from palliative treatment toward an aggressive multimodality approach, despite the fact that several studies have found that patients who underwent resection for synchronous liver metastases have a shorter disease-free survival than patients with metachronous metastases.[4-6]

Surgical resection is the current standard of care in the treatment of patients with synchronous CLM. It is expected that due to the improvement of imaging modalities, the percentage of synchronous CLM will increase. In the South western region of the Netherlands, the number of synchronous metastases in CRC increased from 16% (1995–1999) to 21% (2005–2007, data submitted). Besides the higher detection rate, general improvements in operative and anesthetic technique have resulted in an increase in patient eligible for surgery. Since 2000, the use of radiofrequency ablation (RFA) has been introduced for the treatment of liver metastases and this has made patients with bi-lobar metastases operable who have been contraindicated previously for liver surgery. Moreover, effective chemotherapeutics such as irinotecan, oxaliplatin, and new monoclonal agents achieve clinical response rates of 50–80% and appear to convert 13% of initially deemed unresectable disease to resectable disease.[7,8] A paradigm shift in the criteria of surgical resection and the introduction of new chemotherapeutics regimens are the major factors in the increased resectability rate.[9,10]

To study the potential influence of all abovementioned factors that changed the treatment policy for patients with CLM, the outcome of patients who underwent surgery for synchronous CLM in a single centre treated before and after 2000 was compared.

MATERIALS AND METHODS

From January 1991 to May 2008 all consecutive patients with synchronous CLM who underwent curative resection of both primary and metastatic disease were included. Synchronous liver metastases were defined as liver metastases detected simultaneously with the primary tumour by diagnostic imaging or during resection of the primary. Patients with extra-hepatic metastases were included provided that curative treatment could be reached. Date of resection was divided into two groups: date of hepatic resection before and after the year 2000. Patient files were studied for the following patient characteristics: gender, age, location of the primary tumour, pathological primary tu-

mour and lymph node stage (pTN), location, maximum size, and number of metastases on computer tomography (CT), distribution of liver metastases, type of liver surgery, use of RFA, complications, radicality, site, and treatment of recurrence. Neoadjuvant systemic chemotherapy (CTx) was given in patients with marginal resectable metastases or >3 metastases. All patients received 5-FU-based chemotherapy, including oxaliplatin- or irinotecan with or without bevacizumab. Surgery was planned more than 3 weeks after the last course of CTx. The last cycle of CTx was given without bevacizumab to ensure an interval prior to surgery of at least 6 weeks.[11] Hepatic resections were determined according to standard nomenclature described by Couinaud.[12] Radicality was defined as R0 > 0mm and R1≤ 0 mm.

Overall and disease-free survival was calculated from the date of treatment initiation for the metastatic disease. Follow-up was routinely performed at the outpatient clinic and consisted of endoscopic surveillance of the colon 1-year post-surgery and during the following years depending on relevant findings during examination. Abdominal CT or ultrasonography and CEA were performed every 4 months for the first year, every 6 months in the second year, and once a year thereafter.

Categorical data are presented as percentage frequencies, and differences between proportions were compared using the chi-squared tests or Fischer's exact tests, as appropriate. Continuous data with a significant skewed distribution are expressed as medians and were compared using the Mann–Whitney *U*-test. Mean values of continuous variables with normal distributions were compared by unpaired Student's *t*-test. Survival analysis was performed using the Kaplan–Meier method. The log-rank test was used to identify variables associated with survival. Multivariate analysis was performed using a Cox proportional hazards regression model to identify those risk factors independently associated with survival that had been statistically significant in the univariate analysis. Significance levels were set at $P < 0.05$. All statistical analyses were performed by using SPSS version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

Curative resection of synchronous CLM was performed in 192 patients. Simultaneous and staged resection was performed in 16 and 176 patients, respectively. In the staged group, the time-interval between resection of the primary and liver metastases was 5 (range: 2–38) months. The median age at the time of resection of the primary tumour was 62 (range: 37–84) years and 128 (67%) patients were men. Figure 2-1 shows the number of partial liver resections performed because of synchronous and metachronous CLM over time.

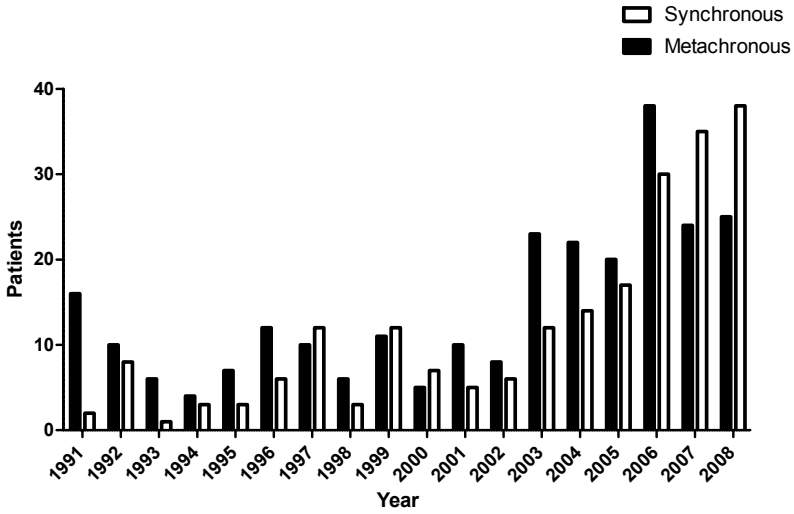

Fig 2-1 Patients with synchronous and metachronous colorectal liver metastases who underwent resection from January 1991 to December 2008

Fifty patients (group 1) underwent resection before 2000 and 142 patients after 2000 (group 2). Table 2-1 shows the differences between the two groups in demographics and characteristics of the primary tumour. The median time-interval between resection of the primary tumour and liver metastases was 4.2 (range: 2–15) months and 5.5 (range: 2–38) months in groups 1 and 2, respectively ($P = 0.004$). Median follow-up of patients in group 1 was 33 (range: 0–203) months and 29 (range: 5–101) months in group 2. Table 2-2 shows the differences between the two groups in characteristics of the metastases. Patient who underwent hepatic surgery after 2000 had more advanced metastatic dis-

Table 2-1 Demographics and characteristics of the primary tumour

	Before 2000 n = 50	After 2000 n = 142	P-value
Gender			0.269
Male	37 (74%)	91 (64%)	
Age (median)	59 (range, 37-79)	63 (range, 37-84)	0.033
> 60	22 (44%)	89 (63%)	
Location primary			0.002
Rectum	10 (20%)	66 (46%)	
Colon	40 (80%)	76 (54%)	
pT			0.451
T0-2	4 (8%)	19 (13%)	
T3-4	46 (92%)	123 (87%)	
pN			0.926
Nneg	19 (38%)	51 (36%)	
Npos	31 (62%)	91 (64%)	

pT, pathological primary tumour stage; pN pathological lymph node stage.

Table 2-2 Characteristics of the metastatic tumour

	Before 2000 n=50	After 2000 n=142	P-value
No. of metastases	2 ± 1.1	3 ± 1.7	<.0001
> 3	4 (8%)	50 (35%)	< 0.001
Size of largest metastasis (cm)	4.1 ± 2.5	3.1 ± 2.2	0.008
> 5	13 (26%)	17 (12%)	0.034
Distribution of metastases			
Bi-lobar	14 (28%)	66 (46%)	0.035
Neoadjuvant CTx			
Yes	1 (2%)	91 (64%)	< 0.001
VPE			
Yes	-	9 (8%)	0.062
Surgery + RFA			
Yes	-	21 (17%)	0.005
Radicality			
R0	46 (92%)	128 (90%)	0.597
Extra-hepatic disease	3 (6%)	12 (8%)	0.408

CTx, chemotherapy; VPE, vena porta embolization; RFA, radiofrequency ablation.

ease, 64% of the patients received neoadjuvant CTx and 17% underwent RFA in addition to surgery. Two patients with uni-lobar disease (2%) received RFA and 19 patients with bi-lobar disease (24%) received RFA in addition to surgery. None of the patients received adjuvant CTx. After 2000 (group 2), significantly more wedge resections/segmentectomies (parenchyma-sparing resections) were performed (62% vs. 48%, P = 0.003) and less extended hepatectomies (1% vs. 14%, P = 0.001). In group 2, as opposed to group 1, median hospital stay was shorter (7 vs. 10 days, P < 0.001) with fewer complications (18% vs. 46%, P < 0.001). Two patients in group 1 died within 30 days after resection due to hepatic insufficiency. There was no 30-day mortality in group 2.

Disease-free survival

In the total study group (n = 192), 5-year disease-free survival was 20%. The estimated median disease-free survival for groups 1 and 2 was 13 and 14 months, respectively. The estimated 5-year disease-free survival before and after the year 2000 was 9% and 27%, respectively (*P* = 0.379; Fig. 2-2a). Variables considered in univariate and multivariate analysis are shown in Tables 2-3 and 2-4a. Pathological positive lymph nodes of the primary tumour and more than three hepatic metastases were independent predictors of disease-free survival in multivariate analysis (Table 2-4a). In group 1, recurrence was seen in 42 patients (84%). Eighteen patients had only intra-hepatic recurrence of which five patients (28%) underwent re-resection. In group 2, 86 patients (61%) had a recurrence of whom 34 patients only intra-hepatic. A considerable higher percentage underwent resection or was treated with local therapy for intra-hepatic recurrence compared to group 1 (62% vs. 28%, *P* = 0.033): Thirteen patients (38%) underwent re-resection, six

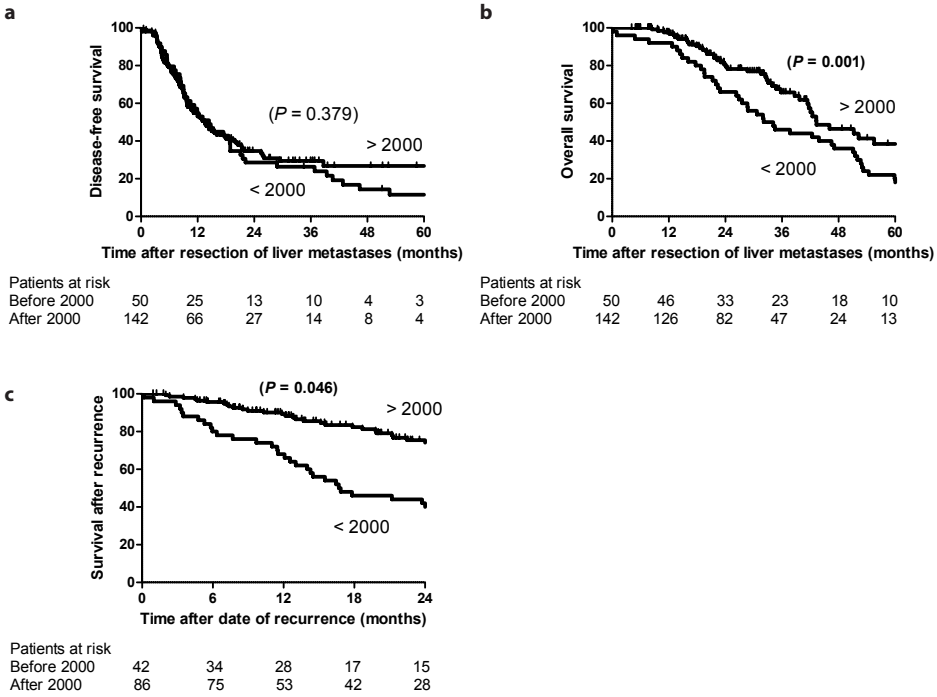

Fig 2-2

a) Disease-free survival of patients with synchronous colorectal liver metastases who underwent resection before and after 2000

b) Overall survival of patients with synchronous colorectal liver metastases who underwent resection before and after 2000

c) Survival after recurrence

patients (18%) were treated with RFA and two patients (6%) received stereotactic body radiation therapy. In both groups, 52% of the patients received palliative chemotherapy.

Overall survival

In the total study group (n = 192), 5-year overall survival was 36%. The estimated median overall survival for group 1 and 2 was 35 and 51 months, respectively. The estimated 5-year survival before and after 2000 was 26% and 44%, respectively (p = 0.001) (Fig 2-2b).Variables considered in univariate and multivariate analysis are shown in Table2-3 and 2-4b. Pathological positive lymph nodes of the primary tumour and neoadjuvant CTx were independent predictors of overall survival in multivariate analysis (Table 2-4b) Figure 2-2c showed the survival of patients with recurrence from date of recurrence with an estimated 2-years survival before and after 2000 of 36% and 61%, respectively (p = 0.046).

Table 2-3 Univariate analysis of prognostic factors on disease-free and overall survival in the total study group

			Disease-free survival		Overall survival
	No. of patients n = 192	5-Year disease-free survival (%)	Univariate analysis (log-rank)	5-Year overall survival (%)	Univariate analysis (log-rank)
Age			0.984	36	0.586
≤ 60	81	11		31	
> 60	111	24			
Gender			0.369	36	0.09
Male	128	15		30	
Female	64	24			
Location primary			0.513		0.842
Rectum	76	15		34	
Colon	111	19		33	
pT			0.174		0.177
T0-2	23	33		41	
T3-4	169	15		33	
pN			0.004		0.023
Nneg	70	33		42	
Npos	122	7		29	
No. of metastases			0.007		0.646
≤3	138	19		32	
>3	54	15		40	
Distribution of liver disease	112	19	0.157	31	0.933
Uni-lobar	80	17		37	
Bi-lobar					
Size of largest metastasis (cm)	162	17	0.202	35	0.047
0-5	30	20		26	
> 5					
Neoadjuvant CTx			0.836		0.002
Yes	92	29		66	
No	100	15		23	
Type of surgery			0.532		0.139
Major	125	19		37	
Minor	67	15		27	
Surgery+RFA			0.021		0.775
Yes	21	0		32	
No	165	21		57	
Complications			0.406		0.391
Yes	48	14		33	
No	144	20		34	
Resection margin			0.859		0.768
R0	174	18		33	
R1	15	14		36	

pT, pathological primary tumour stage; pN, pathological lymph node stage; CTx, chemotherapy; RFA, radiofrequency ablation.

Table 2-4a Multivariate analysis of prognostic factors on disease-free survival in the total study group

Factors	Disease-free survival HR (95% CI)
pN	
Nneg	1
Npos	1.7 (1.2 - 2.6) $p = 0.005$
No. of metastases	
≤3	1
>3	1.7 (1.1 - 2.5) $p = 0.008$
Surgery+RFA	
Yes	1
No	1.5 (0.8 - 2.7) $p = 0.204$

HR, hazard ratio; 95% CI, 95% Confidence Interval; pN, pathological lymph node stage; RFA, radiofrequency ablation.

Table 2-4b Multivariate analysis of prognostic factors on overall survival in the total study group.

Factors	Overall Survival HR (95% CI)
pN	
Nneg	1
Npos	1.8 (1.2 - 2.9) $p = 0.011$
Size of largest metastasis (cm)	
0-5	1
> 5	1.6 (1.0 – 2.8) $p = 0.062$
Neoadjuvant CTx	
Yes	1
No	2.4 (1.4 - 3.9) $p = 0.001$

HR, hazard ratio; 95% CI, 95% Confidence Interval; pN, pathological lymph node stage; CTx, chemotherapy.

DISCUSSION

In the present study patients who underwent resection of synchronous CLM after 2000 have a significantly improved survival. No difference was observed in disease-free survival between the two groups.

The presence of synchronous metastases usually carries a small decline in prognosis compared metachronous metastases.[6] In recent years, the development of improved hepatic imaging with magnetic resonance imaging (MRI), tri-phase CT, positron emission tomography (PET), and PET-CT has resulted in an increase in detection rate of synchronous liver metastases. Besides the higher detection rate, a more aggressive surgical approach and the introduction of new effective chemotherapeutics have resulted in an increased number of patients who are amenable for curative treatment. In the present series, a steadily increase has been demonstrated from three patients who underwent resection of synchronous CLM in 1998 to 39 patients in 2008.

It still presents a challenge to treat synchronous and the optimal management of these patients is under evaluation. Besides the traditionally staged resection (primary tumour first), two other surgical time management procedures can be performed in patients with CRC and synchronous liver metastases, that is, simultaneous surgery and "liver first" approach.[13-16] This last approach may increase the number of patients undergoing possible curative resection of both the primary tumour and metastases.

In patients with synchronous disease it might be beneficial to start treatment with neoadjuvant CTx because hepatic and even colorectal surgery (with possible morbidity) can be avoided in case of incurable metastases during treatment evaluation.[17] It is generally accepted that patients who are progressive under CTx should not be operated upon, as they do not benefit from surgery.[18] Unresectable or marginal resectable metastases might be another reason to start with CTx because modern chemotherapeutics allow 13% of patients with initially deemed unresectable CRLM to be amenable for liver surgery with improved survival.[7,8]

There are numerous differences (number, size, distribution of metastases, and the use of neoadjuvant CTx) between the two groups but no difference in disease-free survival was observed while survival rates increased significantly over time. Our results suggested that a more aggressive treatment approach in patients with recurrence could have contributed to this observation. Re-resection or local treatment for recurrent metastases has become more conventional as a viable life-prolonging and in some cases, life-saving procedure.[19-21] Also in the present series the number of patients who underwent a potential curative local treatment in case of intra-hepatic recurrences increased from 28% in group 1 to 62% in group 2. Moreover, patients who underwent resection and developed unresectable intra- or extra-hepatic recurrence in the recent time period received palliative chemotherapy with more effective agents like oxaliplatin and irinotecan. These two observations will probably explain the difference in 5-year overall survival rates despite the same disease-free survival rates between the two groups.

After 2000, age increased in patients who underwent resection. Reduced morbidity and mortality following major hepatic resections for CLM have changed our traditional conservative approach in elderly patients toward a more aggressive approach.[22-24] As described previously, age cannot be regarded as a medical contraindication for hepatic resection of CLM.[25] More patients with multiple metastases and bi-lobar disease underwent resection after 2000. Some of these patients (24%) with bi-lobar disease could undergo curative treatment due to the addition of RFA to surgery. Factors like high number of metastases or large size of metastases are no longer considered contra-indications for resection and resections could be performed safely in selected patients.[26-30] Size of metastasis was smaller in patients who underwent resection after 2000. This might be ascribed to improved hepatic imaging which resulted in earlier detection of metastases and, as a result, smaller metastases. Detection of smaller metastases can be considered

as a type of lead time bias and may accomplish an improvement of disease-free and overall survival. Although in our series this is unlikely because disease-free survival was not different between the two groups. After 2000, more extra-anatomical resections were performed. A predicted surgical of <1 cm is no longer considered an exclusion criteria for resection[31] and a parenchyma-sparing resection could result in less postoperative hepatic insufficiency. Moreover, in case of recurrence, a larger remaining part of the liver makes a re-resection more feasible.

New and more effective chemotherapeutic agents have recently become available for the treatment of CLM in the neoadjuvant and palliative setting.[32] Both oxaliplatin and irinotecan in combination with 5-FU/leucovorin-based therapy has substantially increased the rate and degree of tumour response. In the present study, the majority of patients (64%) in group 2 were treated with neoadjuvant CTx. This resulted in a selection bias, because patients with progressive disease after CTx did not undergo resection and were not included in this study. The patients in the present study all responded on CTx and may reflect a biological less aggressive behavior of the metastases. However, as mentioned earlier the disease-free survival was similar in the two time periods suggests that patient selection was not improved over the years included in this study.

The optimal treatment for patients with synchronous CLM includes regular surveillance and a multidisciplinary team approach. The treatment strategy frequently depended on the response to earlier therapies and proper treatment of metastases at an early stage is associated with better outcome. A strategy of sequenced multiple treatments are moving the treatment of synchronous CLM to a new multidisciplinary field. This has resulted in increased survival rates in patients with synchronous CLM. The introduction of new chemotherapeutic drugs and a more aggressive treatment approach in patients with liver recurrence are major factors in this progress.

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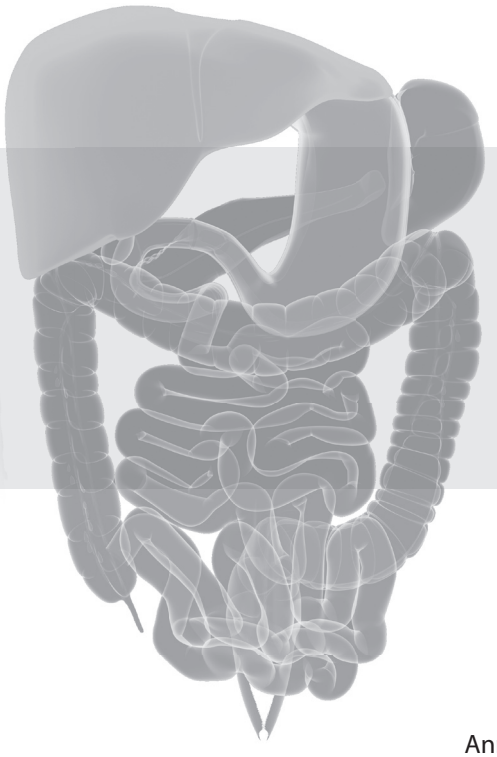
4

"STAGED" LIVER RESECTION IN SYNCHRONOUS AND METACHRONOUS COLORECTAL HEPATIC METASTASES; DIFFERENCES IN CLINICOPATHOLOGICAL FEATURES AND OUTCOME



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ABSTRACT

Aim Approximately 25% of the patients with colorectal cancer already have liver metastases at diagnosis and another 30% will develop them subsequently. The features and prognosis of patients with synchronous and metachronus colorectal liver metastases, treated with primary resection first followed by partial liver resection were analysed.

Method Curative staged resection of liver metastases was performed in 272 consecutive patients. Demographics, characteristics of the primary tumour and metastatic tumours, surgery-related data and outcome were analysed.

Results Synchronous metastases were present in 105 (39%) patients and metachronous metastases in 167 (61%). More patients in the synchronous group had an advanced primary tumour (T3/T4 and/or node positivity), more than three liver metastases and bilobar distribution. A significantly higher percentage of patients in the synchronous group received neoadjuvant chemotherapy. The 5-year survival rate in the group of 272 patients was 38%. Patients with more than three metastases had a significantly worse survival rate. There were no differences in disease-free and overall survival rates between the synchronous and metachronous group.

Conclusion Although patients with synchronous colorectal liver metastases may have poorer biological features, there was no difference in 5-year disease-free and overall survival compared with patients with metachronous metastases. This may be explained by the observation that patients in the synchronous group received significantly more neoadjuvant chemotherapy.

INTRODUCTION

Colorectal cancer has a high incidence in the Western world. At the time of diagnosis, approximately 25% of the patients already have manifest liver metastases and another 30% will develop them following treatment of the colorectal primary.[1,2] Without treatment, life expectancy is usually < 1 year.[3] With modern chemotherapeutic agents, median survival currently reaches 16–22 months.[4,5] Hepatic resection is the only chance of long-term survival, which results in 5-year survival rates of 45–58%.[6-9]

In the past, several investigators have reported a poorer prognosis in patients with synchronous liver metastases.[10-15] Some have included this factor into preoperative scoring systems.[10,12,15] No patient described in these studies received modern chemotherapy agents such as oxaliplatin, irinotecan, bevacizumab or cetuximab.

Recent published studies of survival in patients with synchronous and metachronous hepatic metastases are conflicting.[16-19] There are arguments that for simultaneous resection there is no 'test of time' period to evaluate the development of new (extra)hepatic metastases. This may influence the outcome compared with the metachronous group. Therefore, we included only patients who underwent a staged resection to preserve equal groups. Little is known about the difference in characteristics between synchronous and metachronous liver metastases. For these reasons, clinicopathological data and outcome were analysed in patients with synchronous and metachronous colorectal liver metastases, treated by primary resection first followed by partial liver resection as a second stage.

METHOD

The study population consisted of all consecutively treated patients with colorectal cancer and liver metastases (synchronous and metachronous) who underwent curative resection of both primary and metastatic disease. Patients were treated during the period from January 2000 to May 2008 at the Erasmus University MC, Rotterdam, the Netherlands.

All patients had to fulfil the following criteria:

(1) Radical resection of the primary tumour.
(2) The presence of technically removable hepatic metastases (preserving at least two segments of the liver parenchyma) and the possibility of an oncological radical procedure.
(3) Where patients presented with extra-hepatic disease, only resectable extra-hepatic metastasis was allowed.
(4) Where a traditionally staged approach could be performed (resection of the primary tumour first followed by partial hepatectomy).

All patients diagnosed with colorectal carcinoma underwent an ultrasound or contrast computed tomography (CT) of the liver and a chest X ray. The study group was divided into two based on when the hepatic metastases were discovered. Synchronous liver metastases were defined as liver metastases detected by preoperative imaging on CT or magnetic resonance imaging (MRI) or during resection of the primary tumour. Metachronous metastases were detected during follow up.

The following data characteristics were noted: gender, age, location of the primary tumour, pathological primary tumour (pT) and lymph node (pN) stage, location, maximum size and number of metastases on CT, extra-hepatic disease, cycles of neoadjuvant chemotherapy (CTx) regimens, type of liver surgery, complications and radicality. The clinical risk score (CRS), proposed by Fong *et al.*[10] (node-positive primary, number of hepatic tumours > 1, largest hepatic tumour > 5 cm, preoperative carcinoembryonic antigen (CEA) level > 200 ng/ml and disease-free interval from diagnosis of the primary tumour to discovery of the liver metastases < 12 months) is widely used to predict outcome and survival after hepatic resection for colorectal metastases and is determined in our study population. CTx was given in a neoadjuvant fashion because of bilobar disease, extra-hepatic disease or > 3 metastases according to local protocol. All patients received oxaliplatin- or irinotecan-based CTx with or without bevacizumab. A laparotomy was planned more than 3 weeks after the last course of CTx. The last cycle of CTx was given without bevacizumab to ensure an interval prior of surgery of at least 6 weeks.

The hepatic resection was determined according to standard nomenclature described by Couinaud.[20] Radicality was defined as R0 > 0 mm and R1 ≤ 0 mm. Overall survival and disease-free survival were measured from the date of hepatic resection. Follow up was routinely performed in the outpatient clinic and it consisted of endoscopic surveillance of the colon after 1 year and thereafter depending on the findings. Abdominal CT or ultrasonography and CEA measurements were performed every 4 months for the first year and every 6 months the second year and once a year thereafter. Categorical data were presented as percentage frequencies, and differences between proportions were compared using the χ^2 tests or Fisher's exact test, as appropriate. Survival analysis was performed using the Kaplan–Meier method. The log-rank test was used to identify variables associated with survival. Multivariate analysis was performed using a Cox proportional hazards regression model to identify those risk factors independently associated with survival that had been statistically significant in the univariate analysis. Significance levels were set at $P < 0.05$. All statistical analyses were performed by using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patient characteristics

Between January 2000 and May 2008, 272 patients underwent curative staged resection for colorectal liver metastases at our institution. Resection of the primary tumour was carried out first followed by partial hepatectomy. During this period, more liver resections for colorectal liver metastases were performed, but synchronous resections (primary and metastases) and patients who underwent the liver first approach (metastases first followed by resection of the primary) were excluded for this analysis. The median age at time of resection of the primary tumour was 62 (range: 28–84) years and 168 (62%) were men.

Synchronous metastases were detected in 105 (39%) patients and metachronous metastases in 167 (61%). The interval between resection of the primary and the liver metastases was 6 (range: 2–38) months and 22 (range: 7–195) months for the synchronous and metachronous group respectively. In one patient, in the synchronous group, an abdominal aortic aneurysm was detected and treated after resection of the primary tumour. This patient underwent hepatic surgery 38 months after resection of the primary. There was no significant difference in the male: female ratio or age between the synchronous and metachronous groups. Follow up was 26 (range: 4–101) months in the synchronous group and 25 (range: 0–95) months in the metachronous group.

Table 3-1 compares the synchronous and the metachronous groups of patients with regard to location and stage of the primary tumour. Thirty-six per cent of the patients were treated with neoadjuvant CTx. CTx was given in a median of six (range: 2–15) courses. None of the patients received adjuvant CTx. Table 3-2 compares the synchronous and metachronous groups of patients with regard to the number, size, distribution, CRS, treatment and resection margin of the liver metastases. Patients in the synchronous group had significantly less complications (17% vs. 31%, $P = 0.02$). The 30-day mortality was 2% (6/272) which was not significantly different between the synchronous and

Table 3-1 Characteristics of the primary tumour

Characteristics of the primary tumour	Synchronous n = 105	Metachronous n = 167	P- value
Location primary			0.02
Rectum	33 (31%)	77 (46%)	
Colon	72 (69%)	90 (54%)	
pT			0.01
T0-2	10 (10%)	37 (22%)	
T3-4	95 (90%)	130 (78%)	
pN			0.01
Nneg	31 (30%)	77 (46%)	
Npos	74 (70%)	90 (54%)	

pT, pathological primary tumour stage; pN, pathological lymph node stage.

metachronous groups. Death-related causes were postoperative liver failure (*n* = 3), pulmonary complications (*n* = 2) and one patient had a portal vein occlusion to segments 2/3 after a right extended hemihepatectomy.

Table 3-2 The characteristics of the metastatic tumour and liver surgery

Characteristics of the metastatic tumour	Synchronous n = 105	Metachronous n = 167	P –value
No. of metastases			< 0.001
>3	34 (32%)	20 (12%)	
Size of largest metastasis (cm)			0.06
> 5	15 (14%)	41 (25%)	
CRS			< 0.001
1-2	38 (36%)	139 (83%)	
3-5	67 (64%)	28 (17%)	
Distribution of metastases			0.02
Bi-lobar	51 (49%)	56 (34%)	
Neoadjuvant CTx			< 0.001
Yes	62 (59%)	37 (22%)	
Liver surgery			0.2
Extended hemihepatectomy	2 (2%)	6 (3%)	0.72
Hemihepatectomy	34 (32%)	42 (25%)	0.25
Wedge/segmentectomy	67 (64%)	118 (71%)	0.3
RFA	2 (2%)	1 (1%)	0.6
Extra-hepatic disease			0.8
Yes	9 (9%)	12 (7%)	
Resection margin			0.2
R0	94 (90%)	139 (84%)	

CRS, clinical risk score; CTx, chemotherapy; RFA, radiofrequency ablation.

Disease-free survival

Patients in the synchronous group had an estimated disease-free survival of 13 months and a 5-year disease-free survival of 25% (Fig.3-1a). Independent factors in multivariate analysis were more than three metastases (*P* = 0.003, HR 2.1, 95% CI: 1.3–3.6) and the presence of extra-hepatic disease (*P* = 0.009, HR 2.7, 95% CI: 1.3–5.9).

Patients in the metachronous group had an estimated disease-free survival of 14 months and a 5-year disease-free survival of 27% (Fig. 3-1a). Independent factors in multivariate analysis were bilobar disease (*P* = 0.006, HR 1.8, 95% CI: 1.2–2.8), extra-hepatic disease (*P* = 0.01, HR 2.5, 95% CI: 1.2–5.0) and positive resection margin (*P* = 0.005, HR 2.1, 95% CI: 1.1–1.8).

The risk factors of the total study group (*n* = 272), with an estimated disease-free survival of 14 months and a 5-year disease-free survival of 26% are shown in Tables 3-3 and 3-4.

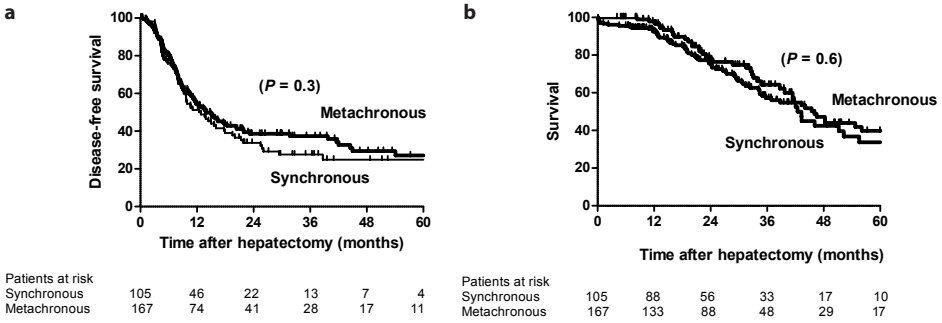

Fig 3-1

a) Estimated 5-year disease-free survival of patients in the synchronous and metachronous group

b) Estimated 5-year overall survival of patients in the synchronous and metachronous groups

Table 3-3 Clinical risk factors for disease-free and overall survival in the total study group

			Disease-free survival		Overall survival
	No. of patients n = 272	**5-Year disease-free survival (%)**	**Univariate analysis (log-rank)**	**5-Year overall survival (%)**	**Univariate analysis (log-rank)**
Age			0.7		0.4
≤ 60	105	22		45	
> 60	167	30		32	
Gender			0.3		0.6
Male	168	24		34	
Female	104	30		46	
Location primary tumour			0.6		0.7
Rectum	110	23		37	
Colon	162	27		38	
pT			0.09		0.05
T0-2	47	35		48	
T3-4	225	24		36	
Primary tumour LN status			0.02		0.14
Negative	108	32		43	
Positive	164	22		34	
CEA level			1.0		0.6
≤200 ng/ml	242	25		38	
> 200 ng/ml	28	33		37	
No. hepatic metastases			< 0.001		0.003
≤3	218	30		42	
>3	54	7		21	
Distribution of liver disease			0.001		0.16
Uni-lobar	165	33		43	
Bi-lobar	107	16		32	
Largest tumour diameter			1.0		0.7
0-5 cm	216	26		37	
> 5 cm	56	22		41	

Continued on next page

Table 3-3 Continued Clinical risk factors for disease-free and overall survival in the total study group

			Disease-free survival		Overall survival
	No. of patients n = 272	**5-Year disease-free survival (%)**	**Univariate analysis (log-rank)**	**5-Year overall survival (%)**	**Univariate analysis (log-rank)**
Diagnostic interval			0.3		0.6
Synchronous	105	25		34	
Metachronous	167	27		40	
CRS			0.06		0.1
1-2	177	29		42	
3-5	95	17		28	
Neoadjuvant CTx			0.35		0.6
No	173	27		36	
Yes	99	22		44	
Extra-hepatic disease			< 0.001		0.3
No	251	27		39	
Yes	21	5		28	
Resection margin			0.01		0.09
R0	233	27		40	
R1	36	18		22	

HR, hazard ratio; 95 % CI, 95% Confidence Interval; pT, pathological primary tumour stage; LN, pathological lymph node stage; CEA, carcinoembryonic antigen; CRS, clinical risk score; CTx, chemotherapy.

Table 3-4 Multivariate analysis of prognostic factors on disease-fee and overall survival in the total study group

Factors	**Disease-free survival HR (95% CI)**	**Overall Survival HR (95% CI)**
No. hepatic metastases		
≤3	1	1
>3	2.2 (1.5 – 3.2) $p < 0.001$	1.8 (1.2 – 2.8) $p = 0.01$
Extra-hepatic disease		
No	1	
Yes	2.9 (1.8 – 4.8) $p < 0.001$	
Resection margin		
R0	1	
R1	1.3 (1.1 – 1.6) $p = 0.01$	

Overall survival

Patients in the synchronous group had an estimated overall survival of 42 months and a 5-year overall survival of 34% (Fig. 3-1b). The presence of more than three metastases was associated with a significantly worse survival on univariate analysis (19%*vs* 40%, $P = 0.004$). Patients in the metachronous group had an estimated overall survival of 46 months and a 5-year overall survival of 40% (Fig. 3-1b). Independent factor on multivariate analysis was pT3/pT4 status of the primary tumour ($P = 0.02$, HR 2.0, 95% CI: 1.0–3.9).

The risk factors in the entire group (n = 272), with an estimated median survival of 44 months and a 5-year overall survival of 38% are shown in Tables3-3 and 3-4.

DISCUSSION

The results of this study suggest that long-term survival and even cure could be achieved after staged resection of colorectal cancer and synchronous or metachronous liver metastases with a median survival of 44 months and an estimated 5-year survival of 38%. No significant differences were found in disease-free and overall survival between the synchronous and metachronous group of patients. In our series, patients with synchronous liver metastases had significantly higher CRS.

In recent years, several authors studied the difference in outcome between patients with synchronous and metachronous disease.[10,15,16,18,19,21,22] Studies included patients with synchronous liver metastases that underwent simultaneous resection of the primary tumour and liver metastases. This might explain why some authors found a worse survival and/or decreased disease-free survival in the synchronous group. The synchronous group did not have a 'test of time' period, that is, the time-interval between detection of the primary and the metastases. During this period, (unresectable) extra-hepatic disease may become evident. In our tertiary referral centre, most of the patients with synchronous metastases were evaluated after resection of the primary tumour in the referral centre. Patients, who developed extensive (extra) hepatic disease during a median time-interval of 6 months, were not selected for operation. This might explain why patients with synchronous hepatic metastases did not have a worse (disease-free) survival compared with the metachronous group in our series.

Patients with synchronous metastases compared with the 'metachronous group' had a worse primary tumour stage, that is, a higher percentage pT3–pT4 tumours and node positivity. In addition, patients in the synchronous group had significantly more metastases and bilobar disease. There is no clear explanation for the fact why poorer prognostic factors were present in the synchronous group. It is surprising that this was found since all these patients were selected before surgery. It may simply be a reflection of more aggressive tumour characteristics in patients with synchronous metastases, which may imply a worse outcome after treatment. It is well known that CRS (in which CEA level, synchronicity, primary tumour stage, number and size of metastases are factors) is highly predictive for survival after partial liver resection[23], which was not seen in our study population.

The percentage of neoadjuvant CTx was significantly higher in the synchronous group. Our policy is to use neoadjuvant CTx in patients with more than three metastases, bilobar disease and/or extra-hepatic disease. The application of neo-adjuvant CTx leads

to a selection bias, because patients with progressive disease after CTx did not undergo resection and were not included in this study. It is generally accepted that patients who progress during CTx should not be operated upon, as they do not benefit from surgery.[24] The patients in this study all responded to CTx and this may reflect a biological less aggressive behaviour of the metastases. The equivalent survival between the synchronous and metachronous groups despite a higher CRS in the synchronous group suggests that neoadjuvant CTx may modify the outcome of the synchronous group to parallel the outcome of the metachronous group.

However, caution is warranted, because this is a selected group of patients. It is not based on randomized data and therefore, our study is only hypothesis-generating.

In our multivariate analysis, the number of liver metastases has a significant prognostic influence on survival. However, this factor is not an absolute factor for patient selection, as patients with poor prognostic factors may gain benefit from surgery and can still reach long-term survival and even cure.[18,25] The inability to identify absolute factors associated with long-term survival makes it impossible to provide good patient selection for including or excluding these patients before initial surgery. Multidisciplinary team meetings with an experienced hepatobiliary surgeon, radiologist and oncologist are necessary to provide each patient with the best possible treatment options.

Conclusion

Synchronous colorectal liver metastases indicated poorer biological features. However, there was no difference in 5-year disease-free and overall survival in patients with synchronous or metachronous metastases. This may be explained by the observation that patients in the synchronous group received significantly more neoadjuvant chemotherapy.

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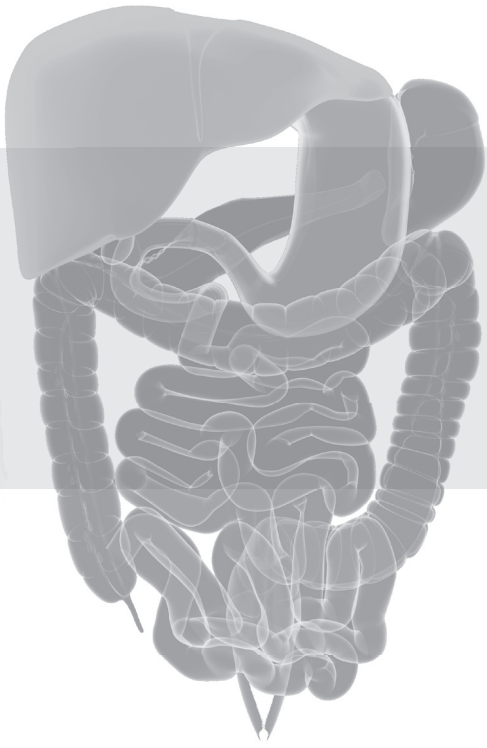
PART II

COLORECTAL LIVER METASTASES: SURGICAL TIME MANAGEMENT

5

THE "LIVER-FIRST APPROACH" FOR PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER AND SYNCHRONOUS LIVER METASTASES



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ABSTRACT

Purpose This study was designed to investigate the outcome of "the liver-first" approach in patients with locally advanced rectal cancer and synchronous liver metastases.

Methods Patients with locally advanced rectal cancer and synchronous liver metastases were primarily treated for their liver metastases. If successful, patients underwent treatment for the rectal tumour.

Results Twenty-three patients were included. One patient had liver resection without neoadjuvant chemotherapy followed by chemoradiotherapy. All remaining 22 patients underwent laparotomy after chemotherapy. Eighteen patients underwent partial liver resection and subsequent chemoradiotherapy for the rectal cancer. One patient underwent in one session a partial liver resection and a low anterior resection. Six patients were not treated according to protocol because of extensive disease. Sixteen patients (73 percent) completed the full treatment protocol and all are alive after a median period of 19 (range, 7-56) months.

Conclusions This is the first sizable report on the "liver-first approach" demonstrating that it may be considered the preferred treatment schedule for patients with locally advanced rectal cancer and synchronous liver metastases. It allows most patients to undergo curative resections of both metastatic and primary disease and can avoid useless rectal surgery in patients with incurable metastatic disease.

INTRODUCTION

Rectal cancer is a common malignancy. In the United States, more than 40,000 new patients were diagnosed in 2007[1] and even in a small country as the Netherlands, each year rectal cancer affects approximately 2,000 new patients. The management of rectal cancer has rapidly changed during the last decade and is one of the great challenges for the surgeon. The increase of new multimodality options to treat this group of patients is continuing and major advances have been made. Local control and survival of rectal cancer depend on stage and adequate resection, in particular in terms of the circumferential resection margins.[2] The standard treatment for early-stage rectal cancer is preoperative radiotherapy (25 Gy) followed by surgery.[3] Patients with locally advanced disease (large T3 and/or T4) have a higher recurrence rate and will receive more benefit from the down staging effect of the neoadjuvant therapy. For this reason, long pelvic irradiation (50 Gy) has been applied in these patients with or without the combination of chemotherapy.[4,5] Approximately 30 percent of the patients with locally advanced rectal cancer present with synchronous liver metastases. Locally advanced rectal cancer is usually treated with a long course of (chemo)radiation therapy ((CTx)RTx), which takes five weeks. Approximately six to ten weeks after the last day of radiotherapy patients will be operated on. Without complications in this treatment schedule, three months pass before the liver will be treated. However, complications in rectal surgery are not uncommon after chemoradiation and it may take more than six months to start adequate metastatic therapy. Because the liver metastases define the prognosis of the patient, it seems reasonable to treat the hepatic metastases first. Therefore, we started with the "liver-first approach" in patients with locally advanced rectal cancer and synchronous liver metastases; our first results are described.

PATIENTS AND METHODS

All consecutive patients presented at the Erasmus University MC-Daniel den Hoed Cancer Centre, Rotterdam, with locally advanced rectal cancer and synchronous liver metastases were included from May 2003 to May 2007. Locally advanced rectal cancer was defined as a histological proven adenocarcinoma with one of the following characteristics: tumour >5 cm at colonoscopy or magnetic resonance imaging (MRI) (= clinically large T3); clinically fixed tumour or with in growth in adjacent organ on MRI (T4); N+ tumour (N+ = lymph node >8 mm on CT scan or MRI). T4 tumours, but also advanced T3 tumours with a close relation to the circumferential margin, should be considered as locally advanced rectal cancer. Regardless of size criteria, any lymph node depicted on MRI with an irregular border or mixed signal intensity was considered suspicious for

metastasis. The included patients were primarily treated with systemic chemotherapy. If there was no progressive disease, a laparotomy was performed with the intention to perform a partial liver resection for the liver metastases. Only after a successful liver resection, patients were treated with (CTx)RTx for the primary rectal tumour. If chest x-ray/CT and abdominal/pelvic CT did not reveal unresectable metastases, surgery of the rectal cancer was performed after finishing (CTx)RTx therapy. A preoperative pelvic MRI was performed to evaluate the extent of the primary tumour.

Chemotherapy

Patients received a combination of 5-fluorouracil (5-FU)/capecitabine and oxaliplatin or irinotecan, and in some recent cases also bevacuzimab. The response to chemotherapy was assessed after two or three cycles by CT scan and carcinoembryonic antigen levels. Further treatment was discussed according to the tumour response and extent of the disease. When the liver metastases were resectable, a laparotomy was planned more than three weeks after the last course of systemic chemotherapy. Bevacuzimab had to be excluded from the last course of chemotherapy to ensure an interval of at least six weeks.

Liver resection

Liver resection was performed by a right subcostal incision. The abdomen was thoroughly inspected and palpated to detect extra hepatic metastasis or second primary tumours. The liver was mobilized, inspected, palpated, and on demand the liver was examined by intraoperative ultrasonography. The hepatoduodenal ligament was palpated and in case of palpable nodes, a radical lymph node dissection of the ligament was performed. The resections were recorded as extra-anatomical resection (segmentectomy or wedge resection), left hemihepatectomy (resection of segments 2, 3, 4), or right hemihepatectomy (resection of segments 5, 6, 7, 8). The segmental anatomy is based on the anatomic description of the liver by Couinaud.[6] All hepatectomies were performed with a curative intent, i.e., with a tumour-free hepatic resection margin status. Radiofrequency ablation (RFA) was restricted to destroy one or two small tumours contralateral to the larger tumours that were resected or to small (<3 cm) ill-located (unfavourably located) tumours in the liver.

(Chemo)radiation and rectal surgery

If the partial liver resection was successful, patients received neoadjuvant radiation therapy for their locally advanced rectal cancer. Radiation therapy consisted of long-course (total dose of 50 Gy or a biologically equivalent dose) therapy or short-course (5 x 5 Gy) therapy. During the study, results from two randomized trials reported improved results for locally advanced rectal cancer patients when 5-FU-based chemoradiation

therapy was given.[4,5] Hereafter, patients were treated with chemoradiotherapy, which included capecitabine 825 mg/m2 twice per day only on radiotherapy days.[7] If CT chest/abdomen after (CTx)RTx did not reveal unresectable metastases, surgery of the primary tumour was planned. Total mesorectal surgery was performed in all patients and adjacent structures at risk were removed en bloc if considered necessary. Intraoperative radiotherapy was applied if the circumferential resection margin was <2 mm.[8] No laparoscopic resections were performed.

Follow-up

Follow-up was performed at the outpatient clinics and consisted of endoscopic surveillance after one year and abdominal CT or ultrasonography and serum carcinoembryonic antigen every four months for the first year and every six months the second year and once per year thereafter. Disease-free and overall survival was calculated from the start of treatment until local recurrence or new metastases.

RESULTS

Inclusion

Between May 2003 and May 2007, 23 consecutive patients with locally advanced rectal cancer and synchronous liver metastases were included. The study group consisted of 15 men and 8 women with a median age of 58 (range, 43-78) years. Patient characteristics are displayed in Table 4-1. Six patients had been operated on for a diversion ileostomy or colostomy: four because of symptoms of bowel obstruction and two were diagnosed with an unresectable rectal tumour at laparotomy at which time a colostomy was performed.

Start therapy

A flow diagram of the treatment overview of all 23 patients is shown in Figure 4-1. One patient refused systemic chemotherapy and underwent a partial liver resection without neoadjuvant chemotherapy. Twenty-two patients were treated with a median of five cycles of chemotherapy (range, 2-10). Seven patients received continuous 5-FU, leucovorin, and oxaliplatin, 13 patients received capecitabine and oxaliplatin, and 2 patients received continuous 5-FU, leucovorin, and irinocetan. In eight patients bevacuzimab was added to the first courses of the chemotherapy. In general, symptoms of presentation, such as bleeding, pain, and diarrhoea, rapidly disappeared after the first or second cycle of chemotherapy. One patient had a blowout of the cecum during his third cycle of chemotherapy (oxaliplatin and capecitabine). He underwent an emergency laparotomy elsewhere and an inoperable mass in the lower pelvic was palpated; this

Table 4-1 Patients and tumour characteristics at presentation

	Patients n = 23
Median age, years	58 (range 43-78)
Sex	
Female	8
Male	15
Presentation	
Obstruction	6
Pain	1
Bloodloss+change of Defaecation	16
Number of metastases	
≤3	14
>3	9
Size of metastases (cm)	
<5	20
≥5	3
Bilobar metastases	
Yes	12
No	11
CEA	
<5	5
≥5	18

patient received a diversion colostomy. After four weeks, CT scanning revealed a partial response of the liver metastases and the large pelvic mass became undetectable. This patient followed the protocol and was operated on for his liver metastases. Of the 22 patients who were evaluated after chemotherapy, 15 patients had a partial response of their liver metastases (68 percent), 6 had stable disease (27 percent) and 1 had complete remission (5 percent) of the metastasis on CT scan.

Laparotomy after chemotherapy for liver resection

Laparotomy was performed after a median interval of five (range, 2-11) weeks after the last chemotherapy. Twenty-two patients underwent a laparotomy for partial liver resection with curative intent (Fig. 4-1). One patient had a synchronous low anterior resection and right hemihepatectomy because his preference for a single operation and refused finally "the liver-first approach" (Patient A). One patient underwent a complete lymph node dissection of the hepatoduodenal ligament because of suspicious palpable lymph nodes, which were proven to be positive with a biopsy and frozen-section examination. One patient had a right hemicolectomy because of an unexpected cecum carcinoma during laparotomy (Table 4-2).

At laparotomy, three patients were diagnosed with extensive disease. One patient had peritoneal carcinomatosis (Patient B), and two patients had unexpected extensive liver

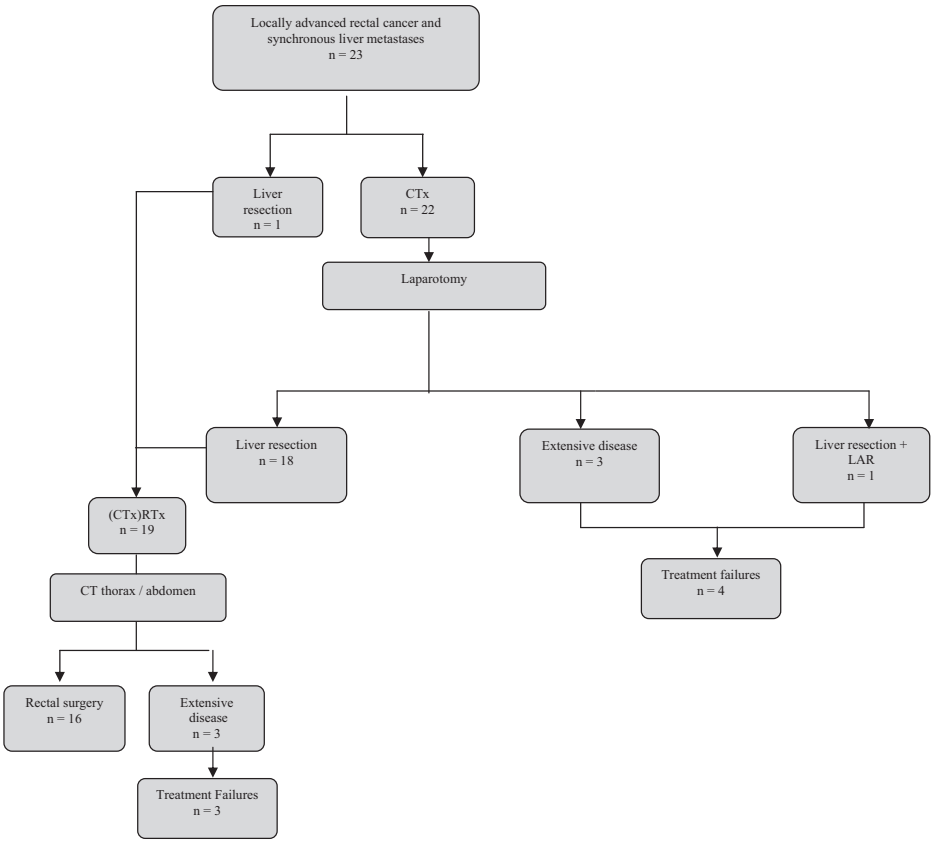

Fig 4-1 Flow chart of the included patients

Table 4-2 Surgical procedures in patients with locally advanced rectal cancer and synchronous liver metastases

	No of Patients
Type of surgery	
Liver resection (n = 20)	
Extra-anatomic resection / RFA	9
Left hemihepatectomy	1
Left hemihepatectomy + extra-anatomic*	2
Right hemihepatectomy	4
Right hemihepatectomy + extra-anatomic*	2
Right hemihepatectomy+LAR	1
RFA + right hemicolectomy	1
Rectal surgery(n = 16)	
LAR	10
APR	6

* extra-anatomic: wedge resection and/or radio frequency ablation

LAR, low anterior resection; APR, abdominal perineal resection; RFA, radiofrequency ablation.

metastases (Patients C and D). Patients C and D were subsequently planned to have a two-stage liver resection but were unfortunately progressive on chemotherapy. These three patients (B, C, and D) were not treated according to the formalized treatment plan (see follow-up). Median hospital stay was 7 (range, 3-11) days, and postoperative complications were observed in two patients; both were suspected to have pneumonia and were treated with antibiotics. On histologic examination, all liver specimens had a tumour-free resection margin and in one resection specimen, no vital tumour cells could be found (complete response).

(Chemo)radiation and rectal surgery

Nineteen patients received (CTx)RTx after a median of four (range, 2-9) weeks after partial liver resection and after a median of ten (range, 5-17) weeks after finishing systemic chemotherapy. Eighteen patients received a long-course of radiation therapy (total dose of 50 Gy or a biologically equivalent dose): 13 patients in combination with chemotherapy (Capecitabine). One patient received a short-course of radiation (5*5 Gy) because of the refusal to travel to our clinic for five weeks daily. Three patients demonstrated new extensive pulmonary and/or hepatic metastases on CT scan five weeks after finishing (CTx)RTx (Patients E, F, and G) and did not undergo rectal surgery. Sixteen patients underwent rectal surgery with a median interval of nine (range, 1-15) weeks after their last course of (CTx)RTx. One patient was treated with intraoperative radiotherapy. Resections performed are depicted in Table 4-2. Median hospital stay was seven (range, 4-14) days. There were no major complications after surgery. All resection specimens except one (R1) had tumour-free resection margins. Further pathologic details are shown in Table 4-3.

Table 4-3 Tumour and node characteristics of the primary rectal tumour

Stage Tumour	Clinical	Pathological
T0	0	4
T2	0	2
T3	20	9
T4	3	1
Node		
Negative	10	13
Positive	13	3

Table 4-4 Treatment failures

Patient	Reason withdrawal protocol after first laparotomy	Reason withdrawal protocol after (CTx) RTx	Follow-up	Status (after start treatment)
A	Hemihepatectomy + low anterior	-	Systemic CTx for liver and pulmonary metastases after 3 months	AWD, 18 months
B	Peritonitis carcinomatosa	-	Systemic CTx	AWD,17 months
C	Extensive liver metastases	-	Progression of liver metastases under CTx	AWD, 20 months
D	Extensive liver metastases	-	Progression of liver metastases under CTx	AWD, 20 months
E	-	New liver and pulmonal metastases after CTxRTx	Palliative treatment	AWD, 22 months
F	-	New liver metastases after RTx	Systemic CTx	DOD, 11 months
G	-	New liver metastases after CTxRTx	Systemic CTx	DOD, 14 months

AWD, alive with disease; DOD, died of disease.

Follow-up

Median follow-up was 18 (range, 7-56) months for all 23 patients. The six patients who did not complete the formalized treatment plan and the one patient who refused after initial consent of the liver-first approach are shown in Table 4-4. Patient A, who finally refused the liver-first approach and underwent in one operative session a low anterior resection and right hemihepatectomy, developed pulmonary and new hepatic metastases on imaging after three months and received subsequently systemic chemotherapy. Patient B underwent a laparotomy for liver resection after chemotherapy. A frozen section of a macroscopic suspect diaphragmatic lymph node showed an adenocarcinoma. Because of uncertainty of final pathologic examination of the lymph node, a second laparotomy was performed after six weeks and an ovariectomy and low anterior resection was performed with progression of the liver metastases and no signs of peritonitis carcinomatosis. Patient B started postoperatively with chemotherapy and had progressive disease while treated with systemic chemotherapy. Patients C and D had extensive liver disease found during first laparotomy and underwent extra-anatomic resections and RFA. Both patients had progressive liver disease under subsequent chemotherapy and were beyond surgical cure. Patients E, F, and G had new metastases on CT scan after radiation therapy and were referred to the medical oncologist for systemic chemotherapy. Only one of the six patients that fell out of the formalized treatment plan underwent rectal surgery. All 16 patients who completed the treatment formalized treatment

Table 4-5 Characteristics of 16 patients who completed the formalized treatment plan.

Patient	cTN	No. of Met	CTx	Response on CTx	Liver surgery	(CTx)Rtx	Rectal surgery	Survival	Months
1	T3N1	2	Xelox	PR	hemi right	50 Gy/ Xeloda	APR	AWD	20
2	T3N0	3	Folfox	PR	hemi right	50 Gy	LAR	NED	56
3	T4N0	2	Xelox	PR	hemi right	50 Gy	LAR	NED	50
4	T3N1	3	Xelox	SD	hemi right+part. segmentectomy	50 Gy	LAR	NED	46
5	T3N0	3	Xelox	PR	part. segmentectomy +RFA+Segmentectomy	50 Gy	LAR	AWD	39
6	T3N0	1			segmentectomy	50 Gy/ Xeloda	APR	NED	25
7	T3N0	4	Xelox	SD	hemi left+partial segmentectomy	25 Gy	APR	NED	24
8	T3N1	5	Folfox	PR	RFA	50 Gy/ Xeloda	APR	NED	20
9	T4N1	4	Folfori/ avastin	PR	hemi right+partial segmentectomy	50 Gy/ Xeloda	LAR	NED	18
10	T3N0	2	Folfox	CR	partial segmentectomy + RFA	50 Gy/ Xeloda	LAR	NED	14
11	T3N0	5	Xelox	PR	hemi left + RFA	50 Gy/ Xeloda	APR	NED	11
12	T3N1	1	Xelox/ avastin	SD	segmentectomy	50 Gy/ Xeloda	APR	NED	11
13	T3N0	1	Xelox/ avastin	PR	partial segmentectomy	50 Gy/ Xeloda	LAR	NED	11
14	T3N1	1	Xelox	PR	partial segmentectomy	50 Gy/ Xeloda	LAR	NED	8
15	T3N1	8	Xelox/ avastin	PR	segmentectomy	50 Gy/ Xeloda	LAR	NED	7
16	T3N0	3	Folfox	PR	hemi right	50 Gy/ Xeloda	LAR	NED	8

PT, patient number; PR, partial repons; SD, stable disease; CR; complete respons; hemi, hemihepatectomy; NED, no evidence of disease.

plan are alive after a median of 19 (range, 7-56) months and are described in Table 4-5. Four patients developed a recurrence of metastases. Two patients with recurrence of hepatic metastases were treated with an extra-anatomic liver resection and RFA, both with curative intent. Both are disease-free, 20 and 35 months after last treatment during follow-up. Irresectable hepatic and pulmonary metastases were demonstrated in two other patients; both are still alive with chemotherapy.

DISCUSSION

In this study, we evaluated the preliminary results of the liver-first approach followed by (chemo)radiotherapy and resection of the primary tumour in an attempt to achieve curative resections of both the metastatic and primary disease in patients with locally advanced rectal cancer and synchronous liver metastases. The results showed that the majority (73 percent, 16/22 patients) could undergo resections with adequate neoadjuvant treatment of the rectal primary and metastases with curative intent. Additionally, one patient refused the two-stage procedure after initial consent and underwent a low anterior in combination with a right hepatectomy. Synchronous metastases and an advanced tumour and nodal stage may confer a worse prognosis than metachronous metastases and/or a low T and N negative stage.[9]

Several studies have demonstrated that the presence of poor prognostic factors does not preclude the possibility of long-term survival and cure.[10-14] Therefore, patients with locally advanced rectal cancer and synchronous liver metastases should be treated with curative intent. Colon surgery and hepatic surgery can be combined safely.[15-18]

Combining partial liver resection and rectal surgery has the appeal of a single operation, but the morbidity of low pelvic surgery after (chemo)radiation therapy is considerably higher than colorectal surgery for nonirradiated patients.[19,20] Combining this with partial liver resection may increase morbidity and mortality, and it is generally accepted that locally advanced rectal cancer is a contraindication for simultaneous resections.[21]

We treated the majority of patients (22/23 patients) primarily with neoadjuvant chemotherapy and hepatic surgery. Another option could be starting with partial liver resection, possibly followed by chemotherapy. This alternative for the liver-first approach has the disadvantage of treating the metastases only, without the primary rectal tumour being treated. If systemic chemotherapy is given as initial treatment, both sites (primary and metastatic disease) are treated. In our experience of the 22 patients described and other patients we treated with this regimen (with nonhepatic metastases), symptoms of the rectal cancer, such as mild obstruction, pain, bleeding, and mucus discharge, improved after the first or second cycle of chemotherapy. A concern of neoadjuvant chemotherapy might be the disappearance of smaller lesions after several lines of chemotherapy and the difficulty identifying these lesions during surgery. At least one study showed the need to resect all tumours seen on the prechemotherapy imaging.[22] Therefore, we recommend an evaluation scan after two or three cycles and, in case of partial response, to stop the chemotherapy and perform a partial liver resection. Moreover, it is known from the literature, that if limited cycles of chemotherapy are given in the neoadjuvant setting, the morbidity or mortality of liver surgery is not increased.[23,24] Another advantage to starting chemotherapy first is the experience of several studies that there is a "relative contraindication" for liver surgery if patients are progressive dur-

ing chemotherapy.[25] Taken this into account, radical rectal surgery with its morbidity and mortality can be avoided in such patients with a particularly poor prognosis.

Recently, Nordlinger et al.[26] showed in his study that per-operative chemotherapy could result in a longer disease-free survival compared with surgery only. This is another argument to start with systemic chemotherapy before liver resection. Other advantages of neoadjuvant chemotherapy may be to test the chemo responsiveness and thereby the rationale for adding postresection adjuvant therapy. Liver metastases rather than the primary tumour determine survival and a liver-first approach could prevent any unnecessary delay in the resection of these metastases and thereby the chance for cure, when the primary tumour is treated first. The recommended treatment for locally advanced rectal cancer is a long course (5 weeks) of (CTx)RTx. Surgery is usually planned six to ten weeks after finishing neoadjuvant therapy. During these three months, no treatment is given to hepatic metastases and these may progress beyond cure. It also is known that the morbidity of extensive pelvic surgery after neoadjuvant radiation therapy is considerable.[19,20] In case of anastomotic leakage, low-pelvic abscess or persistent perineal wound infections, the start of treatment of the hepatic metastases could be extended beyond three months to six months or more. There are several other advantages not to start (chemo)radiotherapy and surgery for the primary rectal cancer first. During laparotomy for partial liver resection, unexpected findings might be discovered, which can change treatment policy. In our experience, a synchronous cecal carcinoma, extensive hepatic metastases, and peritoneal carcinomatosis were found without signs on preoperative imaging modalities. Neoadjuvant (chemo)radiotherapy for a locally advanced rectal cancer should be regarded as futile therapy in these cases and this could be prevented by our approach. Moreover, experimental and preliminary clinical data showed an increased vascularization of metastatic disease after removing the primary colorectal cancer. This could potentially enhance outgrowth of present liver metastases and should be avoided.[27] In the presence of unresectable metastases, resection of the primary colorectal cancer is controversial. Benoist et al.[28] showed in a matched case-control study that systemic chemotherapy without resection of the bowel cancer is the treatment of choice because of reduced costs and avoiding surgery without a detrimental effect on survival. Starting chemotherapy does not impair resection of the rectal and metastatic cancer but might downstage previous unresectable hepatic metastases to resectable.[13] Furthermore, it might downstage the primary tumour, which enables a high number of R0 resections, and even might facilitate sphincter-saving procedures.[29]

In the literature, the traditional two-staged approach of colorectal cancer and synchronous liver metastases used to be defined as resection of the primary tumour followed by the metastases. Recently, Mentha et al.[30] have published their experience in 13 colorectal cancer patients with the "reversed approach" (of the included 20 patients). They included all colorectal primaries and reported only a minority of patients with primary rectal cancer.

The results that they presented were excellent with a median survival of 46 months, but "the liver-first" or "reversed approach" seems especially worthwhile in patients with locally advanced rectal cancer because of the neoadjuvant chemoradiation treatment needed in this latter group. The need of neoadjuvant chemoradiation therapy even after response to systemic chemotherapy is explained in a report by Craven et al.[31] Despite an excellent response on chemotherapy, there still might be viable malignant cells with a close relation to the circumferential resection margin and should be considered as locally advanced.

CONCLUSIONS

The liver-first approach has been demonstrated to be a safe and successful and is considered by us the preferred treatment schedule in patients with locally advanced rectal cancer and synchronous liver metastases. This strategy will allow the majority of patients to undergo curative resections for both the metastatic and primary disease and avoid needless radical rectal surgery in patients with incurable metastatic disease.

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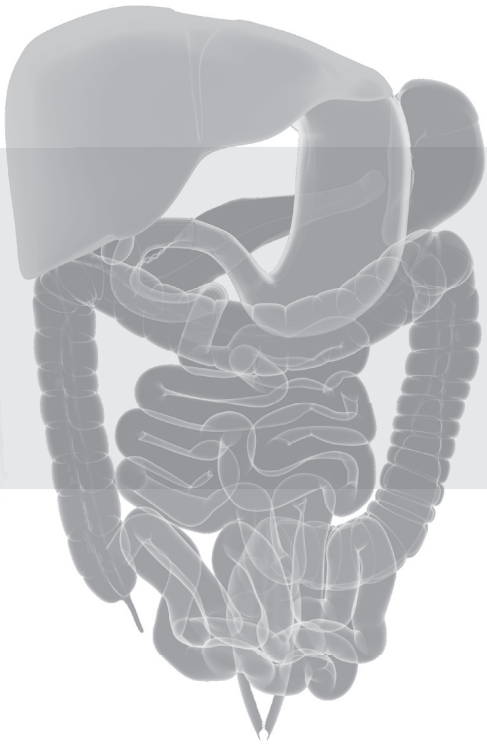
6

OPTIMIZING THE OUTCOME OF SURGERY IN PATIENTS WITH RECTAL CANCER AND SYNCHRONOUS LIVER METASTASES



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ABSTRACT

Background This study evaluated the outcome of patients treated for rectal cancer and synchronous hepatic metastases in the era of effective induction radiotherapy and chemotherapy.

Methods All patients undergoing surgical treatment of rectal cancer and synchronous liver metastases between 2000 and 2007 were identified retrospectively from a prospectively collected database. Three approaches were followed: the classical staged, the simultaneous and the liver-first approach.

Results Of 57 patients identified, the primary tumour was resected first in 29 patients (group 1), simultaneous resection was performed in eight patients (group 2), and 20 patients underwent a liver-first approach (group 3). The overall morbidity rate was 24·6 per cent; there was no in-hospital mortality. Median in-hospital stay was significantly shorter for the simultaneous approach (9 days *versus* 18 and 15 days for groups 1 and 3 respectively; $P < 0{\cdot}001$). The overall 5-year survival rate was 38 per cent, with an estimated median survival of 47 months.

Conclusion Long-term survival can be achieved using an individualized approach, with curative intent, in patients with rectal cancer and synchronous liver metastases. Simultaneous resections as well as the liver-first approach are attractive alternatives to traditional staged resections.

INTRODUCTION

Rectal cancer has a high incidence in the Western world. At diagnosis, approximately 25 per cent of patients already have manifest metastatic disease, which is limited to the liver in 30 per cent. In recent years improvement in hepatic imaging has led to an increase in the detection rate of synchronous metastases. Resection constitutes the only curative option for patients with rectal cancer and liver metastases.[1] Synchronous metastases, multiple metastases or bilobar disease are no longer considered contraindications to resection.[2] Although synchronous metastases may be a predictor of poor prognosis[3-6], several studies have demonstrated that the presence of poor prognostic factors does not preclude the possibility of long-term survival and cure.[7,8]

The traditional approach to the management of resectable synchronous rectal liver metastases involves initial resection of the primary tumour followed by resection of the liver metastases with or without systemic chemotherapy. Since the introduction of neoadjuvant chemotherapy and radiotherapy, the paradigm for the order of treatment of synchronous rectal liver metastases appears to be changing. Three different sequences in treatment schedules have been applied: initial resection of the primary tumour; simultaneous resection of primary tumour and hepatic metastases; and the 'liver-first' approach, in which resection of hepatic metastases precedes resection of the primary tumour.[9,10] In the present study the outcome after resection of rectal cancer with synchronous liver metastases is reported, based on a single-centre experience. To the authors' knowledge, this is the first report focusing on three different 'curative' strategies in patients with rectal cancer and synchronous liver metastases.

METHODS

From a prospectively collected database of 277 patients undergoing partial hepatectomy for colorectal liver metastases between 2000 and 2007, 124 patients with synchronous colorectal liver metastases were selected. From this group, all patients who had treatment for rectal cancer and synchronous liver metastases were enrolled in the study.

Neoadjuvant radiotherapy and total mesorectal excision of the primary rectal tumour has been practised since the mid-1990s.[11] Because effective chemotherapy (oxaliplatin and irinotecan) for metastatic rectal cancer has been in general use since 2000, patients were included from 2000 onwards to ensure, as far as possible, a homogeneous population. All patients were evaluated by the liver board, which comprised hepatobiliary surgeons, medical oncologists, hepatologists, pathologists, (interventional) radiologists and radiation oncologists.

Chemotherapy

Some patients were initially deemed to have unresectable disease and received induction chemotherapy, which was continued until liver metastases were considered resectable. Chemotherapy was given in a neoadjuvant fashion in patients with bilobar disease, extra-hepatic disease or more than three metastases, according to local protocol. Patients received oxaliplatin- or irinotecan-based chemotherapy with or without bevacizumab. A maximum of six cycles was given, because morbidity and mortality rates increase with more than six cycles.[12] The response to chemotherapy was assessed after two or three cycles by computed tomography (CT) and carcinoembryonic antigen (CEA) levels. Further treatment was discussed according to tumour response and extent of disease. When liver metastases were resectable, a laparotomy was scheduled for more than 3 weeks after the last course of systemic chemotherapy. Bevacizumab was excluded from the last course of chemotherapy to ensure an interval before surgery of at least 6 weeks.

Synchronicity

Synchronous liver metastases were defined as liver metastases detected on preoperative imaging by CT or magnetic resonance imaging (MRI), or during resection of the primary tumour. When liver metastases were detected, patients underwent contrast-enhanced abdominal multislice CT and chest radiography or thoracic CT to rule out extrahepatic disease. Colonoscopy and/or colonography were performed in all patients, and a radical resection of the primary tumour was considered appropriate for inclusion in this series.

Type and timing of surgery

Three approaches were followed. In the traditional staged approach (group 1), the primary cancer was resected and the patient restaged approximately 3 months later; if CT and/or positron emission tomography did not reveal extrahepatic disease and conditions remained favourable (good general condition of the patient), hepatic resection was performed. In the simultaneous approach (group 2), resection of the primary tumour and liver metastases was performed in one session. In the liver-first approach (group 3), patients received systemic chemotherapy first and, if no progressive disease was detected, partial liver resection was then performed. After radical resection of the metastases and if imaging studies did not reveal additional or new metastases, the primary tumour was resected last, following adequate neoadjuvant radiotherapy.

The liver-first approach has been employed since 2003 for patients with locally advanced rectal cancer; 16 patients who fulfilled criteria for this approach in the authors' centre have been described previously.[10] Most patients were referred to the authors' centre after the primary tumour had been removed. For patients referred before removal of the primary, simultaneous resection was performed in those with early rectal cancer and

limited liver disease. In patients with advanced liver disease and/or locally advanced rectal cancer, the liver-first approach was the preferred option.

Patient characteristics and prognostic factors

The following data were collected: sex, age, location, distribution, maximum size and number of metastases on CT, CEA level, type of rectal and liver surgery, pathological primary tumour and lymph node stage (pTN), overall length of hospital stay, complications, radicality, and site and treatment of recurrence. Locally advanced rectal cancer was defined as a histologically proven adenocarcinoma with one of the following characteristics: clinically large T3 (diameter greater than 5 cm at colonoscopy) with narrow circumferential margins to the mesorectal fascia on CT or MRI, T4 and/or N+ tumour (lymph node larger than 8 mm on CT or MRI).

The CEA level was determined before treatment (neoadjuvant chemotherapy or resection) of liver metastases was started. The overall length of hospital stay included stay for resection of the primary tumour and partial liver resection. Hepatic resections were determined according to standard nomenclature described by Couinaud.[13] Postoperative complications were listed and classified according to the system of Dindo and colleagues.[14]

Follow-up

Overall and disease-free survivals were determined from the start of treatment. Follow-up was performed routinely at the outpatient clinic and consisted of endoscopic surveillance of the colon after 1 year, thereafter depending on the findings. Abdominal CT or ultrasonography and CEA estimation were performed every 4 months for the first year, every 6 months in the second year, and once yearly thereafter.

Statistical analysis

Categorical data are presented as percentage frequencies. Differences between proportions were compared using χ^2 or Fisher's exact tests, as appropriate. Continuous data with a significant skewed distribution are expressed as medians and compared with the Kruskal–Wallis test. Survival analysis was performed by means of the Kaplan–Meier method, with the log rank test to identify variables associated with survival. Significance levels were set at $P < 0{\cdot}050$. All statistical analyses were performed with the statistical software package SPSS® version 15.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Of 57 patients included in the study, there were 40 men and 17 women with a median age of 61 (range 43–82) years. Twenty-nine patients (51 per cent) had treatment of the primary tumour first, followed by treatment of liver metastases (group 1); eight (14 per cent) underwent simultaneous resection of the primary tumour and liver metastases (group 2); and 20 patients (35 per cent) underwent the liver-first approach (group 3).

Treatment of the primary rectal tumour

Patients with a locally advanced rectal cancer were all treated with chemoradiotherapy, and those with early-stage rectal cancer located in the middle and lower third of the rectum received radiotherapy (5 × 5 Gy) (Table 5-1). Type of rectal surgery is shown in Table 5-2. One patient was treated with intraoperative radiotherapy because the resection margin was less than 2 mm.[16]

Table 5-1 Neoadjuvant treatment

Neoadjuvant treatment	Group 1 n = 29	Group 2 n = 8	Group 3 n = 20
Primary tumour			
Chemoradiotherapy*	8 (28%)	6 (75%)	18 (90%)
Radiotherapy†	3 (10%)	1 (12.5%)	2 (10%)
Liver metastases			
Chemotherapy‡	13 (45%)	2 (25%)	19 (95%)

*Capecitabine 825 mg/m^2 twice daily on radiotherapy days[15] plus 25 x 2 Gy; †5 x 5 Gy; ‡combination chemotherapy with oxaliplatin or irinotecan.

Treatment of metastases

The median (range) number of liver metastases on CT was 2 (1–7), 1 (1–4) and 3 (1–8) in groups 1, 2 and 3 respectively. Twenty-six patients (46 per cent) in the total study group had a bilobar distribution of metastases. Type of hepatic surgery is shown in Table 5-2. Five patients underwent portal vein embolization and two had a two-stage resection. In patients treated with the liver-first approach, neoadjuvant chemotherapy was administered to all but one patient (Table 5-1). In total, 34 patients (60 per cent) received induction or neoadjuvant chemotherapy for a median of 6 (range 2–13) courses. Twenty-four of these 34 patients were referred to the authors' centre before starting chemotherapy; they received a maximum of six cycles. Five patients were deemed to have unresectable disease; they received induction chemotherapy and were downstaged to a resectable status. The remaining five patients were treated with neoadjuvant chemotherapy before being referred to the centre. Most patients (27 of 34) received oxaliplatin-based chemotherapy; seven had irinotecan-based chemotherapy. Bevacizumab was given as

Table 5-2 Rectal and liver surgery

	No. of patients n = 57
Rectal surgery	
LAR	43
(Sub)total colectomy	2
APR	9
Pelvic exenteration	3
ypT	
T0	7
T1	1
T2	5
T3	37
T4	7
ypN	
negative	25
positive	32
Liver treatment	
Right hemihepatectomy	17
Left hemihepatectomy	3
Extra-anatomic resection	36
Radiofrequency ablation	1

Values in parenthese are percentages. ypT/N, pathological primary tumour/lymph node stage, with or without neoadjuvant therapy.

an additional drug to 14 of the 34 patients. All 57 patients had a macroscopically radical resection, but in five (9 per cent) the final pathology report indicated a microscopically irradical resection (margin less than 1 mm). No patient received adjuvant chemotherapy.

Time interval

In group 1, the interval between resection of the primary tumour and resection of liver metastases was 6 (range 2–38) months. In one patient, an abdominal aortic aneurysm was detected and treated after resection of the primary tumour; this patient had hepatic surgery 38 months after resection of the primary. In group 3, the interval between resection of liver metastases and the primary tumour was 4 (range 2–5) months.

Morbidity and mortality

In five patients (9 per cent) who had chemotherapy first, a diverting ileostomy was performed because of problems associated with the rectal tumour (obstruction, pain, bleeding). The overall complication rate after rectal and liver surgery was 24·6 per cent (28 of 114) (Table 5- 3). In group 1, three of 29 patients suffered from severe morbidity (pelvic abscesses and splenectomy owing to intractable bleeding) and treatment of the liver metastases was delayed for at least 4 months. There were no significant differences in complications after rectal (P = 0·590) or liver (P = 0·390) surgery between the three treatment groups (Table 5-3). There were no in-hospital deaths. Median (range) length

Table 3 Complications

Complications	Group 1 n = 29	Group 2 n = 8	Group 3 n = 20
Primary tumour			
None	20 (69%)	6 (75%)	16 (80%)
Mild*	6 (21%)	2 (25%)	3 (15%)
Severe†	3 (10%)	-	1 (5 %)
Liver metastases			
None	24 (83%)	6 (75%)	14 (70%)
Mild*	4 (14%)	2 (25%)	6 (30%)
Severe†	1 (3%)	0	0

* Dindo et al.[14] classification 1 and 2; †Dindo et al.[14]classification 3 and 4.

of hospital stay was significantly shorter for the simultaneous approach: 18 (13–95), 9 (7–15) and 15 (7–30) days for groups 1, 2 and 3 respectively (P < 0·001).

Recurrence

Estimated median disease-free survival was 15 months. Recurrence was seen in 42 patients (74 per cent); the liver was the only site of recurrence in 14 patients (25 per cent). There was no correlation between microscopic irradicality of the liver resection and recurrence (P = 0·311). When intrahepatic or extrahepatic recurrence appeared to be curable, surgical removal was the first treatment option, performed in 13 patients. Two patients were treated with radiofrequency ablation and four with stereotactic body radiation therapy.[17,18] If there was advanced unresectable metastatic disease, systemic chemotherapy was offered.

Survival

Estimated median overall survival was 47 months, and the estimated overall 5-year survival rate was 38 per cent (Fig. 5-1). Median (range) follow-up was 40 (20–94), 34 (10–69) and 28 (17–72) months in groups 1, 2 and 3 respectively, with 5-year survival rates of

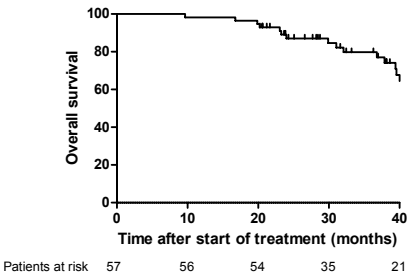

Fig 5-1 Kaplan-Meier overall survival curve for the whole study group

28, 73 and 67 per cent respectively. Seventeen of the 20 patients who underwent the liver-first approach were still alive at the time of writing; 13 patients had no evidence of disease and four were receiving palliative treatment for recurrent disease.

Prognostic factor analysis

In univariable analysis, patients with a preoperative CEA level of 200 ng/ml or less tended to have better survival than those with a level above 200 ng/ml (P = 0·051) (Table 5-4).

Table 5-4 Univariate analysis of risk factors associated with overall survival after resection for rectal synchronous liver metastases among 57 patients

Variable	No. of patients n = 57	5-Year survival (%)	Median (months)	Overall survival Univariate analysis (log-rank)
Age (years)				*p = 0.959*
≤ 60	25	36	58	
> 60	32	39	45	
Gender				*p = 0.119*
Female	17	31	40	
Male	40	42	58	
pT				
Primary tumour				*p = 0.111*
T0-2	13	50	58	
T3-4	44	36	43	
pN				
Primary tumour				*p = 0.288*
Negative	25	39	43	
Positive	32	35	47	
CEA level (ng/ml)				*p = 0.051*
≤200	53	40	47	
> 200	4	0	39	
No. hepatic metastases				*p = 0.151*
≤3	36	41	58	
>3	21	35	42	
Distribution of liver metastases				*p = 0.299*
Unilobar	31	48	46	
Bilobar	26	29	47	
Neoadjuvant chemotherapy				*p = 0.391*
No	23	21	46	
Yes	34	51	81	
Extrahepatic disease				*p = 0.189*
No	51	44	47	
Yes	6	0	46	
Resection margin				*p = 0.189*
R0	52	44	47	
R1	5	0	58	

pT/N, pathological tumour/lymph node stage; CEA, carcinoembryonic antigen; *Log rank test for overall survival.

DISCUSSION

This study has provided data in support of the concept that patients with rectal cancer and synchronous liver metastases should be evaluated carefully to determine whether a treatment approach with curative intent is possible. Long-term survival and even cure can be achieved, as shown by the median survival of 47 months and estimated 5-year survival rate of 38 per cent after resection of both the rectal tumour and synchronous liver metastases.

Common prognostic factors, such as more than three metastases, size greater than 5 cm and bilobar disease, were not found to be prognostic in the present study, in contrast to other published findings.[4,19] A possible explanation for this difference might be the fact that, in the present series, most patients with these characteristics received neoadjuvant chemotherapy. Patients who had progressive disease after chemotherapy did not undergo resection and were not included in the study. It is generally accepted that patients with hepatic metastases that progress under chemotherapy should not be operated on, because they do not benefit from liver surgery.[20] This selection of patients with tumours that responded to chemotherapy may reflect biologically less aggressive metastases.

In the catchment area of the authors' institution, less than 4 per cent of all patients with rectal cancer and synchronous liver metastases undergo surgery with curative intent (unpublished data from the regional cancer registry). Recently, Meulenbeld and colleagues[21] showed that, in unselected patients from the south of the Netherlands, 5 per cent of patients underwent hepatic metastasectomy with curative intent. It is possible that patients with advanced liver disease are not referred to the authors' centre. The proportion of patients with small metastases, and low number of metastases, in the present study could be the result of referral bias. That liver metastases were detected when small may also be a result of the strict follow-up protocol with improved liver imaging.

The low percentage of patients with rectal cancer and synchronous liver metastases who have surgery with curative intent might be due to the frequency of postoperative complications after rectal surgery. Thus, a primary-first approach could lead to postponement or even cancellation of hepatic surgery.[22-24] A prospective randomized trial has demonstrated that after rectal surgery many patients (up to 50 per cent) do not undergo further optimal treatment, because of postoperative complications.[25] Two other approaches may be adopted in the timing and type of surgery in patients with rectal cancer and synchronous liver metastases: the simultaneous and liver-first approach. This may increase the proportion of potentially curative resections of both the primary tumour and the liver metastases. However, the optimal strategy with respect to timing for resectable synchronous rectal liver metastases remains controversial.

In the present study, most patients had resection of the primary tumour before referral for treatment of the liver metastases to the authors' institution. Therefore, a relatively large number of patients in this study had the classical, staged, primary-first approach. Several studies have compared simultaneous resection with the classical staged resection[26-35]; the literature has shown no statistically significant difference in survival and morbidity between the two approaches, but no randomized trials are available. Comparison of survival between the three groups in the present study is probably not reliable because of the small sample size and the retrospective nature of the study.

Data for the liver-first approach in rectal cancer and synchronous liver metastases are sparse. Mentha and co-workers[9] published a series of seven patients with rectal cancer and synchronous liver metastases that fulfilled the treatment plan: initial treatment of the liver metastases (neoadjuvant chemotherapy plus resection) followed by complete rectal treatment (radiotherapy plus rectal surgery). Mentha *et al.*[9] emphasized that the reversed approach is preferred in patients with advanced liver disease. Recently, the authors' group published data for the liver-first approach where it appeared that advanced primary disease was also an important indicator for this approach.[10] The main advantage of the reversed approach in patients with locally advanced rectal cancer and synchronous hepatic metastases is that chemotherapy treats both diseases. Mild colonic obstruction, pain, bleeding and mucous discharge usually resolve after the first or second cycle of chemotherapy. Starting chemotherapy does not impair resection of the rectal and metastatic cancer, and may downstage previously unresectable hepatic metastases.[36] Furthermore, it may downstage the primary tumour, enabling a higher rate of R0 resection. In patients with incurable metastases found during treatment evaluation or unexpected findings at hepatic resection, neoadjuvant (chemo)radiotherapy and resection of a locally advanced rectal cancer with high morbidity should be regarded as futile therapy, and may be prevented by the present approach. It is questionable whether chemoradiotherapy should be given following a good response to chemotherapy in patients with locally advanced primary disease. Neoadjuvant chemoradiation therapy may be required even after response to systemic neoadjuvant chemotherapy because of microscopic foci of malignancy near the circumferential resection margin.[37]

A customized treatment strategy for patients with rectal cancer and synchronous liver metastases, determined by the stage of the primary tumour and the extent of metastasis, would be the following: in early rectal cancer (stage T3 N0 or lower) with limited liver disease (four or fewer segments), surgical morbidity and mortality rates are usually low. Therefore, the combination of rectal surgery with minor hepatic resection (four or fewer segments) in one session is an attractive option. In patients with early-stage rectal cancer and extensive liver disease (more than four segments), simultaneous resection may lead to an increased complication rate.[38,39] In this situation, the liver-first approach can be considered the treatment of choice. If patients have extensive liver metastases

(for example in bilobar disease), partial liver resection in one session may not always be possible. This group of patients may require a so-called 'two-stage hepatic resection'.[40,41] The rectal resection can be safely combined following irradiation with 5 × 5 Gy, with a minor hepatectomy during the first laparotomy. In locally advanced rectal cancer and limited or extensive liver disease, it is preferable, as mentioned above, to treat the liver first.

The management of rectal cancer with synchronous liver metastases is changing. Long-term survival can be achieved by using an individualized approach to treat patients with rectal cancer and synchronous liver metastases with curative intent. Simultaneous resections as well as the liver-first approach are attractive alternatives to traditional staged resections.

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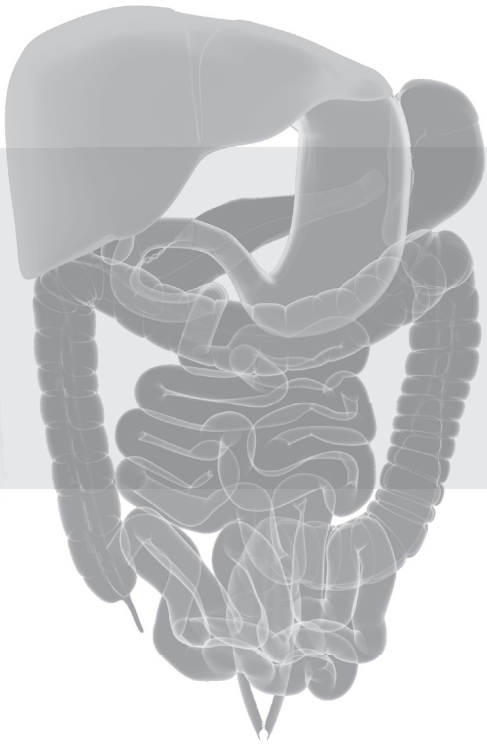
PART III

NEOADJUVANT CHEMOTHERAPY

7

HEPATIC TOXICITY AS A RESULT OF CHEMOTHERAPY IN THE TREATMENT OF COLORECTAL LIVER METASTASES



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COLORECTAL LIVER METASTASES

Colorectal cancer is a leading cause of cancer death. The liver is the most common site of metastases, with 25% of patients presenting with liver metastases at diagnosis; an additional 25% to 35% develop liver metastases in follow-up. Surgical resection is still the gold standard in the curative treatment of colorectal liver metastases (CLM) with 5-year survival rates reported to be 30-50%.[1, 2] Unfortunately, most patients (80%) are unresectable at presentation because of extra-hepatic disease involvement or insufficient future liver remnant. In addition, 60% to 80% of patients who underwent hepatic surgery develop disease recurrence.

New effective systemic chemotherapeutics and the introduction of advanced surgical and anesthesiological techniques have increased the percentage of patients with initially unresectable CLM who become candidates for curative hepatic resection.[3] In patients with normal underlying liver the future liver remnant should be at least 20%.[4] The question nowadays has shifted from "What should be resected" to "What should be left".

CHEMOTHERAPY

Over the past decade, as a result of improved chemotherapy regimens for colorectal liver metastases, a rising number of patients with unresectable and resectable disease are treated with systemic chemotherapy (CTx) before undergoing a potentially curative liver resection. Theoretical advantages include the treatment of undetectable distant micro-metastases, both in the future remnant liver and at extra-hepatic sites, thereby reducing the risk of disease recurrence after resection. It may also be useful to determine chemo-responsiveness of the tumour to select the optimal adjuvant therapy and identify patients with progressive intra- or extra-hepatic disease under chemotherapy in whom surgery would be inappropriate. Furthermore, preoperative CTx is being increasingly used to downsize colorectal liver metastases and appear to convert 10-20% of initially deemed unresectable disease to resectable disease.[5, 6] Neoadjuvant chemotherapy may also allow for a smaller resection (the potential to preserve hepatic parenchyma) and may increase the probability to achieve margin-negative resection. It must be stressed that up to now, no randomized trial has proven the use of neoadjuvant CTx after hepatic colorectal metastases to prolong survival. The European Organisation for Research and Treatment of Cancer (EORTC) 40983-trial[7] showed that peri-operative chemotherapy did not influence overall survival but could result in longer disease free survival compared to surgery only. In a consensus meeting, the panel's recommendation was that most

patients with colorectal carcinoma (CRC) liver metastases should be treated up front with chemotherapy, irrespective of the initial resectability status of their metastases.[7]

CHEMOTHERAPY REGIMENS

In the late 1950s 5-fluorouracil (5-FU) was developed and for many years it was the CTx of choice, delivered in various bolus schedules. In the 1980s, many studies demonstrated superior response rates for 5-FU combined with leucovorin (LV), as compared to 5-FU alone and this combination has response rates up to 20%. Since 2000 the introduction of new chemotherapy regimens has dramatically improved the outcome for CLM by combining fluoropydimines with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). The addition of irinotecan, a topo-isomerase I inhibitor, and oxaliplatin, a platinum derivative, to 5-FU and LV have yielded clinical response rates up to 55%, with a median survival of 22 months, in patients with stage IV colorectal cancer.[8,9] In addition to these novel cytotoxic agents, new molecular targeted therapies have been developed. Both bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), and cetuximab, a monoclonal antibody against epidermal growth factor receptor (EGFR), have produced clinical response rates approaching 70% when combined with cytotoxic agents.[10] The possible advantage of combining different chemotherapy regimens is shortening the length of chemotherapy while receiving the same (or even better) tumour response.

RESPONSE TO CHEMOTHERAPY

Several studies indicated the response to chemotherapy before resection as a powerful predictor of outcome following resection of CLM.[11-13] When disease is stable, outcome following resection is good, and when disease responds to chemotherapy, outcome is even better. In addition, several studies showed that a "relative contraindication" exists for liver surgery if disease progression occurs under chemotherapy; Adam et al.[11] reported in patients with multiple (≥4) colorectal metastases not only that response to preoperative chemotherapy was a prognostic indicator for survival but that progressive disease under chemotherapy could represent a contraindication to surgery. Allen et al.[12] showed that the administration of CTx did not statistically influence survival but that patients on CTx showing clinical response or stable disease while on chemotherapy had significantly improved survival compared with patients with progressive disease (87% vs. 38%, 5-years specific survival, p=0.03). In contrast, Gallagher et al.[14] found in his study that response to neoadjuvant chemotherapy was not related to survival after hepatic resection for patients with resectable synchronous CLM.

COMPLETE RESPONSE

A concern of effective neoadjuvant chemotherapeutics may be the complete disappearance of lesions after several lines of chemotherapy and the complexity identifying these lesions during surgery. The question arises as to what should be resected in such clinically complete responders. Several studies demonstrated that a complete clinical response to chemotherapy with a complete pathological response remains elusive. Adam et al.[5] found that only 0.3% (2/767) of patients showed a radiographic complete response after treatment with preoperative chemotherapy and 4% (29/767) of patients were found to have a pathologic complete response. Moreover, none of the patients with a complete radiologic response had a complete pathologic response, and vice versa. Benoist et al.[15] support the need for surgical resection of CLM despite the radiologic disappearance of the lesions after computed tomography (CT): 83% of tumours that disappeared on CT recurred upon follow-up or contained viable tumour cells at pathological examination after liver resection. Tan et al.[16] showed that 81% of patients whose tumours disappeared on fluorodeoxyglucose-positron emission tomography (FDG-PET) were not pathological complete responders. For these reasons, we recommend an evaluation scan after two or three cycles in our centre and in cases of partial response, to stop the chemotherapy and perform a partial liver resection if the disease is still resectable. Although, it has been demonstrated that a pathologic response predicts survival after preoperative chemotherapy and resection of CLM[17, 18] and that complete pathological response is associated with high survival rates.[13] Concern has arisen regarding the 'loss of opportunity to resect' due to progressive disease under preoperative chemotherapy. This was of significant relevance in the study by Nordlinger et al,[19] who demonstrated comparable percentages of patients who were resected in the chemotherapy group (83%) as in the group randomized to surgery directly (84%). In this study, only 7% progressed on chemotherapy. Further, the non-therapeutic laparotomy rate in this prospective study (only 5% of patients in the chemotherapy group underwent a laparotomy but no resection versus 11% of patients in the surgery-only group). This higher rate of unnecessary laparotomy in the surgery-only group may suggest that patients were better selected for surgery after using chemotherapy.

The rising use of chemotherapy combinations for CLM raises concerns about the potential hepatotoxicities induced by systemic drugs and the effects of these drugs on perioperative and postoperative outcome. The hypothesis that systemic chemotherapy before hepatic surgery can adversely affect the liver parenchyma is strongly suggested by the increased fragility of the liver parenchyma as observed in some patients during hepatic surgery. The phenotype of hepatic injury after preoperative chemotherapy is regimen specific.[20] In the following paragraphs, this aspect will be further elucidated.

5-FLUOROURACIL/LEUCOVORIN

The combination of 5-fluorouracil and leucovorin (LV) has been in clinical use for several decades. Metabolically, 5-FU acts by blocking the enzyme thymidylate synthase and inhibiting both RNA and DNA synthesis. Like most chemotherapeutic agents, 5-FU induces marked apoptosis in sensitive cells by excessive production of reactive mitochondria-derived oxygen species (ROS). Paradoxically, ROS can promote normal cellular proliferation and carcinogenesis, and can also induce apoptosis of tumour cells. Primarily, 5-FU affects the tumour itself, which lead to tumour necrosis and tumour fibrosis.

Hepatoxicity of 5-FU is mediated by excessive production of ROS. which results in accumulation of lipid vesicles in hepatocytes with the histomorphological correlate of steatosis. The association of 5-FU with liver steatosis has been shown in several studies:

Zeiss et al.[21] reported steatosis in parts of the liver parenchyma that were overperfused with floxuridine via hepatic artery infusion. Peppercorn et al.[22] reported CT findings of steatosis associated with 5-FU and folinic acid administration. Furthermore, high body mass index (BMI) and administration of 5-FU resulted in marked steatosis.[23] More recently, it has been demonstrated that all chemotherapeutic agents used in colorectal cancer may cause steatosis.[24]

Several case series observed that moderate to severe steatosis is associated with greater post-operative morbidity.[25, 26] Patients with severe steatosis are at higher risk of developing postoperative liver dysfunction, infectious complications, and longer intensive-care unit stay. However, no difference in mortality rates has been described.[23, 27] Although 5-FU based chemotherapy may cause profound changes in liver parenchyma, it can be safely applied.

OXALIPLATIN

Oxaliplatin is a diaminocyclohexane platinum compound and acts as an alkylating cytotoxic agent, inhibiting DNA replication by forming adducts between two adjacent guanines or guanine plus adenine. Most cancer cell lines are sensitive to oxaliplatin and it has synergistic activity with 5-FU. The EORTC 40983 trial[19] showed an absolute increase in rate of progression-free survival at 3 years of 7% in patients who received preoperative oxaliplatin-based CTx, but no difference in overall survival was found.

Various studies have demonstrated that oxaliplatin's liver injury appears to be directed against the endothelial cells lining the sinusoids. [20, 24, 28, 29] Oxaliplatin leads to depletion of glutathione and impairs mitochondrial oxidation, which results in the production of reactive oxygen species that may induce this injury.[30] Damage to the endothelial cells will lead to circulatory compromise of centrilobular hepatocytes with fibrosis and ob-

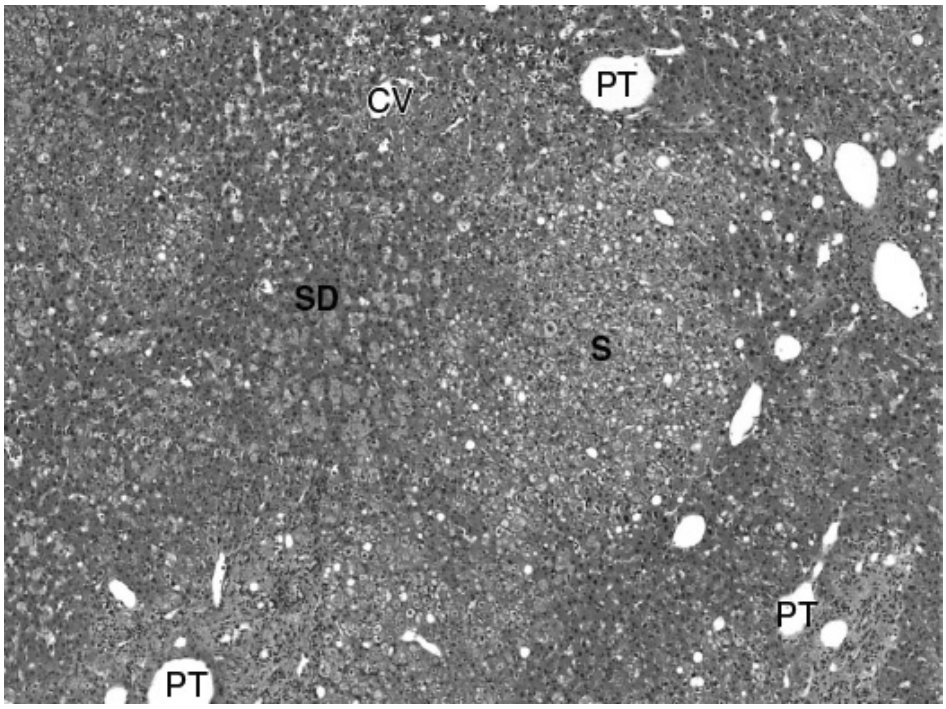

Fig 6-1 Liver parenchyma after treatment with XELOX (capecitabine plus oxaliplatin) ; areas with sinusoidal dilatation (SD) are seen together with foci of steatosis (S)

struction of the liver blood flow-the sinusoidal obstruction syndrome. These histopathological alterations result in a characteristic discolouration of the liver with associated edema and spongiform consistency, referred to as "blue liver syndrome". In severe cases, sinusoidal obstruction can lead to portal hypertension, ascites, and jaundice. One of the histological marks of sinusoidal obstruction syndrome is sinusoidal dilatation (Fig 1) Oxaliplatin is also associated with other parenchymal hepatic injuries, like nodular regenerative hyperplasia, peliosis, and centrilobular vein fibrosis. Rubbia-Brandt et al.[28] showed that 51% of post oxaliplatin-based chemotherapy liver resection specimens had sinusoidal dilatation. Other studies have confirmed this observation, with an incidence of 10–52% in patients receiving preoperative oxaliplatin.[20, 24, 29]

No study to date has demonstrated increased mortality after hepatic resection in patients who have received preoperative oxaliplatin-based CTx, but several studies revealed that postoperative complications could be associated with the use of preoperative oxaliplatin-based CTx.[20, 31, 32] Nordlinger et al.[19] showed that the use of oxaliplatin-based chemotherapy appeared to be associated with some increased and reversible morbidity (25% vs. 16%, p=0.04). This may be related to the short interval between cessation of chemotherapy and surgery (the protocol initially mandated surgery within 3 weeks of chemotherapy, but was later amended). The duration of time off chemotherapy before

surgery may have an impact on complications. Karoui et al.[33] found prolonged CTx (≥ 6 cycles of oxaliplatin) to be a risk factor for postoperative complications after major liver resection Therefore, in patients undergoing an extended liver resection after a high number of CTx cycles (>6) additional risk factors, such as a high degree of steatosis, should be ruled out. Vauthey et al.[24] found that grade 2 to 3 sinusoidal dilatation was associated with oxaliplatin-based CTx (19% vs. 2%, $p < 0.001$), but found no increase in postoperative morbidity or mortality. Aloia et al.[32] noted that patients with liver injury due to oxaliplatin-based chemotherapy required more perioperative blood transfusions than patients who received 5-FU. Perioperative blood transfusion has been shown to be a risk factor for poor outcomes following hepatic resection.[34] Another study found that sinusoidal injury was associated with higher morbidity and longer hospital stay in patients undergoing major hepatectomy, and that it resulted in an impaired liver functional reserve before hepatectomy.[35] The association between postoperative morbidity and sinusoidal injury might be attributable to the intensive chemotherapy given in this study: 90 patients received an average of nine cycles, and 27% (24/90) received two different lines of chemotherapy. The link between sinusoidal injury and morbidity is still under debate.

IRINOTECAN

Irinotecan is a semisynthetic analogue of the natural alkaloid camptothecin and is commonly used in combination with 5-fluorouacil and leucovorin. After administration it is hydrolized into SN-38, a topoisomerase inhibitor, which prevents DNA replication and transcription. It is mainly used in patients with metastatic colorectal cancer and has shown increased response rates (>50%) and improved survival.

However, an important downside of the use of irinotecan is the induction of chemotherapy associated steatohepatitis (CASH). CASH is characterized by increased accumulation of hepatic fat in combination with hepatic inflammation following chemotherapy treatment. It is closely related to the upcoming Western disease non-alcoholic fatty liver disease (NAFLD), a condition inextricably associated with the current obesity epidemic. In NAFLD, simple steatosis can progress over time into non-alcoholic steatohepatitis. Although the exact mechanism is still under debate, a theory put forth to explain disease progression in NAFLD refers to the 'two-hit' mechanism. The first hit is the unbridled hepatic fatty acid accumulation caused by a high caloric intake and insulin resistance. The second hit consists of increased oxidative stress response caused mainly by mitochondrial dysfunction through excessive microsomal and peroxisomal ω- and β-oxidation of fatty acids. This leads to activation of Kuppfer cells and a consequent inflammatory cascade. As was mentioned in a previous section, 5-FU, with or without LV, is the founda-

tion to which other chemotherapy regimes are added. This regimen alone is already associated with steatosis induction by impaired mitochondrial function. In the FOLFIRI regimen, irinotecan is added to 5-FU and LV. In a small study by Fernandez et al.[36] 28% (4/14) patients developed steatohepatitis following the FOLFIRI regime. Lower rates of steatohepatitis were detected after FOLFIRI by Pawlik et al.[20]; 2 of 55 (4%) patients. In a larger study, Vauthey et al.[24] showed irinotecan treatment was associated with steatohepatitis in 20% (19/94) of patients. Furthermore, this study showed a higher degree of steatohepatitis development occurred in obese (BMI > 25kg/m^2) patients (25% ,15/61) as opposed to patients with a normal BMI (<25 kg/m^2)(12%;4/33). A similar association between obesity and increased steatohepatitis induction following irinotecan treatment was also seen by Pawlik et al.[20] and Fernandez et al.[36] Mechanistic studies shedding light on increased induction of steatohepatitis are lacking. It can be postulated that 5-FU treatment serves as the 'first hit', leading to hepatic fatty acid accumulation (i.e. simple steatosis). Subsequently, the addition of irinotecan can be considered the 'second hit', finally resulting in an inflammatory cascade and consequent steatohepatitis. Additionally, obese patients already suffer from steatosis before undergoing chemotherapy and when exposed to irinotecan are at higher risk for development of steatohepatitis.

The largest study investigating liver resection outcome following irinotecan treatment was performed by Vauthey et al.[24] Investigastors found that 90-day mortality was significantly higher in patients with steatehepatitis, as compared to patients without steatohepatitis (14.7% vs 1.6%, *P*=0.001). An almost a six-fold higher incidence of liver failure was observed as a cause of death in patients with steatohepatitis, as compared to chemo-naïve patients. It was suggested that because of limited regenerative capacity progressive liver failure occurs in the remnant liver affected by steatohepatitis. In contrast to findings of the latter study Pawlik et al.[20] reported a lower incidence of steatohepatitis induction and consequently no difference in morbidity and mortality following liver resection. Ideally, patients should be evaluated for the presence of steatohepatitis before, during and after irinotecan treatment prior to a liver resection. However, a liver biopsy is an invasive procedure that can be associated with serious complications. Instead, non-invasive tests could be employed for the possible detection of steatohepatitis. For instance, a combination of elevated transaminases and increased hepatic fat content on radiological studies could serve as an indication to perform a biopsy preoperatively. For non-invasive detection of hepatic fat, several modalities are available, such as ultrasound, CT scan, MRI scan with the latter considered the most reliable. When steatohepatitis is detected, a limited liver resection should be performed to prevent postoperative liver failure of the remnant liver. In general, a remnant liver volume in a healthy liver can be as low as 20%. However in the setting of steatosis or steatohepatitis, a safer margin of 40% is recommended.[37] This, on the other hand could be a negative influence of the radicality of a liver resection.

BEVACIZUMAB

VEGF mediates liver growth through hepatocyte and sinusoidal endothelial cell proliferation and is essential for wound healing.[38, 39] Activation of the VEGFR1 receptor results in secretion of paracrine cytokines (including hepatocyte growth factor and interleukin-6), which stimulate hepatocyte division; binding of VEGF to VEGFR2 receptors induces proliferation of the sinusoidal endothelium. Several studies have demonstrated that VEGF prevents hepatocyte injury, reduces the severity of acute liver injury, and initiates hepatic regeneration after CCL4, D-galactosamine, and lipopolysaccharide-mediated liver damage.[40] Bevacizumab is a recombinant humanized version of a murine monoclonal antibody with angiogenesis inhibiting effects. It binds to the VEGF, preventing activation of the corresponding receptor kinases VEGFR-1 and VEGFR-2. It neutralizes free VEGF and thus inhibits VEGF-mediated endothelial cell proliferation, survival and migration in vitro. On the other hand, bevacizumab induces apoptosis in hypoxia-susceptible tumour cell lines.

Prospective, randomized trials have shown that bevacizumab added to oxaliplatin-based CTx regimens in patients with stage IV colorectal cancer improves overall survival, progression-free survival and response rate.[41, 42] As a result it might allow a higher proportion of patients with unresectable disease to become resectable. It would also be likely that bevacizumab has an effect on dormant micrometastases, promoting tumour shrinkage and inhibition of angiogenesis. The anti-angiogenic effect and the long half-life of bevacizumab have raised concerns about wound healing and liver regeneration.[43, 44] The addition of bevacizumab in the TREE-2 (Three Regimens of Eloxatin in Advanced Colorectal Cancer) study caused more grade 3 or 4 hypertension, impaired wound healing and bowel perforation.[45] On the other hand, Kesmodel et al.[46] showed that neither the use of bevacizumab nor the timing of its administration was associated with an increase in complication rates in patients treated with different types of CTx regimens. Other studies[40, 47] have shown that bevacizumab can be given before hepatectomy without affecting postoperative morbidity, if the interval between discontinuation of bevacizumab and hepatic resection is at least 8 weeks. The results from a study by Gruenberger and colleagues[48] suggest that this interval could be shortened to 5 weeks without an increase in per operative complications. Bevacizumab is associated with gastrointestinal perforation and poor wound healing across clinical trials but their incidence is rare.[49] Moreover, bevacizumab does not impair liver regeneration, even in response to portal vein embolization (PVE).[50]

Evidence suggests that bevacizumab might decrease the incidence of sinusoidal injury: Ribero et al.[51] showed that bevacizumab reduces the occurrence of sinusoidal injury related to oxaliplatin when therapy is relatively short: Sinusoidal dilatation of any grade was reduced in patients who received oxaliplatin plus bevacizumab (27 vs. 54% without

bevacizumab), and severe (grade 2-3) sinusoidal obstruction was reduced significantly by the addition of bevacizumab to oxaliplatin (8 vs. 28%, p=0.006). Ribero et al[8] also showed an improved pathological response. Klinger et al.[29] found no improved clinical tumour response with the addition of bevacizumab but demonstrated that when given in five cycles, bevacizumab protects against the sinusoidal obstruction syndrome. The exact mechanism responsible for this is still unknown, but it is possible that the VEGF blockade acts by downregulating metalloproteinases, thereby decreasing the rate of apoptosis in endothelial cells.

CETUXIMAB

One of the new members of the family of biological agents for treatment of colorectal cancer is cetuximab. This mouse/human chimeric monoclonal antibody has inhibiting effects on epidermal growth factor receptor (EGFR). Several studies have shown an increased response rate, when added to the FOLFIRI regimen.[10, 52-54] In particular, patients with KRAS wild-type metastatic colorectal cancer may greatly benefit from this regime. In a recent study, response rates up to 70% were reported.[10] Also, increased resection rates following metastatic disease irresponsive to traditional regimes have been reported, of which the largest study (CRYSTAL) was performed by van Cutsem et al.[53] In this study 1198 irresectable patients were randomized to either FOLFIRI or FOLFIRI + cetuximab chemotherapy. The addition of cetuximab resulted in a significantly increased resection rate (7.0% vs 3.7%) and an increase in R0 resections (4.8% vs 1.7%). Similarly, in the OPUS trial[52] the addition of cetuximab to FOLFOX resulted in increased RO resections (4.7% vs 2.4%).

Reported side-effect of cetuximab included skin reactions and in select cases infusion reactions and hypomagnesemia.[52] Unfortunately, no histological analysis of liver tissue was performed in either study. As far as we know, the only study performing histological analysis of liver tissue following cetuximab treatment in patients was by Adam et al.[54] Twenty-seven patients of 151 were downsized after irresponsiveness to traditional regimes. Hepatic lesions were found in 37% of patients; they were not attributable to cetuximab but were related to traditional chemotherapy regimes. No clinical studies to date have investigated whether cetuximab impairs regenerative capacity. In this respect, experimental reports are contra-dictionary. Natarajan et al.[55] indicated that EGFR is a key regulator of liver regeneration. However van Buren et al.[44] showed that inhibition of EGFR by cetuximab, as opposed to bevacizumab, does not impair liver regenerative capacity in a murine model. Additional clinical studies will have to be employed to investigate whether cetuximab can be used safely before liver resection is performed.

Because it is one of the newest biological agents available, only a few studies have been performed on perioperative outcome after liver resection following cetuximab treatment. Adam et al.[54] showed encouraging operative results in a modest series of 27 patients. One of 27 patients (3.7%) died as a consequence of liver failure after a second partial liver resection was performed. The overall complication rate was 50%. It must be noted that in this study patients had received several different combinations of chemotherapy treatment before undergoing liver resection, thus making it difficult to point out the exact influence of cetuximab on outcome of liver resection alone. With respect to measures for the safe preoperative use of cetuximab, too few studies have been completed to allow any recommendations to be put forth regarding safe use of this type of chemotherapy.

In summary, increased use of preoperative chemotherapy in initially resectable patients or in those converted to a resectable status offers several theoretical benefits, but outcomes have enhanced awareness of the adverse effects of chemotherapy on the liver parenchyma. Concerns regarding chemotherapy-associated liver injury may prevent clinicians from offering potentially curative therapy, and such treatment may increase morbidity in some patients. Prolonged use of preoperative chemotherapy should be avoided, and choice of therapy should be individualized on the basis of respectability status, extent of hepatic resection required, and associated comorbid conditions.

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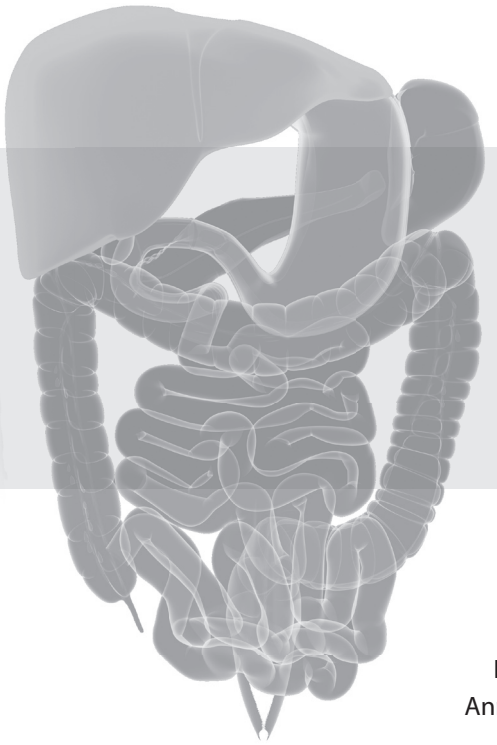
8

STEATOSIS ASSESSMENT AFTER NEOADJUVANT CTX; CT OR MRI



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ABSTRACT

Purpose Preoperative radiological assessment of hepatic steatosis is recommended in patients undergoing a liver resection, but few studies investigated the diagnostic accuracy after neoadjuvant chemotherapy. The aim of this study was to compare diagnostic accuracy of preoperative CT or MRI measurements of steatosis in patients with colorectal liver metastases after induction chemotherapy.

Methods MRI measurements (relative signal intensity decrease; RSID), N=36, and CT scan measurements (Hounsfield units; HU), N=32, were compared with histological steatosis assessment. Diagnostic accuracy was determined for detecting any (>5%) or marked macrovesicular steatosis (>33%).

Results MRI showed the highest correlation with histology ($r=0.82$, $p<0.001$), compared to CT measurements ($r=-0.65$, $p<0.001$). Based on linear regression analysis, radiological cut-off values for 5% and 33% macrovesicular steatosis, corresponded to 0.7% and 19.2% RSID in the MRI-group, and 60.4 HU and 54.2 HU in the CT-group, respectively. Sensitivity and specificity for the detection of any and marked macrovesicular steatosis using MRI was 87% and 69%, and 78% and 100%, respectively, and for CT, 83% and 64%, and 70% and 87%, respectively.

Conclusion In patients treated with neoadjuvant chemotherapy MRI measurements of steatosis showed the highest correlation coefficient and the best diagnostic accuracy, as compared to CT measurements.

INTRODUCTION

The optimal treatment of patients with colorectal liver metastases consists of surgical resection resulting in 5-year survival rates up to 58%.[1,2] New effective chemotherapeutic agents, including oxaliplatin, irinotecan, bevacuzimab and cetuximab added to '5-fluorouracil (5-FU) based regimes increase the rate and degree of tumour response and improve median survival.[3-6] The downside of neoadjuvant chemotherapy treatment is the risk of hepatoxicity, which can manifest as chemotherapy associated steatohepatitis (CASH), as mainly seen with irinotecan, or as the sinusoidal obstruction syndrome ('blue liver syndrome') caused by oxaliplatin.[7-9] The presence of sinusoidal obstruction and CASH can result in increased postoperative complications following liver resection, especially after application of a high number of cycles.[5,10-12] Another important risk factor for postoperative complications in patients undergoing a liver resection is preexisting hepatic steatosis.[13] Patients with an increasing amount of steatosis are encountered more frequently in the Western world, and the incidence is expected to rise in the near future due to the current obesity epidemic.[14] While mild steatosis (5-33%) is relatively harmless, the presence of moderate (33-66%) and severe (>66%) macrovesicular steatosis should be taken into consideration, before performing an extended liver resection.[15,16]

In an era in which neoadjuvant chemotherapy is being applied more frequently and steatosis is being encountered more often, it is becoming of greater importance to preoperatively screen patients for the presence of a marked degree of macrovesicular steatosis (>33%). In order to identify steatosis, histological evaluation of a liver biopsy has been the diagnostic tool of choice, but this procedure is not regularly employed due to the invasive character and the sampling variability.[17,18] Computed tomography (CT) and magnetic resonance imaging (MRI) are widely available and relatively accurate for steatosis assessment in patients with normal liver parenchyma.[19-24] However, there are no studies yet that evaluated the accuracy of CT or MRI for the detection of steatosis in patients after neoadjuvant chemotherapy. Therefore, the aim of this study was to compare MRI and CT measurements of steatosis in patients treated with neoadjuvant chemotherapy prior to liver resection.

PATIENTS AND METHODS

Study subjects and design

Patients who received neoadjuvant chemotherapy (CTx) for colorectal liver metastases prior to a liver resection in the period 2003-2008 were identified from a prospectively maintained database. All patients underwent radiological follow-up using CT or MRI after several CTx cycles for the evaluation of therapy response. Patients were included in the

study when oxaliplatin-based CTx therapy was administered, an MRI with an in-phase/ opposed-phase (IP/OP) T1-weighted sequence, or a CT-scan including an unenhanced phase was performed, and sufficient non-tumour bearing liver tissue was available in the resected liver specimen for histopathological analysis. Slides were randomly evaluated by two independent pathologists, blinded to the radiological measurements, for the degree of macrovesicular steatosis, steatohepatitis and sinusoidal dilatation. Preoperative clinical characteristics from all patients were retrieved, including sex, age, body mass index (BMI), diabetes mellitus (DM) and number of metastases. Furthermore, oncological nurse practitioners from referring centres were approached for type of CTx regime, number of cycles and the date of last CTx administration.

CT procedure and determination of hepatic fat

Patients were included on condition that an unenhanced CT-scan was available, since this is considered the most reliable CT-phase for the assessment of steatosis.[20-22] All patients underwent a CT scan using a multidetector helical CT scanner (SOMATOM Sensation 64; Siemens Medical Solutions, Erlangen, Germany). The unenhanced CT-images were reviewed with 5-mm collimation on a picture archiving and analysis system (Impax; Agfa, Mortsel, Belgium) and the amount of steatosis was determined by assessing amount of liver attenuation, represented by Hounsfield units (HU), as described by Kodama et al.[19]. Attenuation was recorded in 12 regions of interest (ROI) in the liver, each measuring 1-2 cm^2, placed in predetermined positions in 3 different slices in the right posterior, right anterior, left medial and left lateral part of the liver. Care was taken to avoid major vessels, bile ducts, or tumourous lesions when placing the ROI's. A decreased attenuation is indicative for the presence of a pathological amount of hepatic fat.

MRI procedure and determination of hepatic fat

At the end of the study period the MRI scan was introduced as the modality of choice for the assessment of tumour response after induction CTx. A 1.5 T MRI unit (Philips Medical Systems, Best, The Netherlands, or Sigma, General Electric, Milwaukee, WI, USA), using identical scan protocols with a four-channel body-array coil was used. Hepatic fat content measurements were performed on T1 weighted in and opposed-phase GRE sequences (TR/TE msec: shortest/ 4.6 and 2.3, respectively, flip angle _ 80°). Calculation of hepatic fat content was performed by measuring signal intensity (SI) values in IP/ OP MR images as described by Qayyum et al.[19], using a picture archiving and analysis system (Impax; Agfa, Mortsel, Belgium). For measurements, ROI's (1-2 cm^2) were placed in the liver at paired anatomical positions on IP/OP MR images, avoiding major vessels, bile ducts and tumourous lesions. The mean liver SI in IP/OP images was calculated from a total of 12 ROI's placed in four different hepatic regions (left and right lobe) on three different transversal planes. Similarly, the mean SI in the spleen as an internal standard

was calculated in IP/OP MR images in corresponding transversal planes; 9 ROI's in total. The amount of hepatic fat (%RSID) was calculated using the formula ([SIin – Siout]/SIin) x 100%, where SIin is the mean in-phase SI in the liver divided by the mean in-phase SI in the spleen, and SIout is represented by the mean opposed-phase SI in the liver divided by the mean opposed-phase SI in the spleen. A relative SI decrease (%RSID) in the liver on OP images reflects the presence of an increased hepatic fat content.

Histopathological analysis

Hematoxylin and eosin (H&E) stained slides containing sufficient non-tumourous liver tissue were selected by two independent pathologists for histological evaluation. Before the start of the study, inter-observer variability was determined by evaluating 10 randomly selected set of slides for the assessment of macrovesicular steatosis and sinusoidal dilatation. Hepatic macrovesicular steatosis and steatohepatitis score was determined according to Kleiner et al.[25] Macrovesicular steatosis, present as a lipid vacuole larger than the diameter of the nucleus, was graded as follows; none (0-5% = 0), mild (5-33% = 1), moderate (33-66% =2) and severe (66-100% = 3). Lobular inflammation was scored by the presence of inflammatory foci per 200x high power field, where nil foci = 0, 2-4 foci = 1, > 4 foci = 3. Ballooning was scored as 0, 1 = few ballooning, 2 = prominent ballooning. A Kleiner score of ≥5 was considered compatible with steatohepatitis, and a Kleiner score of 4 with 'bordeline' steatohepatitis. Sinusoidal dilatation was graded as described by Rubbia-Brandt[9]; no sinusoidal dilatation, involvement of 1/3 of the lobule (mild), 2/3 (moderate) or complete lobular involvement (severe).

Statistical analysis

All data were analyzed with the statistical software package SPSS 14.0 (SPSS, Chicago, IL). Differences in nominal variables were studied using a Chi-Square test and difference in ordinal variables was studied using a Mann-Whitney test. Correlations between hepatic fat measurements, using MRI or CT, and histological assessment of steatosis and sinusoidal dilatation were analyzed by Spearman' coefficients. Diagnostic accuracy was determined for the radiological detection of patients with any (>5%), and for the detection of marked (>33%) macrovesicular steatosis, indicating patients with an increased surgical risk profile. The corresponding radiological cut-off values for 5% and 33% macrovesicular steatosis were calculated from linear regression functions between MRI or CT measurements and histological steatosis scores. Based on these cut-off values, the sensitivity, specificity, positive and negative predictive values for CT- and MRI-measurements of 5% and 33% macrovesicular steatosis were determined.

RESULTS

Patient characteristics

During the study period (2003-2008) 139 patients underwent a liver resection following neoadjuvant CTx treatment. Thirty-two patients had oxaliplatin based neoadjuvant CTx, availability of an unenhanced CT scan, and sufficient non-tumour bearing liver tissue present for histopathological analysis. In the other 107 patients, one of the three items (oxaliplatin/CT-scan/sufficient liver tissue) were not available. In the same study period 36 patients had a complete IP/OP MRI scan, revealed a sufficient amount of non-tumour bearing liver tissue, were treated with neoadjuvant oxaliplatin based therapy and were consequently included in the study. In both groups the radiological follow-up was performed no more than 4 months preoperatively. The patient demographics, male:female ratio, the mean age at the time of resection, BMI and DM were not significantly different between the two groups, as shown in Table 7-1.

Table 7-1 Patient demographics

	MRI n = 36	**CT n = 32**	**P-value**
Male:Female	1.4:1	1.6:1	NS
Age	59.6 ± 9.0	58.5 ± 8.8	NS
BMI	26.0 ± 4.0	25.0 ± 3.7	NS
Comorbidity			
None (%)	25 (70%)	20 (63%)	NS
DM (%)	3 (8%)	3 (9%)	NS

NS, non significance; BMI, Body Mass Index (kg/m^2); DM, diabetes mellitus.

Tumour and CTx characteristics

Tumour and CTx characteristics are outlined in Table 7-2. There were no significant differences between the MRI- and CT group with respect to the number of metastases and the timing of metastases. All patients received oxaliplatin combined with 5-FU (Ox/5FU), however in some patients bevacizumab was added to this regime; i.e. 36% (13/36) and 28% (9/32), in the MRI and CT-group, respectively. There was no difference in the number of Ox/5-FU cycles administered in both groups. The number of bevacizumab cycles administered in the CT group, 6.3 ± 4.4, was slightly higher as compared to the MRI-group, 4.9 ± 3.1, although not statistically different (P=0.384). This was due to 3 patients in the CT-group rendered resectable after palliative CTx treatment, receiving 15, 11 and 8 bevacizumab-cycles in addition to the Ox/5FU regime, respectively. The mean interval between the last administration of CTx and the liver resection was 8 weeks in both study groups.

Table 7-2 Tumour and chemotherapy characteristics

	MRI n = 36	CT n = 32	P-value
Metastases	3.2 ± 1.8	3.1 ± 1.6	NS
Synchronous	29 (81%)	24 (75%)	NS
Metachronous	7 (19%)	8 (25%)	NS
Chemotherapy			
Oxaliplatin/5-FU	14 (39%)	23 (72%)	NS
Oxaliplatin/5-FU andbevacizumab	13 (36%)	9 (28%)	NS
Nº of oxaliplatin/5-FU cycles	6.1 ± 2.8	6.3 ± 3.3	NS
Nº of bevacizumab cycles	4.9 ± 3.1	6.3 ± 4.4	NS

Histology, MRI and CT measurements

A low inter-observer variability (results not shown) was found between the two pathologists in grading macrovesicular steatosis percentage and sinusoidal dilatation grade in 10 randomly selected slides. Based on this finding, a random selection of half of all slides was scored by one of the two pathologists. Measurements of hepatic fat content by MRI (%RSID, mean ± SEM) in patients with no steatosis (n=10) was -0.9 ± 6.5%, and in patients with mild macrovesicular steatosis (n=13) 5.2 ± 9.3% (Fig 7-1a). In patients

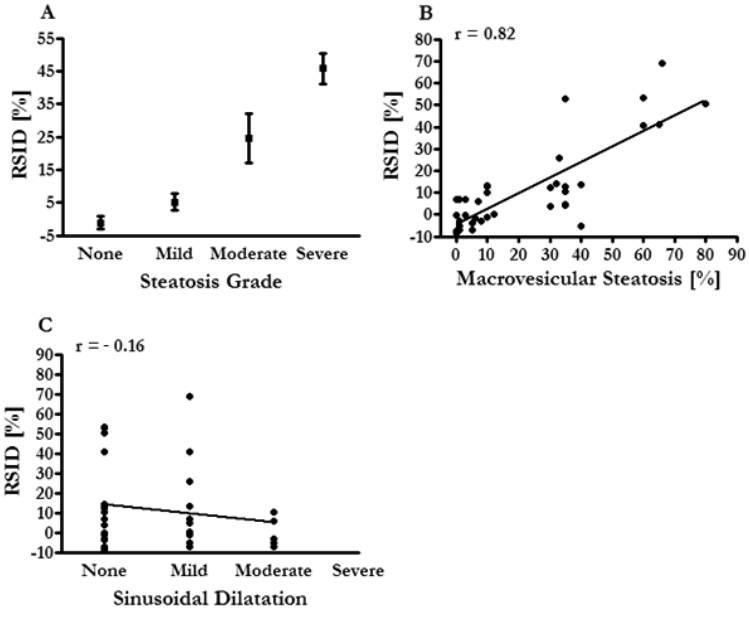

Fig 7-1

a Measurements of hepatic fat content by MRI

b Correlation between MRI measurements (RSID) and histological percentage of macrovesicular steatosis

c Correlation between MRI measurements (RSID) and sinusoidal dilatation.

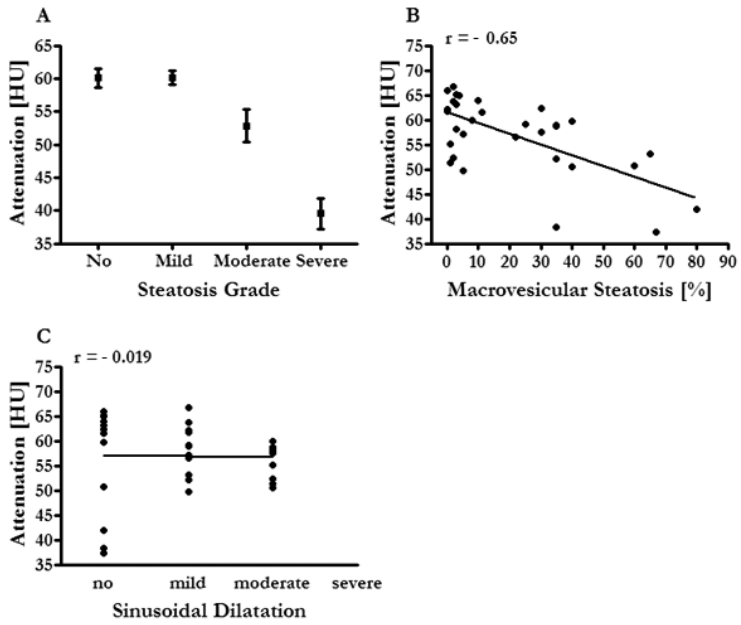

Fig 7-2

a Measurements of hepatic fat by CT

b Correlation between CT attenuation (HU) and histological determination of macrovesicular steatosis

c Correlation between CT measurements (HU) and sinusoidal dilatation

with moderate (*N*=11) and severe (n=2) macrovesicular steatosis, the mean RSID's were 24.6 ± 24.7 and 50.5 ± SD, respectively. A high correlation (r = 0.82, $p < 0.0001$) was detected between RSID and histological percentage of macrovesicular steatosis (Fig. 7-1b). Sinusoidal dilatation was present in 15 patients, of which 10 had mild (1/3 lobular involvement) and 5 patients moderate sinusoidal dilatation (2/3 lobular involvement). There was no correlation between MRI measurements and sinusoidal dilatation (r = -0.16, p=0.344) (Fig. 7-1c).

In the CT-group, the mean attenuation (HU) (Fig. 7-2A) in patients with no steatosis (n=14) was 60.1 ± 5.7, and in patients with mild macrovesicular steatosis (n=7), 60.1 ± 2.7. Hepatic attenuation in patients with moderate (n=8) and severe (n=2) macrovesicular steatosis, were 52.8 ± 7.0, and 39.6 ± 3.3, respectively. Determination of the correlation between CT attenuation and histological determination of macrovesicular steatosis yielded a lower coefficient (r = -0.65, $p < 0.0001$), as compared to MRI measurements (Fig. 7-2B). Sinusoidal dilatation was absent in 12 patients, mild dilatation was detected in 12 patients, and moderate sinusoidal dilatation was present in 8 patients. Similar to the MRI-group, there was no correlation found between CT measurements and sinusoidal dilatation (r=-0.019, p=0.920) (Fig 7-2C).

In the MRI-group borderline steatohepatitis was present in 19% (7/36) and one patient had a definite steatohepatitis Kleiner score (>5); 3% (1/36). Similarly, in the CT-group 19% (6/32) of patients had borderline steatohepatitis, and one patient had definite steatohepatitis; 3% (1/32). In both groups an increased steatosis degree was associated with a high BMI (results not shown), except for two patients with severe steatosis in the MRI-group (BMI 23.3 ± 2.0*)*.

Diagnostic accuracy of MRI and CT measurements of hepatic fat content

The accuracy of MRI and CT for the assessment of hepatic fat content was determined for the histological cut-off values of >5% (any), and >33% (marked) macrovesicular steatosis. Using the linear regression function of MRI measurements and histological determination of macrovesicular steatosis (y = -4.305 + 0.713x), RSID values corresponding to the histological cut-off values of 5% and 33% were determined; -0.74% and 19.22%, respectively. Similarly, for the CT measurements corresponding attenuation values (HU) for 5% and 33% macrovesicular steatosis were determined using the linear regression function (y = 61.46 – 0.22x); 60.4 HU and 54.2 HU, respectively.

The results of the sensitivity, specificity, positive, and negative predictive values from CT and MRI measurements are summarized in Table 7-3. From 23 patients with >5% macrovesicular steatosis, MRI correctly identified 20 cases, resulting in a sensitivity of 87%. In 13 patients with <5% macrovesicular steatosis, 9 patients were correctly identified, resulting in a specificity of 69%. The accompanying positive and negative predictive values were 83% and 75%, respectively. In the CT group, liver attenuation values correctly identified 15 of 18 patients with >5% macrovesicular steatosis, resulting in a sensitivity of 83%. Comparable to MRI, specificity was lower, 64%, owing to the correct identification of <5% steatosis in only 9 of 14 patients. The accompanying positive and negative predictive values were both 75%.

Table 7-3 Sensitivity, specificity, positive and negative predictive values from CT and MRI measurements

	MRI				CT			
MaS %	Sensitivity	Specificity	PPV	NPVw	Sensitivity	Specificity	PPV	NPV
5 %	88%	69%	83%	75%	83%	64%	75%	75%
33 %	77.8%	100%	100%	93%	70%	86%	70%	86%

MaS, macrovesicular steatosis; PPV, positive predictive value; NPV, negative predictive value.

For accurate detection of patients with a marked macrovesicular steatosis degree of >33%, MRI yielded a 78% sensitivity, owing to correct measurements in 7 out of 9 patients. All 27 patients with <33% macrovesicular steatosis were correctly identified by MRI, resulting in 100% specificity. The positive predictive value was 100% and the negative predictive value 93%, due to false-negative results in 2 patients. The detection of

>33% steatosis using CT was more prone to false positive and negative results, as compared to MRI. CT correctly identified 19 of 22 patients with <33%, and 7 of 10 patients with >33% macrovesicular steatosis, resulting in a specificity of 86%, and a sensitivity of 70%, respectively. The corresponding positive and negative predictive values were 70%, and 86%, respectively.

DISCUSSION

This is the first study comparing diagnostic accuracy of CT and MRI measurements of hepatic fat content with histological confirmation in patients treated with neoadjuvant CTx treatment. We found that MRI yielded the highest correlation and the highest diagnostic accuracy for the detection of a clinically relevant marked (>33%) steatosis degree, as compared to CT.

While liver surgery has become safer due to improved surgical techniques and peri-operative care[26], the negative influence of steatosis on patients undergoing an extended liver resection remains significant, especially in an era where obesity is becoming epidemic and no effective therapy for steatosis is available yet.[13,14] Marked macrovesicular steatosis (>33%) is associated with increased blood transfusions, higher infectious complications, and total postoperative complications after large liver resections.[16,27] In addition to the injurious effects of steatosis, patients are increasingly being exposed to another risk factor for postoperative morbidity and mortality; neoadjuvant chemotherapy. Vauthey et al.[12] showed increased 90-day mortality following liver resection after mainly irinotecan based chemotherapy treatment. In two studies evaluating patients following mainly oxaliplatin based neoadjuvant CTx, postoperative morbidity was also significantly higher, as compared to control patients.[10,11] The findings of these retrospective studies were recently confirmed in a prospective randomized trial (EORTC 40983), in which patients receiving peri-operative oxaliplatin-based CTx had a higher rate of complications after a liver resection (25%), versus patients undergoing surgery without CTx (16%, $p = 0.04$).[5] Furthermore, Karoui et al.[10] showed postoperative morbidity was associated with an increased number of cycles; 45% after 6-9 cycles, as compared to 19% after ≤5 cycles. Therefore, in patients undergoing an extended liver resection after a high number of CTx cycles (>6) additional risk factors, such as a high degree of steatosis, should be ruled out.

To our knowledge, this is the first study investigating accuracy of hepatic fat measurements using either MRI or CT in a patient group treated with neoadjuvant chemotherapy. Many studies have evaluated either CT, or MRI measurements of steatosis in patients with non-injured liver parenchyma[19-24], but only few studies compared both modalities in one study. One of the first studies evaluating multiple modalities for steatosis assess-

ment was performed by Saadeh et al.[28] In 25 patients diagnosed with non-alcoholic fatty liver disease, US, CT and MRI were correlated with histological evaluation of a liver biopsy, performed within 3 months. They concluded that only with CT-scan, accurate detection of >33% steatosis was feasible. In the latter study the hepatic fat content in CT scans was not quantified using Hounsfield units, but by a semi-quantitative scoring system as assessed by the radiologist. Positive predictive values for the detection of >33% steatosis using CT was 76%. In comparison, the positive predictive value of CT quantification using liver attenuation in our study was 70%. Unfortunately, for the MRI measurements in the study by Saadeh et al. performed similar to our study (%RSID), diagnostic accuracy was not mentioned, and no correlation studies with histological analysis were performed. Furthermore, in contrast to the large wedge biopsies used in our study, histological analysis was performed in needle biopsies, shown to be hampered by staging inaccuracies.[18] Another shortcoming was the lack of patients without steatosis included in the study, making it difficult to investigate diagnostic accuracy for the detection of low steatosis degrees. In spite of these shortcomings, the study by Saadeh et al. is unique in its design, evaluating three different modalities in a single patient with histological confirmation. In contrast, our study evaluated two modalities in two different patient groups, albeit with highly similar demographic features (BMI, DM, age, sex distribution, steatosis degrees). Another study comparing MRI and CT for steatosis assessment in single patients was performed by Yoshimitsu et al.[29] From a total of 58 patients, consisting of 38 living donor liver transplantation candidates, and 20 liver resection patients, 34 patients underwent both modalities. For MRI measurements, decrease in liver intensity on in- and opposed-phase images was calculated, without correcting for the spleen intensity. For CT measurements, attenuation differences between the liver and spleen were used. Similar to our study, MRI resulted in a higher correlation rate, compared to CT; $r = 0.833$ vs $r = -0.742$ (Spearman). Also, diagnostic accuracy of MRI for the differentiation of mild steatosis was superior to CT. However, this study has two major drawbacks; the MRI and/or CT scan in the liver resection patients were performed within two weeks after surgery, during which the biopsy was taken. From experimental studies it is known that liver regeneration after partial hepatectomy is associated with an increased hepatic fat accumulation[30,31], which could have influenced the study outcome. Furthermore, 12 of the included living donor candidates were on diet therapy for weight reduction preoperatively, after radiological analysis of hepatic fat content, which also leads to a measurement discrepancy.

A possible explanation for the increased accuracy of steatosis detection by MRI, as opposed to CT, can be found in the working principles of the two modalities. CT scan only reflects the permeability of tissue for the passage of X-ray beams. The in-phase/out of phase measurements with MRI reflects the agility of protons in tissue to react to a magnetic field switch. The fatty liver consists of a significant higher amount of long

fatty acid chains, which are abundant in protons, as compared to lean livers. After exposure to a strong magnetic field (in-phase) followed by a 180° switch in field direction (out-phase), the higher amount of protons in fatty livers result in a phase cancellation, which is shown in the MR image as a drop in signal intensity. Furthermore it is a widely accepted principle that MRI is far superior to CT in characterizing soft tissue contents, even so in fatty liver.

Many studies have been performed investigating accuracy of hepatic fat measurements using either MRI, or CT, and more recently ^{1}H-magnetic resonance spectroscopy. There are only a few studies comparing these modalities in one study, and our study is the first study selectively evaluating an upcoming patient group in liver surgery; the chemotherapy treated patient undergoing liver resection.

In conclusion, measurement of hepatic fat content in patients treated with chemotherapy using MRI was superior as compared to CT. The correlations and diagnostic accuracies of MRI measurements found in this study are comparable to studies in chemonaïve patients and justify future application of MRI in risk assessment of patients undergoing liver resection after neoadjuvant chemotherapy treatment.

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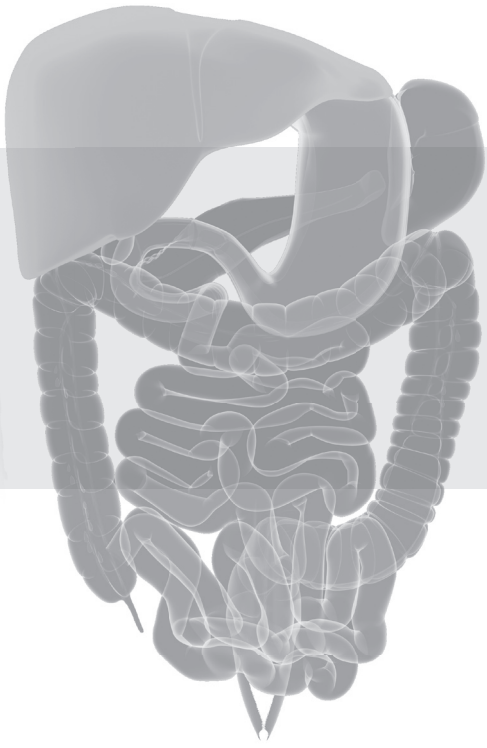
9

EFFECT OF BEVACIZUMAB ADDED PREOPERATIVE TO OXALIPLATIN ON LIVER INJURY AND COMPLICATIONS AFTER RESECTION OF COLORECTAL LIVER METASTASES



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ABSTRACT

Aim To ascertain whether adding bevacizumab, a monoclonal antibody against VEGF, to oxaliplatin-based chemotherapy (CTx) has an influence on liver injury and postoperative complications.

Patients and methods Patients with colorectal liver metastases who received neoadjuvant chemotherapy and underwent resection between 2003-2008 were divided into two groups: patients with and without bevacizumab added to oxaliplatin-based CTx.

Results The total study group existed of 104 patients: 53 patients received oxaliplatin-based CTx and 51 patients received oxaliplatin-based CTx and bevacizumab**.** The overall complication rate (29%) was not significantly different between the two groups. The bevacizumab group exhibited less moderate sinusoidal dilatation (8% vs. 29%, $p = 0.01$). No difference in complication rate was found between patients given fewer than 6 cycles of oxaliplatin-based CTx and those given 6 or more cycles, or between patients with a short (<5 weeks) interval between the last dose of oxaliplatin and resection and those in which the interval was longer.

Conclusions Bevacizumab added to oxaliplatin-based CTx protects against moderate sinusoidal dilatation without significantly influencing morbidity. Neither duration of oxaliplatin-based CTx nor the time interval between cessation of oxaliplatin-based CTx and surgery were associated with postoperative complications.

INTRODUCTION

In recent years, there is an increased use of systemic chemotherapy (CTx) before resection of colorectal liver metastases (CRLM). When given prior to liver surgery it may downsize tumour mass, increase the number of patients, who are amenable for curative treatment, treat undetected micro-metastases and improve selection of patients for surgery.[1-2] Fluoropyrimidines with oxaliplatin is a commonly applied combination of CTx used since 2000 in patients with CRLM. It yields clinical response rates of 55% and median survival of 22 months.[3-4] However, several studies have demonstrated that oxaliplatin-based CTx can cause injury (sinusoidal dilatation) in the nontumour-bearing liver, which may influence the surgical outcome.[5-6]

Nowadays, even higher clinical and pathological response rates can be achieved by combining cytotoxic agents with bevacizumab, a molecular-targeted therapy.[7-8] Bevacizumab is a recombinant humanized version of a murine monoclonal antibody with angiogenesis inhibiting effects. It binds to the vascular endothelial growth factor (VEGF), preventing activation of the corresponding receptor kinases VEGFR-1 and VEGFR-2. VEGF mediates liver growth by both hepatocyte and sinusoidal endothelial cell proliferation and is essential for wound healing.[9-10] Adding bevacizumab to oxaliplatin-based CTx might have detrimental consequences on outcomes after resection of CRLM.[11-12] Questions also remain about the optimal timing and safety of surgery in patients receiving bevacizumab.

The rising use of chemotherapy combinations for CRLM raises concerns about the potential hepatotoxicities induced by systemic drugs and the effects of these drugs on per- and postoperative outcome. Partly based on the study of Ribero et al.[8] and Rubbiabrandt et al.[6] this study was conducted to ascertain whether adding bevacizumab to oxaliplatin-based CTx has an influence on liver injury. Moreover, the influence of bevacizumab added to oxaliplatin-based CTx on postoperative complications was evaluated. Histopathological changes of the liver and surgical outcomes in patients who did and did not receive bevacizumab were compared.

PATIENTS AND METHODS

Demographics

All patients who had received chemotherapy from 2003-2008 prior to liver resection were identified from a prospectively maintained single centre database that included patients with resected colorectal liver metastases. The inclusion criteria were macroscopic radical resection of the liver metastases and the use of oxaliplatin-based chemotherapy in neoadjuvant setting. To ensure homogeneity within groups, we excluded patients

who had undergone a portal vein embolisation (PVE) or portal vein ligation (PVL) and patients who had been treated with other chemotherapeutics besides oxaliplatin-based CTx. PVE may cause histopathological changes affecting the nontumourous hepatic parenchyma.[13] The study population was divided into two groups: patients with and without bevacizumab added to oxaliplatin-based CTx. These were further divided into subgroups based on number of cycles of oxaliplatin-based CTx and the time interval between the last dose of oxaliplatin-based CTx and resection.

Chemotherapy

Oxaliplatin-based CTx was given in a neoadjuvant fashion if the patients had bi-lobar disease, extra-hepatic disease or >three metastases. Some patients became resectable if CTx had downsized unresectable liver metastases. By preference, patients received no more than 6 cycles of oxaliplatin, since a higher number of cycles may increase morbidity and mortality.[14] An interval of 5 weeks between last dose of oxaliplatin-based CTx and resection has been recommended, in order to reduce postoperative complications yet at the same time to avoid a long delay in treatment and minimize the risk of tumour progression.[15-16] In our study population, patients who had received bevacizumab, the last dose was preferably administered six weeks prior to surgery. This is due to the long half-life (21, range 11-50 days) of the drug.[17] Most of the patients received neoadjuvant chemotherapy in referral centres; it was up to them to add bevacizumab.

Patient characteristics

Data on patient and tumour characteristics, CTx treatment regimens, and operative factors were extracted from the database. The patient and tumour characteristics included age, gender, co morbidities (diabetes mellitus, hypertension), body mass index (BMI), number, size and distribution of metastases and type of resection. Radiofrequency ablation (RFA) in addition to surgery has been used in patients with multiple bi-lobar metastases who were unable to treat curative with liver surgery only. BMI was calculated as BMI=weight [kg]/ (height[m])^2. The following details were recorded for the CTx treatment regimens: number of cycles and time interval from completion of oxaliplatin and bevacizumab to surgery. Hepatic resections were described according to the standard nomenclature of Couinaud.[18] Major hepatic surgery was defined as a resection of > three segments. Complications were defined as any deviation from the normal postoperative course and were graded according to Dindo et al.[19] Grades 1 and 2 were defined as mild complications, ≥ grade 3 was defined as a severe complication. A Pringle manoeuvre had been performed only when an extensive bleeding occurred during hepatic transaction.

Histopathology

All the archival histological slides, relating to the selected patients (originally prepared from formalin-fixed, paraffin-embedded tissue) were reviewed, and representative slides of non-tumoural tissue located at some distance from the tumour were examined. The morphological analyses were based on hematoxylin and eosin. Two independent pathologists (J.H., W.C.), unaware of the clinical data, analyzed the slides in a blinded fashion. Before the start of the study, inter-observer variability was determined by examining 10 randomly selected sets of slides for the assessment of macrovesicular steatosis and sinusoidal dilatation grades. The following histological features were scrutinized: sinusoidal dilatation, perivenular fibrosis, nodular hepatic regeneration/atrophy, hepatic ballooning, lobular inflammation, portal inflammation, and steatosis. Sinusoidal dilatation was graded as described by Rubbia-Brandt et al.[6]; 0, absent; 1, mild (centrilobular involvement limited to 1/3 of the lobular surface; 2, moderate (centrilobular involvement extending in two-thirds of the lobular surface); 3, severe (complete lobular involvement). Ballooning was scored as absent or present. Lobular inflammation was scored by the presence of inflammatory foci per 200x high power field, where no foci = 0, <2 foci = 1, 2-4 foci = 2, > 4 foci = 3. Macrovesicular steatosis, estimated as the percentage of hepatocytes involved with a lipid vacuole larger than the diameter of the nucleus, was classified as follows: none (<5%), mild (5-33%), moderate (33-66%) and severe (>66%). Hepatic macrovesicular steatosis and steatohepatitis score were determined according to Kleiner et al.[20]: the sum of ballooning, lobular inflammation and steatosis. A Kleiner score of ≥5 was considered steatohepatitis, and a Kleiner score of four "borderline" steatohepatitis.

Statistics

Categorical data are presented as percentage frequencies, and differences between proportions were compared using the chi-square tests or Fischer's exact tests, as appropriate. Continuous data with a significant skewed distribution are expressed as medians and were compared using the Mann-Whitney U test. A univariate analysis was performed to identify if any clinical characteristic was associated with postoperative complications or the presence of sinusoidal dilatation. Significance levels were set at $P < 0.05$. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

Demographics

From a database of 310 patients, 113 patients met the inclusion criteria. Pathological resection material was examined. Samples from nine patients were inconclusive because they contained insufficient nontumour-bearing liver. The final study population was 104

patients: 51 patients (49%) had received oxaliplatin-based CTx with bevacizumab and 53 patients (51%) had received oxaliplatin-based CT without bevacizumab. Demographics showed no significant differences between the two groups (Table 8-1).

Table 8-1 Demographics of the patients and characteristics of chemotherapy

	Non-bevacizumab group n = 53	Bevacizumab group n = 51	P-value
Demographics			
Age	62 (41-79)	64 (41-77)	0.87
Male	33	29	0.4
BMI median(kg/m^2)	25 (18-35)	25 (18-35)	0.39
Co morbidity			0.96
Hypertension	5	5	
Diabetes mellitus	5	4	
No. of metastases			
Median (range)	3 (1-7)	2 (1-8)	0.95
No. of metastases			
>3	23	18	0.43
Size of metastases			
Median (range)	3,5 (1-7)	2.8 (1-18)	0.88
Size of largest metastasis (cm)			
>5	12	8	0.62
Distribution of metastases			
Bi-lobar	31	34	0.42
Type of surgery			
Major	14	9	0.35
Surgery + RFA			
Yes	6	12	0.1

BMI, body mass index; RFA, radiofrequency ablation

Chemotherapy

Twenty-seven of the patients had received 5-fluorouracil, leucovorin and oxaliplatin according to the standard FOLFOX4 protocol, administered intravenously. The remaining 77 patients had received oxaliplatin 130 mg/m2/dl iv d1, capecetabine 1250 mg/m2 bid oral d1-d7, q2w according to the XELOX protocol. The 51 patients receiving bevacizumab were given 7.5 mg/kg iv d1. Patients in the non-bevacizumab group received a median of six (range, 2-12) courses of oxaliplatin-based CTx. Patients in the bevacizumab group received a median of six (range, 3-15) courses of oxaliplatin-based CTx and a median of four (range, 1-15) courses bevacizumab. Ten patients (10%) became resectable after they had been downsized by chemotherapy. Median interval between the last administration of oxaliplatin-based CTx and resection was six (range, 1-16) weeks in the non-bevacizumab and eight (range, 3-38) weeks in the bevacizumab group ($P = 0.016$). In one patient in the bevacizumab group, complete clinical response of metastases occurred after three cycles of CTx. In follow-up, metastases were detected on MRI and this patient

underwent resection 38 weeks after the last dose of CTx. Median interval between the last dose of bevacizumab, and resection was 11 (range, 5-38) weeks.

Intra-operative characteristics

Surgery-related factors were not significantly different between the two groups (Table 8-2)**.** Of the 74 patients (73%) who underwent wedge resections and/or segmentectomies, most were in the bevacizumab group (55% vs. 45%, $p = 0.07$). Six patients (11%) in the non-bevacizumab group and 6 patients (12%) in the bevacizumab group underwent associated procedures (colorectal surgery, inguinal hernia repair, lung resection, lymph node dissection and hernia cicatrialis repair). The overall complication rate was 29% and was not significantly different between the bevacizumab and non-bevacizumab groups (Fig. 8-1a). None of the patients died within 90 days. Univariate analysis revealed that none of the clinical variables was associated with the presence of adverse postoperative outcome.

Table 8-2 Intra-operative characteristics and postoperative complications

	Non-bevacizumab group n = 53	Bevacizumab group n = 51	P-value
Vascular clamping	7	1	0.03
No. of patients requiring blood transfusion (%)	17 (32%)	15 (29%)	0.8
Blood transfusion (packed red cell units)	2 (range, 1-12)	2 (range, 1-16)	1.0
Complications	17	13	0.6
Intestinal tract damage	1	1	
Delirium	2	-	
Intracapsulair hematoma	1	-	
Biloma	2	-	
Subphrenic abscess	-	2	
Pneumonia	2	3	
Pneumothorax	1	-	
Hernia cicatricalis	3	1	
UTI	1	1	
Gastric retention	1	1	
Edema	2	-	
Atelectasis	1	-	
Bile leak	-	1	
Hypokaliemie	-	1	
Hypertension	-	1	
Thrombotic arm	-	1	
Reoperation	1	2	0.61
Hospital stay	7 (3-23)	6 (3-54)	0.91

UTI, urinary tract infection

Histopathology

The inter-observer variability between the two pathologists grading the macrovesicular steatosis percentage and sinusoidal dilatation in 10 randomly selected slides was found

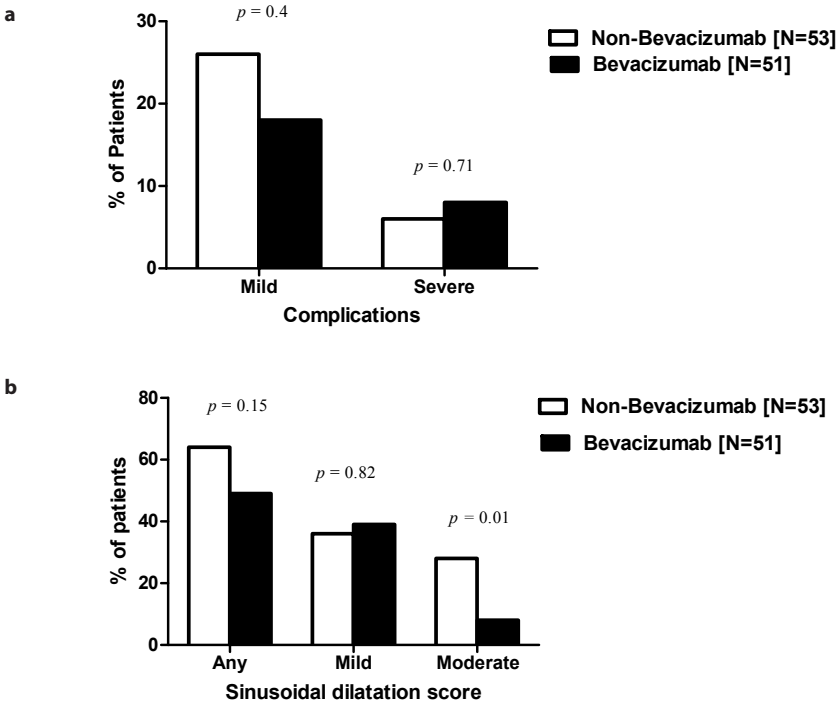

Fig 8-1

a) Complications in patients who received oxaliplatin-based CTx with or without bevacizumab

b) Sinusoidal dilatation score in patients who received oxaliplatin-based CTx with or without bevacizumab

to be low (result not shown). The two pathologists were therefore each randomly assigned to score half of the slides. No significant differences were observed between the two groups in perivenular fibrosis, portal inflammation, nodular regenerative hyperplasia, ballooning, lobular inflammation and steatosis (Table 8-3). They found sinusoidal dilatation in 57% of patients in the total study group (n=104) but this was not associated with postoperative complications (31% vs. 27%, $p = 0.83$). Figure 8-1b shows the distribution of sinusoidal dilatation grades among the non-bevacizumab and bevacizumab groups. In the bevacizumab group, a reduction of moderate sinusoidal dilatation was observed (8% versus 29%, $p = 0.01$). One patient in the bevacizumab group showed severe dilatation compared to none in the non-bevacizumab group ($p = 0.45$). Univariate analysis revealed that none of the clinical variables was associated with the presence of sinusoidal dilatation.

Table 8-3 Chemotherapy-associated liver injury

	Non-bevacizumab group n = 53	Bevacizumab group n = 51	P-value
Perivenular fibrosis			0.2
Absent	4	10	
< 50%	26	23	
> 50%	21	18	
Portal inflammation			0.6
None to minimal	38	33	
Greater than minimal	15	18	
Nodular regenerative hyperplasia/atrophy	17	12	0.6
Ballooning	-	1	0.5
Lobular inflammation			0.5
No foci	3	6	
< 2	34	34	
2-4	14	10	
> 4	2	1	
Steatosis			0.3
0-5%	22	27	
5-33%	18	18	
33-66%	11	6	
66-100%	2	0	
Kleiner score			
4	7	6	0.17
5	6	-	0.17

Duration of chemotherapy

Of the total study group, 57 patients (55%) received ≥ 6 cycles of oxaliplatin-based CTx. Their demographics did not differ from those of the remaining 47 patients. The patients who received ≥ 6 cycles of oxaliplatin-based CTx required significantly more blood transfusion compared to patients who received < 6 cycles (42% vs. 17%, $p = 0.01$). There was no difference in complication rate between the patients who received less or more than 6 cycles of CTx (Fig. 8-2a). Thirty patients (53%) in this group were treated with bevacizumab. No significant difference was found in sinusoidal dilatation between the bevacizumab and non-bevacizumab group (Fig. 8-2b).

Time interval

In 32 patients (31%), the interval between last dose of oxaliplatin-based CTx and resection was ≤ 5 weeks. No differences were noted in the demographics, operative characteristics, liver injury, or postoperative outcomes of these patients compared with the patients for whom the interval was more than 5 weeks (Fig. 8-3a). Twelve of the 32 patients (38%) were treated with bevacizumab. No significant difference was found in sinusoidal dilatation between these patients and the 20 patients who did not receive bevacizumab (Fig. 8-3b).

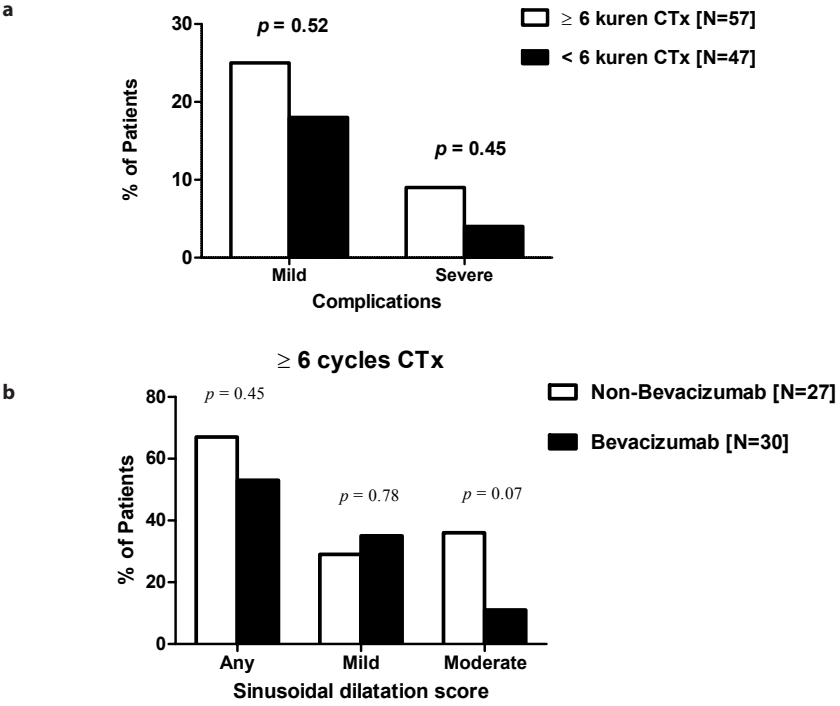

Fig 8-2

a) Complications in patients who received ≥ 6 cycles or < 6 cycles of oxaliplatin-based CTx

b) Sinusoidal dilatation score in patients who received ≥ 6 cycles oxaliplatin-based CTx with or without bevacizumab

DISCUSSION

In the current study, we set out to investigate whether bevacizumab added to oxaliplatin-based CTx has an influence on liver injury and postoperative complications. We revealed that patients, selected for liver surgery, who received bevacizumab had significantly less moderate sinusoidal dilatation than the non-bevacizumab group. No difference in complication rate was observed, however.

The prospective trial of Nordlinger et al.[16] did not show an increased mortality rate after hepatic resection in patients who have received preoperative chemotherapy. Regarding retrospective studies, outcomes are conflicting: Most of the studies did not found any difference in mortality rate between patients with and without neoadjuvant chemotherapy.[5 21-22] Vauthey et al[23] showed a significant higher late (90 days) mortality rate in patients with steatohepatitis.

There is also evidence to suggest that postoperative complications could be associated with the use of preoperative oxaliplatin-based CTx.[5 15 21] In the EORTC 40983

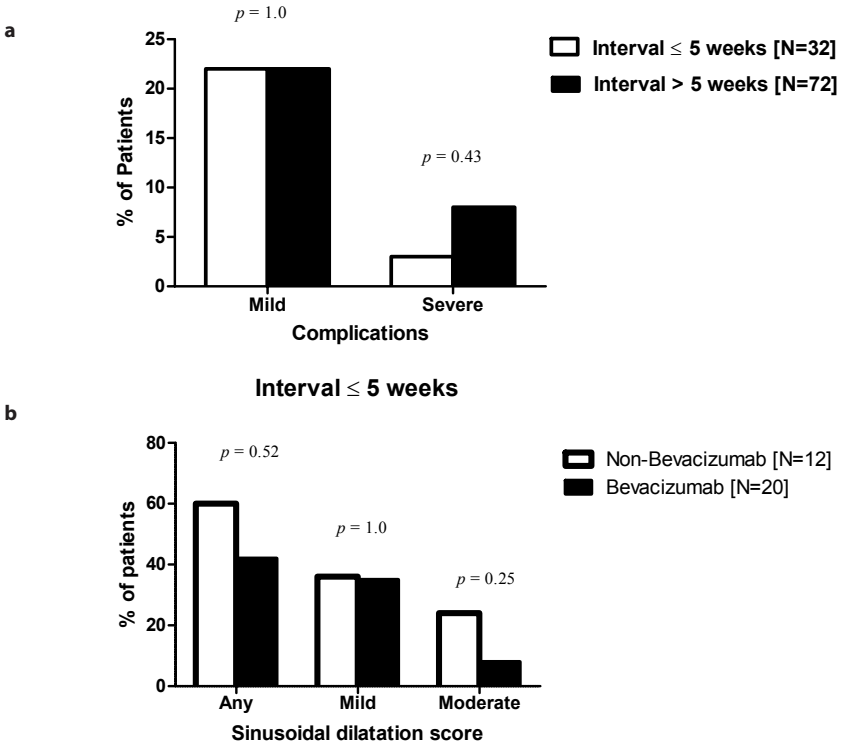

Fig 8-3

a) Complications in patients with a time-interval between oxaliplatin-based CTx and resection of more and less than 5 weeks

b) Sinusoidal dilatation score in patients who received oxaliplatin-based CTx with or without bevacizumab with a time-interval between CTx and resection of ≤ 5 weeks

trial[16], patients who had received per operative oxaliplatin-based chemotherapy had a higher incidence of complications than patients who had surgery alone (25% vs. 16%, $p = 0.04$). This may be related to the short interval between cessation of chemotherapy and surgery (the protocol initially mandated surgery within 3 weeks of chemotherapy, but was later amended). Karoui et al.[14] found prolonged CTx (≥ 6 cycles of oxaliplatin) to be a risk factor for postoperative complications after major liver resection: this risk was mainly due to the higher incidence of transient postoperative liver insufficiency. Though more patients who received ≥ 6 cycles of preoperative CTx in our study required blood transfusions (42% vs. 17%, $p = 0.01$), we found no difference in complication rate.

Various studies have demonstrated that sinusoidal injury of the liver is associated with the use of oxaliplatin-based CTx: Rubbia-Brandt et al.[6] showed that 51% of post-chemotherapy (oxaliplatin) liver resection specimens had sinusoidal dilatation. Vauthey et al.[23] found that grade 2 to 3 sinusoidal dilatation was associated with oxaliplatin-based CTx (19% vs. 2%, $p < 0.001$), but did not find any increase in per operative morbidity

or mortality. Oxaliplatin leads to depletion of glutathione and impairs mitochondrial oxidation, which results in the production of reactive oxygen species which may induce sinusoidal injury.[24] Aloia et al.[5] noted that patients with liver injury due to oxaliplatin-based chemotherapy required more per operative blood transfusions than patients who received 5-FU. Another study found that sinusoidal injury was associated with higher morbidity and longer hospital stay in patients undergoing major hepatectomy, and that it resulted in an impaired liver functional reserve before hepatectomy.[25] The association between postoperative morbidity and sinusoidal injury might be attributable to the intensive chemotherapy given in this study: the 90 patients received an average of nine cycles, and 27% (24/90) received two different lines of chemotherapy. Though we found sinusoidal dilatation in 57% of our patients, it was not associated with postoperative complications (31% vs. 27%, $p = 0.83$). Thus, the link between sinusoidal injury and morbidity is still under debate.

A limitation of this and other studies is the lack of information regarding pre-chemotherapy hepatic parenchymal status. It is possible that various forms of liver abnormality such as steatosis or sinusoidal dilatation could have been present before given chemotherapy.

The anti-angiogenic effect and the long half-life of bevacizumab have raised concerns about wound healing and liver regeneration.[26] However, Kesmodel et al.[27] showed that neither the use of bevacizumab nor the timing of its administration was associated with an increase in complication rates in patients treated with different types of CTx regimens. Other studies[28-29] have shown that bevacizumab can be given before hepatectomy without affecting postoperative morbidity, if the interval between discontinuation of bevacizumab and hepatic resection is at least 8 weeks. The results from a study by Gruenberger and colleagues[30] suggest that this interval could be shortened to 5 weeks without an increase in per operative complications. We were not able to confirm this in our study as none of our patients had an interval of less than 5 weeks between last dose of bevacizumab and resection. As the mean half-life of bevacizumab is 21 days, a waiting period of more than 6 weeks is necessary to achieve sufficient drug clearance for levels of free VEGF to be restored, especially to the level needed for hepatic regeneration. The patients in our centre had received the last dose of oxaliplatin without bevacizumab. The waiting period for resection is six weeks that resulted in a median time interval between last dose of bevacizumab and resection of 11 weeks. This long waiting period may explain why we did not find a difference in complications when bevacizumab was added to oxaliplatin-based CTx.

There is evidence that bevacizumab might decrease the incidence of sinusoidal injury: Ribero et al.[8] showed that bevacizumab reduces the occurrence of sinusoidal injury related to oxaliplatin when therapy is relatively short: Sinusoidal obstruction of any grade was reduced in patients who received oxaliplatin plus bevacizumab (27 vs. 54% without

bevacizumab), and severe (grade 2-3) sinusoidal obstruction was reduced significantly by the addition of bevacizumab to oxaliplatin (8 vs. 28%, $p = 0.006$). This study also showed an improved pathological response. Klinger et al.[31] found no improved clinical tumour response with the addition of bevacizumab but also demonstrated that when given in 5 cycles, bevacizumab protects against the sinusoidal obstruction syndrome. The exact mechanism responsible for this is still unknown, but it is possible that the VEGF blockade acts by downregulating metalloproteinases, thereby decreasing the rate of apoptosis in endothelial cells. Our finding of significantly less moderate sinusoidal dilatation in patients who received bevacizumab is further evidence for a protective effect of bevacizumab against sinusoidal injury. There may be a trend toward escape from the protective effect of bevacizumab against sinusoidal liver injury as more and more cycles of oxaliplatin are given (Fig. 2b).

In a study on 750 liver resections (510 with and the remainder without preoperative chemotherapy), the surgical complication rate was highest when surgery was performed less than 5 weeks after discontinuation of chemotherapy.[15] We found no reduction in surgical complications when the interval between cessation of oxaliplatin-based chemotherapy was longer (> 5 weeks), even though the protective effect of bevazicumab on moderate sinusoidal dilatation disappeared with an interval of ≤ 5 weeks. This suggests that the protective effect of bevacizumab from oxaliplatin-induced sinusoidal injury might be the result of a return to normal concentrations of VEGF.

In summary, bevacizumab added to oxaliplatin-based CTx may have a protective effect on moderate sinusoidal dilatation without significant influence on morbidity in patients selected for surgery. Furthermore, neither the duration of oxaliplatin-based CTx nor the time interval between cessation of oxaliplatin-based CTx and surgery were associated with postoperative complications.

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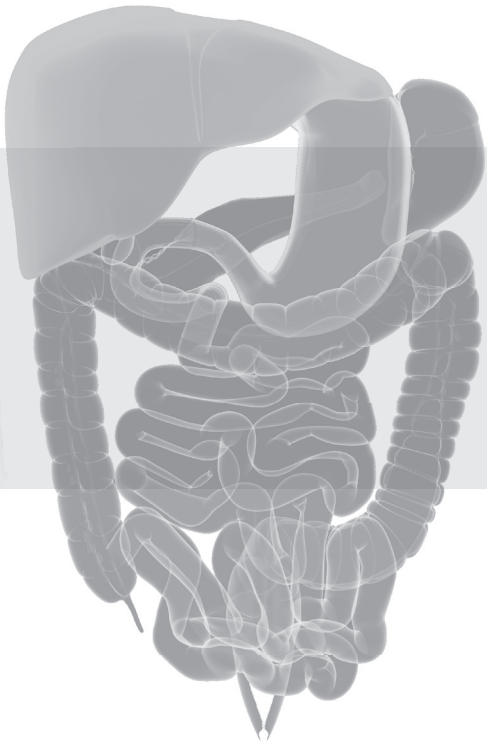
PART IV

TREATMENT FOR RECURRENT COLORECTAL LIVER METASTASES AND THE ROLE OF STEREOTACTIC BODY RADIATION THERAPY

10

LOCAL TREATMENT FOR RECURRENT COLORECTAL HEPATIC METASTASES AFTER PARTIAL HEPATECTOMY



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ABSTRACT

Objective The objective of the study was to identify patients who may benefit from local treatment in recurrent colorectal liver metastases.

Materials and methods A total of 51 consecutive patients were treated for hepatic recurrence(s) after an initial partial hepatic resection. Surgery was considered as the primary treatment option for eligible patients. Patients with a small liver remnant after major hepatectomy were treated with radiofrequency ablation (RFA) or stereotactic body radiation therapy (SRx). SRx was given as an outpatient, emerging local treatment option for patients with intra-hepatic recurrences not eligible for surgery or RFA. Partial liver resection was performed in 36 patients (70%), RFA in ten patients (20%), and SRx in five patients (10%).

Results Median hospital stay was 7 (range, 3–62) days with a morbidity of 16% without in-hospital death. None of the patients received adjuvant chemotherapy. There was no difference in recurrence or survival between the three treatment modalities. Overall 5-year survival was 35% with an estimated median survival of 37 months. Patients with a disease-free interval between first hepatectomy and hepatic recurrence less than 6 months did not survive 3 years.

Conclusions Resection, RFA, and SRx can be performed safely in patients with recurrent colorectal liver metastases and offer a survival that seems comparable to primary liver resections of colorectal liver metastases.

INTRODUCTION

Colorectal cancer is one of the most common malignancies and a leading cause of death. Liver metastases develop in 50–60% of patients[1,2] and surgical resection currently represents the best treatment for long-term survival and even cure in patients with colorectal liver metastases. Despite the curative intent, more than 60% will suffer from recurrence after liver resection, the liver being the most common location.[3] Since liver resection has become safer through improvements in surgical techniques and perioperative management, repeat hepatic resection is being more frequently performed in patients with hepatic recurrences. Several studies on repeat hepatic resection have been reported in the last decade.[4-9]

Recent technologic advances have also made local ablative treatments for liver tumours accessible.[10] Patients with small central recurrences after a prior major liver resection and patients who are poor candidates for surgery are often treated by radiofrequency ablation (RFA). Stereotactic body radiation therapy (SRx) is another emerging local treatment option for patients with intrahepatic malignancies not eligible for surgery or RFA.[11]

Unfortunately, most patients who develop a recurrence after colorectal liver surgery cannot undergo secondary procedures. Systemic chemotherapy (CTx) is used in these patients with increasing median survival rates with current multimodality treatments.[12,13] Approximately 5% to 10% of patients who develop hepatic recurrence after liver resection are amenable to a second resection or local ablative treatment. Most reports are based on small populations or on combined populations from several centres. In this article, we report our experience in a single centre with local treatment for recurrent liver disease. The purpose of this study was to evaluate prognostic factors for overall, disease-free survival and to identify patients who might benefit most from secondary local treatment.

PATIENTS AND METHODS

Between March 1988 and October 2007, 520 partial liver resections were performed in our centre because of colorectal liver metastases. Fifty-one patients were treated for hepatic recurrences after a first partial hepatic resection for colorectal liver metastases.

Criteria for repeat liver treatment were similar to those for first hepatectomy: the presence of technically removable metastases (preserving at least two segments of the liver parenchyma), and the possibility of an oncological radical procedure. Surgery was considered as the primary treatment option for eligible patients. Nowadays, surgery provides the best outcome for the treatment of colorectal liver metastases. To date,

no randomized trial has been performed between resection versus local ablation. Therefore, in colorectal metastases, surgery is still the gold standard.[14,15] For patients with a small liver remnant after major hepatectomy, RFA or SRx were alternatives if the metastases were <3 cm.[10,11] RFA was first treatment option, but in case of ill location of the metastases (nearby main vessel and/or bile ducts), SRx was the alternative.

Patients with extrahepatic disease that was resectable were also included in this study.

RFA was performed with a 200-W RF generator and the cluster RF electrode was introduced into the hepatic malignancies during laparotomy or by imaging guidance percutaneously.[10] SRx was mostly given in three fractions of 15 Gy, and the prescription isodose was 65%.[11]

Data analyzed included demographics, pathological tumour–node–metastases stage of the primary tumour, maximum size and number of metastases on computed tomography (CT), plasma carcinoembryonic antigen (CEA) level, type of liver surgery, overall duration of hospital stay, complications, radicality, site, and treatment of recurrence.

Overall survival and disease-free survival (DFS) were measured from the start of treatment of hepatic recurrence. The nomenclature and extent of hepatic resection were recorded according to the terminology defined by Couinaud.[16] We defined a positive surgical margin as the presence of exposed tumour along the line of transaction.

After partial hepatectomy, patients routinely underwent a physical examination and determination of CEA level and abdominal/chest CT or ultrasonography every 4 months for the first year, every 6 months the second year, and once a year thereafter. Endoscopic surveillance was performed after 1 year and thereafter depending on the findings.

The nonparametric log-rank test was used to identify prognostic variables associated with survival after the second liver resection, with significance at $p = 0.05$.

RESULTS

First partial liver resection

Clinical data of the first partial hepatectomy are depicted for all 51 patients in Table 9-1. At the time of the first hepatectomy, one patient had extrahepatic disease of the lung and underwent a pulmonary lobectomy. In another patient a peritoneal metastasis was detected during laparotomy and resected simultaneously with the liver metastases. The resection margin at permanent section was microscopically not free of tumour in seven patients. There was no in-hospital death, 12 patients had per-operative complications without surgical re-intervention, and median hospital stay was 8 (range 4–72) days.

Intrahepatic Recurrences

Clinical data of the 51 patients who underwent treatment for recurrent metastases are depicted in Table 1. The median interval between first hepatectomy and recurrent hepatic metastases was 11 (range, 3–78) months. Partial liver resection was performed in 36 patients (70%), RFA in ten patients (20%, two open and eight percutaneous procedures) and SRx in five patients (10%). One patient showed peritoneal disease, and the omentum was resected. One patient showed ingrowth of the diaphragm, and a partial resection of the diaphragm was performed. Two patients received additional SRx for solitary lung metastases and one patient for a solitary costal metastasis. There was no in-hospital death. Eight patients had per-operative complications without surgical intervention, and median hospital stay for patients who underwent resection or open RFA was 7 (range, 3–65) days. None of the patients were treated with adjuvant CTx.

Table 9-1 Clinical data on the first and second local treatment

	First hepatectomy n = 51	Second local treatment n = 51
Neoadjuvant CTx		
Yes	26	11
No	25	40
No. of tumours*	2 (1-8)	1 (1-5)
Size of tumour (cm)*	3 (1-10)	2.5 (1-7)
Preoperative CEA-level (µg/L)*	17 (1-5315)	10 (1-126)
Tumour distribution		
Unilobar	30	44
Bilobar	21	7
Liver surgery		
Extended hemihepatectomy	2	-
Hemihepatectomy	16	6
Extra-anatomic	33	30
RFA	-	10
SRx	-	5
Morbidity (%)	12 (24%)	8 (16%)
Mortality (%)	0	0
Hospital stay (days)	8	7
Positive surgical margin (%)	7 (14%)	2 (4%)

*Median

Follow-Up

Median follow-up from secondary treatment for recurrences were 22 (3–115) months. Thirty-two patients (63%) developed a secondary recurrence. Five patients underwent palliative systemic CTx for pulmonary metastases. One patient developed a local recurrence in the pelvis and underwent resection. Of the 26 patients with intra-hepatic recurrence, 14 patients were treated with palliative CTx or analgesic treatment and 12

Table 9- 2 Univariate analysis of prognostic factors for survival after repeat treatment for recurrence of intrahepatic disease

Prognostic Factor	N	Survival 3 years (%)	P-value
Age			$p = 0.57$
≤60	25	54	
>60	26	56	
Gender			$p = 0.05$
Male	34	64	
Female	17	19	
Site of primary tumour			$p = 0.71$
Colon	31	56	
Rectum	20	54	
First metastases			$p = 0.006$
Synchronous	32	68	
Metachronous	19	26	
pT primary tumour			$p = 0.09$
T0-2	6	100	
T3-4	45	50	
pN primary tumour			$p = 0.50$
negative	26	50	
positive	25	59	
Interval (months) of first hepatectomy to date of recurrence			$p = 0.01$
≤ 6	6	0	
> 6	45	62	
Second metastases			$p = 0.86$
No. of tumours			
1	30	54	
>1	21	72	
Size of tumour (cm)			$p = 0.85$
≤ 5	47	58	
> 5	4	33	
Neoadjuvant CTx			$p = 0.68$
Yes	11	64	
No	40	53	
CEA			$p = 0.66$
≤ 50	43	54	
> 50	4	100	
Distribution of metastases			$p = 0.47$
Unilobar	44	57	
Bilobar	7	38	
Extrahepatic disease			$p = 0.32$
Absent	46	59	
Present	5	0	
Type of treatment			$p = 0.71$
Resection	36	53	
RFA/SRx	15	59	
Positive Lymfnodes			$p = 0.62$
No	49	36	
Yes	2	36	
Margin of hepatectomy			$p = 0.72$
R0	34	42	
R1	2	0	

patients with repeat local treatment. Disease-free survival after treatment of hepatic recurrence was 47% at 1 year, and estimated median DFS was 11 months.

Survival

Overall 3-year and 5-year survival rates were 55% and 35%, respectively, with an estimated median survival of 37 months. The results of univariate analysis of overall 3-year survival after treatment of recurrent hepatic metastases are depicted in Table 9-2. Patients with an interval of more than 6 months between first hepatectomy and second local treatment and patients with metastases detected synchronously with the primary tumour have a significantly better survival ($p < 0.01$ and $p < 0.006$, respectively). After a median follow-up of 22 months, 18 patients died, and 33 patients are alive of whom 24 patients are alive without disease.

DISCUSSION

Without treatment, most patients with colorectal liver metastases have a life expectancy of less than 1 year.[17] With the availability of increasingly efficient chemotherapy regimens, median survivals currently reach 16–22 months.[12,18] In our study group, median overall survival was 37 months after local treatment of the intra-hepatic recurrences. Our study reports overall 3-year and 5-year survival rates of 55% and 35% after local treatment of recurrent colorectal liver metastases, which is comparable to the outcome in our series of first hepatectomies that we published previously.[19] Low morbidity (16%) and no in-hospital death showed that repeat local treatment for colorectal hepatic metastases can be performed safely. These results are comparable with those of other studies (Table 9-3). [4-9]

Improvements in surgical techniques and per-operative management increase the number of repeat hepatic resection in patients with isolated hepatic recurrence.[20] A reduction of blood loss, which is associated with preoperative morbidity and mortality, was obtained over the past decade with a corresponding decrease of transfusion requirements. This was related to an increase in parenchymal-sparing resection, performing of resections with a low central venous pressure, and with the advent of portal pedicle ligation maneuvers.[21] The extent of liver resection depends on the size, location, distribution, and the relation of the major afferent and efferent vasculatures and bile ducts to liver metastases. More wedge resections can be performed because several recent studies have indicated that a margin less than 1 cm is not a contraindication to resection of colorectal liver metastases.[22-25] Moreover, a margin of 1 mm seems to be appropriate, despite the fact that the pathological report will define the procedure as a microscopic irradical resection.[24] Current techniques with ultrasonic dissectors aspirate

Table 9-3 Literature review of large series (>50 patients) of repeat local treatment in patients with recurrent colorectal liver metastases in the last 10 years

Reference	Year	No.of centres	No. of patients	Mortality (%)	Morbidity (%)	Median survival months	Survival	
							3 years	5 years
Adam	1997	1	64	0	19	46	60	41
Sugarbaker	1999	20	170	NR	19	34	45	32
Yamamoto	1999	1	70	0	11	31	48	31
Petrowsky	2002	2	126	1.6	28	37	51	31
Thelen	2006	1	94	3.1	23	NR	55	38
Shaw	2006	1	66	0	18	56	68	44
Present series	2008	1	51	0	16	37	55	35

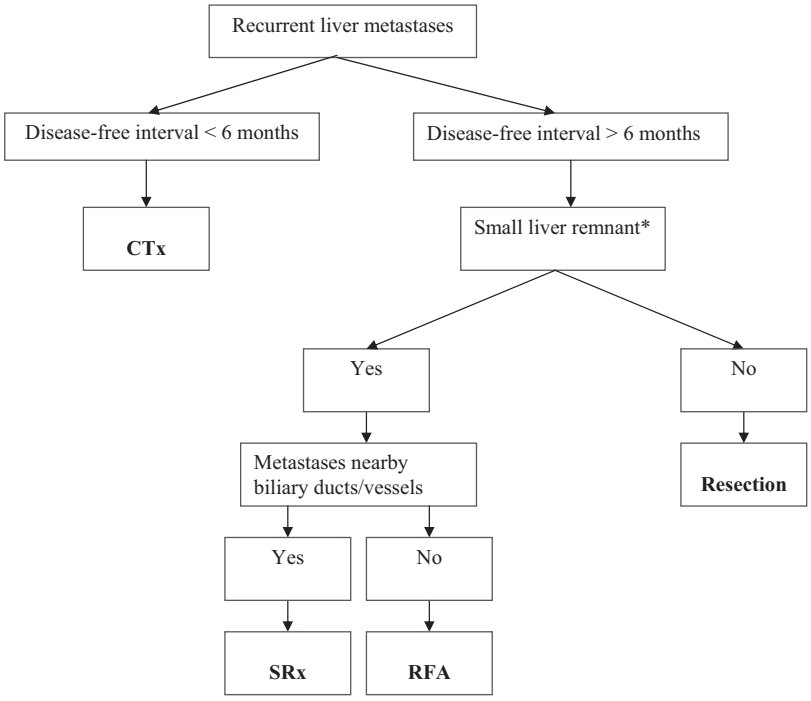
a part of the liver parenchyma interposed between the specimen and the normal liver, making assessment of the true margin difficult.

The rate of wedge resection in our study was higher in repeat hepatectomies than in the initial hepatectomies because the extent of resection at repeat hepatectomy depended on the amount of remnant liver after first hepatectomy. It seems that the extent of hepatic resection does not influence the outcome of secondly resected patients, providing that all metastatic tissue is removed, which is in agreement with the results of Zorzi et al.[26] A deeper knowledge of the segmental anatomy of the liver[16] and the routine use of intraoperative ultrasonography has eliminated the need of "blind" extensive resection, therefore limiting the amount of resected parenchyma.

The present study shows that 3-year survival rate is significantly better for those patients with an interval of more than 6 months between first hepatectomy and hepatic recurrence. Patients who had an interval shorter than 6 months did not survive longer than 3 years (median estimated survival 27 months). This is in agreement with the results of Bhattacharjya et al. who suggest that tumours recurring early following liver resection are less likely to be amenable to re-resection because of adverse tumour characteristics and a higher potential for spread of disease.[27] They concluded in their study that aggressive follow-up during the first 6 months was not advisable because none of the patients could benefit from local treatment. Together with our results, it may be concluded that patients with intra-hepatic recurrences within 6 months after partial hepatectomy should be offered systemic CTx because the median survival of patients who were treated with modern systemic chemotherapy also may exceed 20 months.[28]

The other significant factor was synchronicity of the metastases of the primary tumour. Patients with synchronous metastases showed a significantly (p = 0.006) improved survival after intrahepatic recurrences that could be treated by local treatment than patients with metachronous disease. A clear explanation cannot be given besides the fact that the number of patients is small.

Despite favorable results of repeat hepatic resection for patients with recurrent colorectal liver metastases, there remains controversy regarding the optimal treatment for such patients. The advent of minimally invasive therapies such as RFA or SRx may offer less procedure-associated morbidity and mortality. A concern is the variable rate of local recurrence that can follow such targeted therapies. Lesions treated with RFA have local recurrence rates of 4% to 55%.[10,29] Crude local control rates of 78–100% are reported in tumour-based analysis after SRx.[30] RFA has achieved an important role for patients unfit for surgery with small (<3 cm) liver metastases. Some authors even stated that the time has come to perform a randomized trial between resection and other local ablative methods.[31] In our centre, resection is still the gold standard.[15] The treatment failure rate after radiofrequency ablation even in small tumours is higher than local recurrence rates



* < 2 segments

Fig 9-1 Algorithm

after definitive resection. Again, the results of the local ablative treatments are promising, and therefore, local ablation therapies may be applied in patients not suitable for surgery because of ill location of the tumour and/or the physical state of the patients.

In the current study, no difference was found in recurrence or survival in patients treated with resection, RFA, or SRx. In our practice, patients with small central located intra-hepatic recurrences after a prior major liver resection are often treated by RFA. RFA could be performed percutaneously, avoiding the complications associated with partial hepatectomy. RFA and SRx may be used in conjunction with operative resection to increase resectability. Furthermore, these alternatives to surgery may increase the population considered for treatment of hepatic recurrences in case of patients unfit for operation. A possible algorithm for different treatment modalities of recurrent liver metastases is proposed in Fig. 9-1.

CONCLUSION

These repeat local treatments can be performed safely, without greater risk than first liver resections, and offer a survival rate as good as first liver resections. Resection should be the preferred approach, but RFA and SRx are good alternatives with a beneficial outcome. Patients with intra-hepatic recurrences within 6 months after first partial hepatectomy should be offered systemic chemotherapy.

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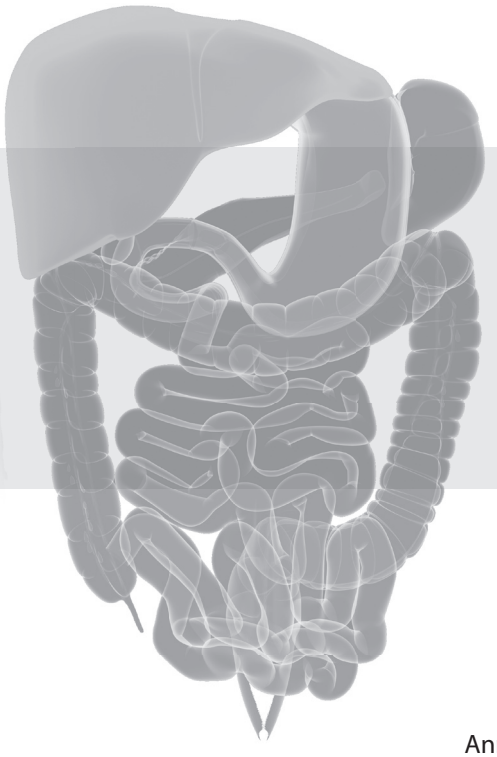
11

STEREOTACTIC BODY RADIATION THERAPY FOR COLORECTAL LIVER METASTASES



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ABSTRACT

Background Stereotactic body radiation therapy (SBRT) is a treatment option for colorectal liver metastases. Local control, patient survival and toxicity were assessed in an experience of SBRT for colorectal liver metastases.

Methods SBRT was delivered with curative intent to 20 consecutively treated patients with colorectal hepatic metastases who were candidates for neither resection nor radiofrequency ablation (RFA). The median number of metastases was 1 (range 1–3) and median size was 2·3 (range 0·7–6·2) cm. Toxicity was scored according to the Common Toxicity Criteria version 3.0. Local control rates were derived on tumour-based analysis.

Results Median follow-up was 26 (range 6–57) months. Local failure was observed in nine of 31 lesions after a median interval of 22 (range 12–52) months. Actuarial 2-year local control and survival rates were 74 and 83 per cent respectively. Hepatic toxicity grade 2 or less was reported in 18 patients. Two patients had an episode of hepatic toxicity grade 3.

Conclusion SBRT is a treatment option for patients with colorectal liver metastases who are not candidates for resection or RFA.

INTRODUCTION

Colorectal cancer is a common malignancy and the second leading cause of cancer-related death in the USA and Europe.[1] Liver metastases develop in 50–70 per cent of patients with colorectal cancer during the course of the disease.[2] Resection of colorectal liver metastases is still the 'gold standard' treatment, with 5-year survival rates ranging from 35 to 60 per cent in highly selected patients.[3] Unfortunately, most patients are not eligible for surgery because of unfavourable tumour factors or poor general condition. Other local treatment techniques, among which radiofrequency ablation (RFA) is the most widely used, offer a high rate of local control in inoperable patients with liver metastases.[4,5] However, RFA is preferably carried out for metastases that are smaller than 3 cm and not located in the proximity of major blood vessels, the main biliary tract or gallbladder, or just beneath the diaphragm.[4]

Traditionally, radiotherapy has had a limited role in the treatment of intrahepatic malignancies owing to the low tolerance of the whole liver to irradiation. However, since the 1990s, groups from the Karolinska Hospital and Michigan Medical School (Ann Arbor) have demonstrated that large doses of conformal radiation can be delivered safely to localized targets in the liver.[6,7]

Stereotactic body radiation therapy (SBRT) is a non-invasive technique that delivers very large doses of radiation in a few fractions.[8] Advances in tumour imaging, motion management, radiotherapy planning and dose delivery have allowed safe use of high-dose conformal radiation therapy in liver tumours.[9] Several papers have reported outcomes after SBRT for liver metastases from various primary tumours.[10-13] This study assessed local control, survival and toxicity after SBRT in a cohort of 20 patients with 31 liver metastases of colorectal origin only.

METHODS

Patients with colorectal liver metastases who fulfilled the following criteria were included in this study. Patients were evaluated by the Erasmus University MC Liver Board, which comprises hepatobiliary surgeons, medical oncologists, hepatologists, (interventional) radiologists and radiation oncologists, and were judged not eligible for surgery owing to unresectable metastases or poor general condition. Metastases were not suitable for RFA because of their proximity to vessels, bile ducts or the diaphragm. The Karnofsky index was at least 80 per cent. Maximum lesion size was 6 cm and a maximum of three lesions was acceptable. Of patients with extrahepatic disease, only those with metastases eligible for curative treatment were eligible.

Radiotherapy

Patients were positioned in a stereotactic body frame (Elekta Oncology Systems, Stockholm, Sweden) with maximum tolerated abdominal compression to reduce respiratory tumour motion for planning and treatment purposes.[14] Three computed tomography (CT) scans per patient were acquired: two contrast-enhanced scans in the arterial and venous phases for tumour definition and one large-volume scan for dose planning. The border of contrast enhancement was taken as the boundary of the metastasis. The tumour delineations were reviewed by an experienced radiologist. The tumour volume was then expanded with safety margins to compensate for the residual breathing motion and other uncertainties in tumour position, resulting in the planning target volume (PTV). Initially, equal safety margins were selected for all patients based on the Karolinska experience (5 mm in the left–right and anterior–posterior directions, and 10 mm in the craniocaudal direction).[14] Later, the margin was individualized in all three directions by measuring the residual motion of fiducials implanted around the tumour using video fluoroscopy registrations.

Up to June 2006, patients received three fractions of SBRT starting at 12·5 Gy, according to a phase I–II design.[15] Thereafter, doses were escalated based on published data.[16] Treatment plans were generated with the CadPlan treatment planning system (Varian Oncology Systems, Palo Alto, California, USA) with a median of 7 (4–10) beams. The dose was prescribed in such a way that at least 95 per cent of the PTV received a dose of 12·5 Gy (15 Gy in two patients). The length of the treatment course was 5–6 days and the dose was delivered in fractions every other day.

Follow-up

Treatment results and side-effects were evaluated prospectively by clinical and laboratory examination and CT or magnetic resonance imaging at 1 and 3 months after irradiation, followed by further examinations every 3 months during the first 2 years, and every 6 months thereafter. Toxicity was evaluated with the Common Toxicity Criteria (CTC), version 3.0, of the National Cancer Institute (http://ctep.cancer.gov). Local failure was defined as an increase in tumour size or tumour regrowth, with rates calculated on a tumour basis. Patients were monitored for local control even if distant or new liver metastases developed. Progressive disease included any intrahepatic or extrahepatic disease progression. If local failure or progressive disease was diagnosed, the date of recurrence was defined as the first date on which an abnormality was recognized on CT.

Statistical analysis

To assess local control and survival, Kaplan–Meier analyses were generated using SPSS® version 15.0 software (SPSS, Chicago, Illinois, USA). The log rank test was used to identify variables associated with local control.

RESULTS

Between December 2002 and July 2008, SBRT was administered with curative intent to 20 consecutively treated patients with 31 lesions. In 19 patients the metastases were not amenable to resection or RFA owing to an unfavourable location and/or limited liver remnant. One patient had cardiac co-morbidity and non-invasive treatment was preferred.

One patient received radiotherapy three times for recurrent lesions, first elsewhere and the second and third times at this centre. Characteristics of the 31 metastases treated with SBRT are shown in Table 10-1. The median number of metastases was 1 (range 1–3) and median size was 2·3 (range 0·7–6·2) cm.

Table 10-1 Patient, target- and treatment characteristics of 20 patients with 31 hepatic metastases

Patients	**n = 20**
Gender	
Male/Female	15/5
Age (years)	
Median (range)	72 (45-81)
Location primary tumour	
Rectum	5
Colon	15
Metastatic site	n=31
Segments	
1	3
2	0
3	1
4	3
4/5	1
5	3
6	1
6/7	1
7	5
8	13
Fractionation	
3x12,5 Gy	29
3x15 Gy	2

Local control

Thirteen patients had SBRT as a second-line treatment after resection, isolated hepatic perfusion, RFA or SBRT elsewhere. None of the 20 patients received adjuvant chemotherapy after SBRT. Fourteen patients had complete local control of all 22 lesions. Size of metastases was not a predictive factor of outcome. Local failure occurred in nine lesions in six patients after a median interval of 22 (range 12–52) months. One patient who had two local failures in two lesions received chemotherapy, with an excellent response. This allowed extended liver surgery with curative intent. Three patients received palliative

chemotherapy and died, and a further two patients were still receiving chemotherapy at the time of writing. Actuarial 1- and 2-year local control rates were 100 and 74 per cent respectively (Fig.10-1a).

Overall survival

Nine patients had died after a median follow-up of 26 (range 6–57) months. Median time to progression of disease was 11 (range 1–52) months. Median overall survival was 34 months, and actuarial 1- and 2-year survival rates were 100 and 83 per cent respectively (Fig.10-1b).

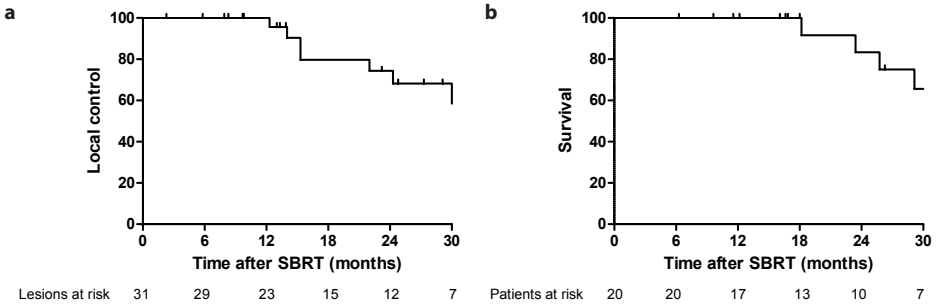

Fig 10-1
a) Local control rate
b) Overall survival after stereotactic body radiation therapy (SBRT)

Toxicity

Eighteen patients had hepatic toxicity of grade 2 or less, whereas two patients had grade 3 toxicity (CTC version 3.0) with an increase in γ-glutamyl transferase level. One patient showed no changes in liver function parameters but developed portal hypertension syndrome with oesophageal varices (grade 1 toxicity) with one episode of melaena, and was treated conservatively. After the second radiation treatment this patient presented with hepatic toxicity and ascites (both grade 2), which responded well to temporary diuretic medication. Oesophageal bleeding evidenced by melaena occurred again, and the varices were treated with endoscopic band ligation. One patient became physically weak (grade 3) during the first month after treatment but recovered spontaneously during the second month. Grade 2 pain owing to rib fractures occurred in one patient 10 months after irradiation of a subcapsular liver metastasis located in the vicinity of the ribs. No grade 4 or 5 (death), or stomach, bowel, kidney or spinal cord toxicity was found.

DISCUSSION

The present study has shown that SBRT for colorectal liver metastases can achieve 2-year local control and survival rates of 74 and 83 per cent respectively with acceptable toxicity in patients who are not eligible for surgery or RFA. Three patients developed CTC toxicity grade 3, and late toxicity of grade 1 and 2 was reported in two patients.

Resection should be regarded as the standard curative treatment in patients with hepatic metastases from colorectal cancer. However, only a minority of patients are suitable for liver resection.[17] RFA has certain advantages over hepatic resection, such as a shorter hospital stay and a lower complication rate[5,18], although the authors do not advocate it as an alternative to hepatic resection because it is associated with a higher local recurrence rate, with median time to local tumour progression of between 4 and 9 months.[19] RFA should be reserved for those in whom resection of all metastases is not possible.[20] SBRT has been used for liver metastases that are unsuitable for, or refractory to, liver resection or RFA in an attempt to control disease locally.

SBRT involves the precise delivery of large doses of highly conformal radiation to extracranial targets using a small number of fractions. This treatment has several advantages over RFA. Owing to the heat-sink effect of large vessels, tissue close to the vessels is not amenable to RFA and major bile ducts are at increased risk of heat injury during ablation.[18] To avoid these problems, centrally located liver lesions and metastases near large vessels may be treated with SBRT instead of RFA. SBRT is non-invasive and can be offered to patients who are not eligible for invasive or minimal invasive interventions; it is also feasible in the outpatient setting, with no requirement for hospitalization or general anaesthesia. SBRT may be as effective as RFA for small tumours but may be less suitable for multiple tumours.

Herfarth and Debus[10] reported poorer local control of colorectal metastases than of tumours with other histology (45 versus 91 per cent after 18 months). This is in line with other studies that showed a lower local control or survival rate in patients with metastases from colorectal cancer compared with metastases from other primary tumours.[12,21] In contrast, Rusthoven and co-workers[22] reported an improved median survival of 32 months after treatment of liver metastases from favourable primaries (breast, colorectal, renal, carcinoid, gastrointestinal stromal tumour and sarcoma) compared with a median survival of 12 months for those from unfavourable primary sites (primary tumours of the lung, ovary and non-colorectal gastrointestinal malignancies). This raises the question of whether it is justified to group liver metastases from primary colorectal cancer together with those from other primary cancers when evaluating the results of SBRT. Therefore, the present study focused on colorectal metastases only.

A 2-year local control rate of 74 per cent was achieved for colorectal metastases generally treated with $3 \times 12{\cdot}5$ Gy, with a median survival of 34 months. Previous studies

Table 10-2 Reported local control rates after treatment of colorectal liver metastases with stereotac tic body radiation therapy

Reference	No. of patients	No. of liver lesions	Dose-fractionation scheme (isodose)	Median follow-up (months)	Actuarial local control (%)		Actuarial survival (%)	
					1 year	2 years	1 year	2 years
10	35	-	1 x 20-26 Gy (80%)	15*	-	45†	-	-
13	-	23	3-4 x 7-12,5 Gy (65%) or 1x 26 Gy (80%)	15	88‡	56‡	-	-
11	20	-	7-20 x 2-6 Gy (80%)	15	-	-	80‡	26‡
12	40	-	6 x 4.6-10 (-)	11	-	-	63	-
Present series	20	31	3 x 12,5-15 Gy (65%)	26	100	74	100	83

Values in parentheses are percentages isodose. *Mean. †Eighteen months. ‡Data from figures.

describing the outcomes of SBRT for colorectal liver metastases are summarized in Table 10-2. Hoyer and colleagues[23] achieved a 2-year local control rate of 86 per cent after SBRT with 3 × 15 Gy for colorectal metastases in the liver, lung or suprarenal lymph nodes, or at two of these sites; median follow-up was 4·3 years. When liver metastases were analysed separately, a 2-year local control rate of 78 per cent was noted (M. Hoyer, personal communication). This is in line with the present results, probably because the dose was similar in the two studies and median follow-up was adequate (more than 2 years). Rusthoven and co-workers[22] reported a 2-year local control rate of 92 per cent in liver metastases from a variety of primary tumours treated with 36–60 Gy. This clinical experience is consistent with the knowledge that escalated doses of radiation are associated with improved local control and survival[21,24]. Dose escalation in the present cohort was limited owing to the small functional liver remnant because most patients had already undergone several partial liver resections and RFA procedures before SBRT. However, it is generally difficult to compare studies on SBRT for liver tumours. Conflicting results regarding patient outcome might be explained by differences in patient selection criteria, site of metastases, dose prescription, assessments of local failure or control, and duration of follow-up. In the present series median follow-up was 26 months and the median time to local failure was 22 (range 12–52) months. Median follow-up in the series of Rusthoven et al.[22] was only 16 months, which may be too short to allow reliable estimation of local control.

Only a minority of patients with colorectal liver metastases in this clinic were treated with SBRT. The 20 patients in this study represent a negative selection as they were not eligible for surgery and/or RFA because of tumour size and/or location. Lesions were centrally located or near to biliary ducts and vessels. In this respect, these patients represent a group with a poor prognosis.

Median survival of patients with stage IV colorectal cancer is about 24 months with modern chemotherapy.[25,26] In the present series, median survival was 34 months after SBRT; no serious acute toxicity was encountered, in keeping with previous reports[10,27,28]; and none of the patients received adjuvant chemotherapy. The low toxicity after SBRT, and at least comparable survival to that after systemic chemotherapy, may justify its use in this patient group. The median time to disease progression after SBRT was 11 months, similar to that after liver resection in the authors' experience.[29] The lower median survival of 34 months after SBRT, compared with 44 months after partial liver resection, can be explained by the generally poorer prognosis of the cohort.

Further research is needed to define the role of SBRT within the treatment armamentarium for colorectal liver metastases. A phase III trial has been proposed by this centre among others (International Liver Group) to compare SBRT in three fractions with RFA for the treatment of unresectable colorectal liver metastases up to 4 cm in diameter. Combined treatment with radiation sensitizers should be pursued in addition to randomized trials of SBRT for colorectal liver metastases. It has already been hypothesized that the combination of radiotherapy and angiogenesis inhibitors may have a synergistic effect.[30] Proper selection of patients for this treatment in high-volume hepatobiliary centres with a multidisciplinary team is advocated.

In conclusion, SBRT is indicated in patients with unresectable colorectal liver metastases or as a second-line therapy for recurrence after liver surgery.[31] SBRT achieves adequate local control, and appears to be safe with respect to both acute and late toxicity in selected patients if normal tissue dose restrictions are respected.

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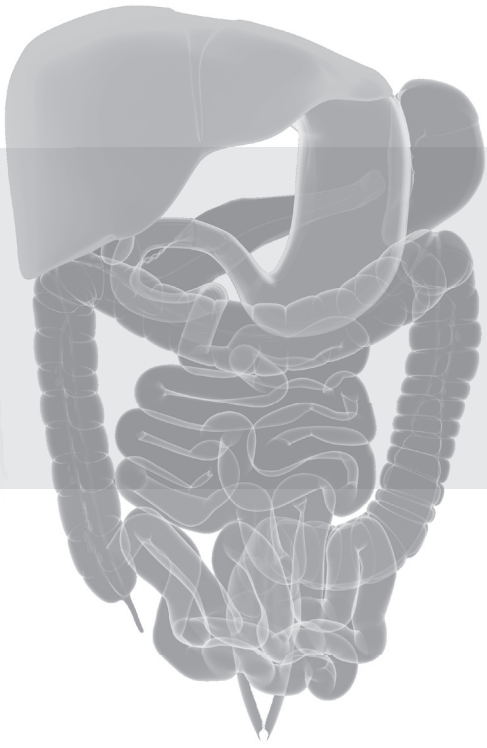
12

GENERAL DISCUSSION



OUTCOME OF THE THESIS AND FUTURE PERSPECTIVES

Colorectal cancer is the second leading cause of death in many parts of the Western World due to formation of distant metastases. At the time of diagnosis, approximately 20% of the patients already have manifest liver metastases (synchronous); another 25-30% will develop these metastases following treatment of the colorectal primary (metachronous).[1-2] Only a limited number of patients (15-20%) with colorectal cancer and synchronous liver metastases appear to be candidates for resection, far more patients prove to have unresectable disease. Without treatment of liver metastases, life expectancy is usually less than 1 year.[3] With the advanced modern chemotherapeutic agents, median survival currently reach 16-22 months.[4-5] Hepatic resection remains the only chance on long-term survival with a median survival of 42 months and 5-year survival rate of 34% *(chapter 4)*. Resection should be considered in all patients with metastatic disease confined to the liver when complete removal is feasible and sufficient functional liver parenchyma can be preserved.

In *chapter 4* we compared patients with synchronous and metachronous colorectal liver metastases who underwent a staged resection (i.e. primary tumour first). In our series, patients with synchronous colorectal liver metastases (SCLM) have significant more poor biological features like a higher percentage pT3-T4 tumours and node positivity. In addition, patients in the synchronous group had significantly more metastases and bilobar disease. However, no difference in 5-year disease-free and overall survival in patients with synchronous or metachronous metastases was found. This may be explained by the observation that patients in the synchronous group received significantly more neoadjuvant chemotherapy. Most retrospective studies comparing metachronous versus synchronous colorectal disease showed a difference in survival favouring metachronous disease.[6-9] Besides the explanation that synchronous metastases are possibly detected at a later stage, differences in tumour biology may also explain the aggressiveness of synchronous disease. Several biological peptide markers have been investigated and TGF-a was found to be higher in patients with synchronous metastases and predicted shorter survival, suggesting an unfavourable tumour biology.[10] Also cyclin-dependent kinase inhibitor p27, a tumour suppressor, was reduced in primary tumours with synchronous lesions compared to metachronous metastases.[11] Histological examination has shown that the incidence of venous invasion is higher in patients with synchronous liver metastases compared to primary tumours without metastases.[12] Rather than a intrinsic tumor difference, this may represent a different stage in tumour genesis when the cancer cells obtain further mutations that allow it to metastasise. Histological specimens showed also greater angiogenesis within metachronous lesions compared to synchronous lesions. It is possible that synchronous lesions grow faster with necrosis accounting for decreased vascularity.[13] Moreover differences in host immunity are described between

the two groups which may account for the poorer survival of the synchronous group.[14] Very discrete evidence for biological differences exist but a "unified theory" explaining the disparity in tumour behaviour of SCRLM has yet to be found.

In recent years, advances in imaging modalities, surgical techniques and modern chemotherapeutics have introduced changes in the multidisciplinary management of patients with SCLM. Trends in the incidence of SCLM in the South western region of the Netherlands were studied in *chapter 2*. The detection rate of SCLM increased over time and may be explained by differences in registration or incidence, but may also be due to increased use and better imaging modalities. With the introduction of new agents such as irinotecan, oxaliplatin, bevacizumab and cetuximab, chemotherapy has become more effective in recent years. By using these novel drugs increased clinical response rates of metastases can be achieved which will lead to higher hepatectomy rates.[15-17] In our series, chemotherapy in palliative and neoadjuvant setting increased as did the number of patients who underwent hepatic surgery (from 4% in 1995 to 10% in 2007).

Probably as a result of the increased use of chemotherapy and the increase of patients who underwent hepatic surgery survival for patients with SCLM improved over time. Surprisingly, the proportion of patients who underwent a resection of the primary tumour remained stable over time in our series. Non-curative resection of the primary tumour is associated with high mortality (6-10%) and morbidity (18-24%).[18-20] This may caused by nutritional and immunologic factors in patients with significant systemic disease burden.[21] For patients with stage IV colorectal disease, the main goal of therapy is to prolonge survival and focus on symptom control to optimize quality of life. Traditionally, prophylactic resection of the primary tumour has been advocated for patients with stage IV disease due to its potential survival benefit and to avoid the future risk of intestinal obstruction or perforation.[20, 22] Moreover emergent surgery is associated with higher mortality compared with elective procedures.[19, 23-24] In the absence of randomized controlled trials between survival of patients managed with or without primary tumour resection for stage IV colorectal cancer retrospective studies suggests that non-curative resection of asymptomatic colorectal primary tumours may prolong survival.[24-26] After correcting for some cancer-related confounding factors, resection status was no longer associated with survival.[27] Colorectal disease seems to be no longer a chemorefractory disease. By using triple-drugs chemotherapy good response rates are reported and the incidence of major complications that involved the primary tumour and that required surgery is low.[27-29] These studies concluded also that resection of the primary tumour delays the start of palliative chemotherapy and no survival benefit was reported. Post-operative complications and the time required to recover from resection may diminish chemotherapy's survival benefits. Risks of unnecessary surgical morbidity and mortality should be reserved for patients in whom complications arise. Also in our experience,

minor symptoms of patients with colorectal cancer, such as obstruction, pain, bleeding and mucus discharge, reduced after the first or second cycle of chemotherapy. Moreover, it has been suggested that the majority of patients with incurable stage IV colorectal cancer who present with only minimal symptoms of the primary tumour may die of progressive systemic disease before the development of major complications related to the primary tumour.[30] In our opinion, systemic chemotherapy without resection and close clinical monitoring of the primary is the optimal approach. A randomized trial still has to confirm this and we expect that the trial will be running in the Netherlands in 2011.

Patients who underwent resection of SCLM after 2000 compared to before have a significantly improved survival *(chapter 3)*. No difference was observed in disease-free survival between the two groups. Besides the higher detection rate, the introduction of more effective chemotherapeutics and a more aggressive surgical approach have broadened the role of hepatic resection in the management of patients with SCLM. Re-resection or local treatment for recurrent metastases has become more conventional as a viable life-prolonging and in some cases, life-saving procedure.[31-33] Also in the present series the number of patients who underwent a potential curative local treatment in case of intra-hepatic recurrences increased from 28% in group 1 (before 2000) to 62% in group 2 (after 2000). Moreover, patients who underwent resection and developed unresectable intra- or extra-hepatic recurrence in the recent time period received palliative chemotherapy with more effective agents like oxaliplatin and irinotecan. These two observations will probably explain the difference in 5-years overall survival rates despite the same disease-free survival rates between the two groups.

The optimal timing of the surgical treatment of SCLM is a matter of controversy. There are different surgical time management strategies for patients with synchronous colorectal cancer; besides the traditionally staged resection (primary tumour first), two other procedures can be performed in patients with colorectal cancer and synchronous liver metastases i.e. simultaneous surgery and "liver first" approach.[34-37] In case of patients with locally advanced rectal cancer and synchronous liver metastases we prefer, if possible, to perform the liver first approach. In our series 16 patients (73%) underwent a curative resection of both the diseases *(chapter 5)*. When given chemotherapy first there is the possibility to downstage liver metastases and the primary tumour. Patients who are progressive under CTx or with incurable new metastatic spread which is noticed peri-operative or after liver resection could be prevented from needless irradiation (CTxRTx) and/or unnecessary rectal surgery. If the rectum was treated first we know from literature that up to 50% do not undergo further optimal treatment, due to post-operative complications.[38] Moreover, liver metastases rather than the primary tumour

determine survival and a 'liver first approach' could prevent any unnecessary delay in the resection of these metastases and thereby the chance for cure, when the primary tumour is treated first.

In case of patients with rectal cancer and synchronous liver metastases different treatment strategies are possible *(chapter 6)*. Determined by the stage of the primary tumour and the extent of metastasis, a customized treatment strategy for patients with rectal cancer and synchronous liver metastases would be the following: in early rectal cancer (stage T3 N0 or lower) with limited liver disease (≤ 4 segments), surgical morbidity and mortality rates are usually low. Therefore, the combination of rectal surgery with minor hepatic resection (≤ 4 segments) in one session is an attractive option. In patients with early-stage rectal cancer and extensive liver disease (four or more segments), simultaneous resection may lead to an increased complication rate[39-40]. In this situation, the "liver-first" approach can be considered the treatment of choice. If patients have extensive liver metastases (for example in bilobar disease), a so-called 'two-stage hepatic resection' can be performed[41-42]. The rectal resection (following irradiation with 5×5 Gy) can be safely combined with a minor hepatectomy during the first laparotomy.[43] In locally advanced rectal cancer and limited or extensive liver disease, it is preferable, as mentioned above, to treat the liver first. It is difficult to perform a randomized trial with comparable groups to confirm these findings due to each individual clinical characteristic. It is important that the treatment of a patient with rectal cancer and synchronous liver metastases is a tailor-made approach based on the decision of a multidisciplinary team.

The rising use of chemotherapy combinations for SCLM raises concerns about the potential hepatotoxicities induced by systemic drugs and the effects of these drugs on per- and postoperative outcome. The hypothesis that systemic chemotherapy before hepatic surgery can adversely affect the liver parenchyma is strongly suggested by the increased fragility of the liver parenchyma, observed in some patients during hepatic surgery. The phenotype of the hepatic injury after preoperative chemotherapy is regimen specific *(chapter 7)*. Preoperative chemotherapy is linked to the development of hepatic steatosis and increase postoperative complication rates.[44-45] The prevalence of steatosis has mirrored the increasing epidemic of obesity and the metabolic syndrome.[46-47] While liver surgery is becoming safer due to improved surgical techniques and peri-operative care, the negative influence of steatosis on patients undergoing an extended liver resection remains significant.[48-51] Moreover, a meta-analysis revealed a significant association between degree of steatosis and increased risk of postoperative complications and mortality.[52] It is important to diagnose steatosis especially in an era where obesity is becoming epidemic and no effective therapy for steatosis is available yet. In our study MRI yielded the highest correlation and the highest diagnostic accuracy

for the detection of a surgically relevant marked (>33%) steatosis degree, as compared to CT *(chapter 8)*. To confirm our findings this should be further investigated in a prospective trial. In *chapter 9* we found that bevacizumab, a monoclonal antibody against VEGF, has a protective effect on moderate sinusoidal dilatation without any significant difference in complications. If chemotherapeutics are well chosen and the duration of treatment is monitored with care during multidisciplinary meetings, benefits largely outweigh potential disadvantages.

At least 60-80% of patients who undergo a resection of SCLM will develop a local, regional of distant recurrence which is in approximately 30% of the cases limited to the liver. A re-resection is a safe approach due to the regeneration capacity of the liver. In patients not candidates for surgical resection, novel treatment approaches to control and potentially cure the liver disease were explored; radiofrequency ablation (RFA) and stereotactic body radiation therapy (SBRT) are local treatments for patients with liver metastases who are not amendable for surgery. RFA is a localized application with small electrode deliver radiofrequency energy to the tissue which leads to destruction of tumour cells. SBRT is a non-invasive technique that delivers precise biologically very large doses of irradiation in a few fractions to liver metastases.

In our series *(chapter 10)* resection, RFA and SBRT in patients with recurrent colorectal liver metastases offer a survival that seems comparable to primary liver resections of colorectal liver metastases without greater risk. Resection should be the preferred approach but RFA and SBRT are good alternatives with a beneficial outcome. Patients with intra-hepatic recurrences within 6 months after first partial hepatectomy did not survive longer than 3 years and should be offered palliative systemic chemotherapy because the median survival of patients who were treated with modern systemic chemotherapy also may exceed 20 months.[53]

SBRT has demonstrated to be a treatment option for patients with colorectal liver metastases, who were neither candidates for resection nor for RFA, with encouraging local control rates *(chapter 11)*. SBRT has some advantages compared to RFA: due to the heat-sink effect of large vessels, the tissue close to the vessels is not amendable for RFA. Major bile ducts and extra-hepatic organs are at increased risk of heat injury during ablation.[54] Therefore, centrally located liver lesions or lesions nearby large vessels may preferably be treated with SBRT instead of RFA to avoid the above mentioned risks. SBRT is non-invasive. It can be offered to patients not eligible for invasive or minimal invasive interventions and it is also feasible in the outpatient setting, with no requirement for hospitalization or general anaesthesia.

In conclusion, the treatment of patients with SCLM is a challenge but the results of the different treatment strategies for SCLM are encouraging. We recommend tailoring the therapeutic approach according to each patient's individual characteristics by an experienced multidisciplinairy team of medical oncologists, radiation oncologists,

(interventional) radiologists, gastroenterologists, pathologists and liver surgeons. Population-based studies are required to get evidence of the treatment is representative for the population as a whole. Evidence based answers to the questions raised in this thesis seem difficult to be answered soon due to few ongoing randomized ongoing trials. The future is further selection of patients, probably by better harnessing tumour biology, by profiling of gene expression or by other methods.

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SAMENVATTING

Dikke darmkanker is met een incidentie van 12.000 patiënten per jaar in Nederland een frequent voorkomende ziekte. Bovendien is het de op één na belangrijkste kankergerelateerde doodsoorzaak in de Westerse wereld. Deze hoge sterfte kan met name worden toegeschreven aan het ontstaan van uitzaaiingen (metastasen) die zich verspreiden via de lymfebanen en bloedvaten. Metastasen vanuit de darm nestelen zich vooral in de lever. Bij diagnose van een tumor in de dikke darm (colon) of endeldarm (rectum) heeft ongeveer 20% van de patiënten al levermetastasen. We spreken dan van synchrone colorectale levermetastasen. Nog eens 25-30% ontwikkelt deze metastasen na behandeling van de primaire tumor. Dit zijn de metachrone colorectale levermetastasen. De synchrone presentatie van colorectale levermetastasen heeft door het agressieve gedrag van de colorectale (primaire) tumor een slechte prognose. Slechts een beperkt aantal patiënten (15-20%) met synchrone colorectale levermetastasen (SCLM) komt in aanmerking voor chirurgie met curatieve intentie. Het merendeel van de patiënten kan dus niet operatief behandeld worden. De behandeling van patiënten met SCLM is complex en vereist een multidisciplinaire aanpak. Zonder behandeling van de levermetastasen is de gemiddelde overleving minder dan een jaar. Met de moderne effectievere chemotherapie is de overleving momenteel 16-22 maanden. Ontwikkelingen binnen de radiotherapie en lokale ablatieve methoden verruimen de behandelingsstrategieën voor deze groep patiënten. Toch blijft chirurgie de eerste keuze in de behandeling van de colorectale levermetastasen. Door betere per-operatieve zorg en geadvanceerde chirurgische technieken wordt leverchirurgie veiliger en heeft het een steeds belangrijkere rol in de behandeling van patiënten met colorectale levermetastasen.

Dit proefschrift bestaat uit vier delen: deel I bespreekt de trends in de behandeling van synchrone colorectale levermetastasen en de verschillen tussen metachrone en synchrone colorectale levermetastasen. Deel II beschrijft de verschillende chirurgische behandelopties. Deel III bespreekt de rol van neoadjuvante (preoperatieve) chemotherapie en in deel IV wordt de behandeling van patiënten met een recidief van colorectale levermetastasen uiteengezet. Tevens wordt in deel IV de rol van stereotactische radiotherapie besproken.

Trends in de incidentie, behandeling en uitkomst van patiënten met SCLM in het Zuidwestelijk deel van Nederland van 1995-2007 worden beschreven in *hoofdstuk 2*. Het aantal patiënten met SCLM nam in deze periode toe. Dit kan worden toegeschreven aan verschillen in registratie of incidentie maar is het beste te verklaren door verbeteringen in het afbeeldend onderzoek. Kortom, de levermetastasen worden eerder gedetecteerd. In onze serie steeg het gebruik van chemotherapie in palliatieve (levensverlengend) en neoadjuvante setting net zoals het aantal patiënten dat leverchirurgie onderging (van 4% in 1995 tot 10% in 2007). Mogelijk als een gevolg hiervan steeg de mediane overleving over deze periode (van 7 naar 12 maanden). Het percentage patiënten dat een resectie van de primaire tumor onderging bleef stabiel.

Patiënten die een resectie van zowel de primaire tumor als de synchrone levermetastasen ondergingen na 2000 in vergelijking met daarvoor hebben een significant betere 5-jaars overleving (44% vs. 26%) *(hoofdstuk 3)*. Echter, significante verschillen in de 5-jaars ziektevrije overleving werden niet waargenomen (27% vs. 9%). De re-resectie of de lokale behandeling (radiofrequente ablatie of stereotactische radiotherapie) voor recidiverende levermetastasen wordt steeds meer toegepast. Ook in de huidige reeks nam het aantal patiënten toe dat een curatieve lokale behandeling onderging voor recidiverende levermetastasen (28% vs. 62%)**.** Aan de andere kant, patiënten met recidiverende levermetastasen die niet meer lokaal te behandelen zijn ontvangen meer effectievere palliatieve chemotherapie zoals oxaliplatin en irinotecan. Deze twee observaties hebben mogelijk geleid tot het verschil in 5-jaars overleving ondanks dezelfde ziektevrije overleving tussen de twee groepen. In *hoofdstuk 4* vergeleken wij patiënten met synchrone en metachrone colorectale levermetastasen die een gestageerde resectie ondergingen (resectie van de primaire tumor gevolgd door leverchirurgie). In onze studie bleken de patiënten met synchrone colorectale levermetastasen significant slechtere biologische karakteristieken te hebben. Nochtans werd er geen verschil in de ziektevrije en totale overleving gevonden. Dit kan worden verklaard doordat patiënten in de synchrone groep significant meer werden behandeld met neoadjuvante chemotherapie.

De optimale timing van de chirurgische behandeling van patiënten met SCLM is een kwestie van controverse. Er zijn verschillende chirurgische strategieën voor patiënten met SCLM. Naast de traditionele behandeling (colorectale tumor eerst gevolgd door resectie van de levermetastasen) kunnen er twee andere procedures in patiënten met SCLM worden uitgevoerd: de simultane resectie (gelijktijdige resectie van de primaire tumor en de metastasen) en de 'liver first' (resectie van de levermetastasen gevolgd door resectie van de primaire tumor). In het geval van patiënten met een lokaal vergevorderd rectumcarcinoom en synchrone levermetastasen kiezen wij ervoor**,** indien mogelijk**,** de lever eerst te behandelen ('liver first'). In onze serie ondergingen 16 patiënten (70%) met SCLM een curatieve resectie volgens de 'liver first'(*hoofdstuk 5)*. De patiënten worden eerst behandeld met neoadjuvante chemotherapie. Zowel de metastasen als de primaire tumor kun je hiermee verkleinen. Hierna vindt resectie van de levermetastasen plaats. Het rectumcarcinoom wordt vervolgens behandeld met preoperatieve radiotherapie gevolgd door een resectie. De levermetastasen bepalen eerder dan het rectumcarcinoom de overleving en met de `liver first' kan elke onnodige vertraging in de behandeling van de metastasen worden vermeden. Op deze manier kan ook onnodige radiotherapie en/of bekkenchirurgie met een hoge morbiditeit vermeden worden in patiënten met uitgebreide gemetastaseerde ziekte. In het geval van patiënten met een minder vergevorderd rectumcarcinoom en synchrone levermetastasen zijn verschillende behandelingsstrategieën mogelijk *(hoofdstuk 6)*. In patiënten met een minder

vergevorderd rectumcarcinoom (≤ stadium T3N0) met beperkte levermetastasen (in ≤ 4 van de 8 segmenten), is de morbiditeit en mortaliteit van resectie over het algemeen laag. Daarom is simultane resectie een aantrekkelijke optie. In patiënten met een minder vergevorderd rectumcarcinoom en uitgebreide levermetastasen (in >4 van de 8 segmenten) kan een simultane resectie tot een verhoogd complicatierisico leiden. In deze situatie kan de 'liver first' als de behandeling van keuze worden beschouwd. Bij patiënten met een lokaal vergevorderd rectumcarcinoom en beperkte of uitgebreide levermetastasen, is het verstandig, om de lever eerst te behandelen. Het is belangrijk dat de behandeling van een patiënt met een rectumcarcinoom en synchrone levermetastasen geïndividualiseerd is en op het besluit van een multidisciplinair team gebaseerd is.

Het toenemende gebruik van preoperatieve chemotherapiecombinaties voor colorectale levermetastasen kan leverschade veroorzaken met zowel per- als postoperatieve consequenties. De hypothese dat neoadjuvante chemotherapie het leverparenchym ongunstig kan beïnvloeden wordt bevestigd door de beschadigde macroscopische lever die tijdens de operaties kan worden waargenomen. In *hoofdstuk 7* wordt een overzicht gegeven van de literatuur over de werking van chemotherapie, de schade die het kan veroorzaken aan de lever en de postoperatieve complicaties. Het fenotype van leverschade na neoadjuvante chemotherapie is regimespecifiek. Als de chemotherapie goed wordt gekozen en de lengte van behandeling zorgvuldig in een multidisciplinair team wordt gecontroleerd, zijn de voordelen groter dan de potentiële nadelen. Naast de schade die preoperatieve chemotherapie kan veroorzaken is steatose (vervetting) van de lever een risicofactor voor postoperatieve complicaties in patiënten die een uitgebreide leverresectie ondergaan. Dit in een tijdperk waar obesitas epidemisch wordt en er geen efficiënte therapie voor steatose voorhanden is. Milde steatose (5-33%) is relatief onschuldig maar matige (33-66%) en ernstige macrovesiculaire steatose (>66%) zou van invloed kunnen zijn op de uitkomst van patiënten die een uitgebreide leverresectie ondergaan. Het kan daarom van waarde zijn om deze patiënten preoperatief te screenen. In onze studie bracht de magnetic resonance imaging (MRI) de hoogste correlatie en de hoogste kenmerkende nauwkeurigheid voor de opsporing van een chirurgisch relevante steatose graad (>33%), in vergelijking met computed tomography (CT) *(hoofdstuk 8)*. In *hoofdstuk 9* vonden wij dat bevacizumab, een monoclonaal antilichaam tegen de vascular endothelial growth factor, een beschermend effect heeft op gematigde sinusoïdale dilatatie (veroorzaakt door oxaliplatin) zonder enig significant verschil in complicaties.

In het geval van recidiverende levermetastasen zorgt de behandeling middels resectie, radiofrequente ablatie (RFA) en stereotactische radiotherapie (SRx) in goed geselecteerde patiënten voor een overleving die met de overleving van patiënten zonder recidief te vergelijken is *(hoofdstuk 10)*. Chirurgie blijft de eerste keuze maar RFA en SRx zijn alternatieven met een goed resultaat. Bij patiënten met recidiverende levermetasta-

sen binnen 6 maanden na de eerste operatie zou palliatieve chemotherapie, in plaats van resectie of een lokale behandeling, de voorkeur genieten. Dit gezien het feit dat de overleving na chirurgie dan erg kort is. In *hoofdstuk 11* wordt aangetoond dat SRx een goede behandelingsoptie is voor patiënten met colorectale levermetastasen met een 2-jaars lokale controle en overleving van 74% en 83% met een acceptabele toxiciteit.

De behandeling van patiënten met synchrone colorectale levermetastasen is een uitdaging. De resultaten van de verschillende behandelingsstrategieën voor patiënten met SCLM zijn bemoedigend. De behandeling van een patiënt met SCLM moet op individuele kenmerken gebaseerd zijn en uiteengezet worden door een ervaren multidisciplinair team van internist-oncologen, radiotherapeuten, (interventie)radiologen, MDL-artsen, pathologen en leverchirurgen. Door de weinige gerandomiseerde studies is het is erg moeilijk om antwoord te krijgen op vragen die in dit proefschrift naar voren komen. In de toekomst moet een betere selectie van deze patiëntengroep, door een beter begrip van de tumorbiologie en door genprofileratie, zorgen voor een betere uitkomst.

LIST OF PUBLICATIONS

Published and accepted articles

- **van der Pool AE**, *Damhuis RA, IJzermans JNM, de Wilt JHW, Eggermont AMM, Kranse R, Verhoef C. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer; a population-based series Accepted Colorectal Disease*
- **van der Pool AE**, *Verheij J, IJzermans JNM, Verhoef C. Anatomical versus non-anatomical resection of colorectal liver metastases: Is there a difference in surgical and oncological outcome?Accepted World J Surg*
- **van der Pool AE,** *Lalmahomed ZS, de Wilt JH, Eggermont AM, IJzermans JN, Verhoef C. Trends in treatment for colorectal synchronous liver metastases: differences in outcome before and after 2000 J Surg Oncol 2010 Jun 11.*
- **van der Pool AE,** *de Wilt JH, Lalmahomed ZS, Eggermont AM, IJzermans JN, Verhoef C. Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases* Br J Surg. 2010 Mar;97(3):383-90.
- **van der Pool AE**, *Méndez Romero A, Wunderink W, Seppenwoolde Y, Nowak PJ, de Wilt JH, Heijmen BJ, Levendag PC, Verhoef C, IJzermans JN. Stereotactic body radiation therapy for colorectal liver metastases Br J Surg. 2010 Mar;97(3):377-82.*
- **van der Pool AE**, *Harlaar JJ, den Hoed PT, Weidema WF, van Veen RN. Long-term follow-up evaluation of chronic pain after endoscopic total extraperitoneal hernia repair of primary and recurrent inguinal hernia Surg Endosc.2010 Jul;24(7):1707-11.*
- **van der Pool AE,** *Lalmahomed ZS, Özbay Y, de Wilt JH, Eggermont AM, IJzermans JN, Verhoef C. "Staged" liver resection in synchronous and metachronous colorectal hepatic metasases; differences in clinicopathological features and outcome Colorectal Dis. 2009 Nov 14 [Epub ahead of print].*
- *Verhoef C,* **van der Pool AE,** *Nuyttens JJ, Planting AS, Eggermont AM, de Wilt JH The "liver-first"approach for patients with locally advanced rectal cancer and synchronous liver metastases* Dis Colon Rectum. 2009 Jan;52(1):23-30.
- **van der Pool AE,** *Lalmahomed ZS, de Wilt JH, Eggermont AM, Ijzermans JN, Verhoef C. Local treatment for recurrent colorectal hepatic metastases after partial hepatectomy.* J Gastrointest Surg. 2009 May;13(5):890-5.
- *Numanoglu A, McCulloch MI,* **van der Pool AE,** *Millar AJ, Rode H.* J Laparoscopic salvage of malfunctioning Tenckoff catheters Lap Adv Surg Tech A. 2007 Feb;17(1):128-30.

Chapter in books

- **van der Pool AE,** *Marsman HA, Van Gulik T, Verhoef C. Hepatic toxicity as a result of chemotherapy in the treatment of colorectal liver metastases Supportive Oncology*

Submitted

- **van der Pool AE**, *Marsman HA, Verheij J, ten Kate FJW, IJzermans JNM, Verhoef C. Effect of the addition of bevacizumab to oxaliplatin-based pre-operative chemotherapy on liver injury and complications after resection of colorectal liver metastases*
- *Marsman HA,* **van der Pool AE,** *Verheij J, Padmos J, ten Kate FJW, Dwarkasing RS, van Gulik TM, IJzermans JNM, Verhoef C. Hepatic steatosis assessment with CT or MRI in patients with colorectal liver metastases after neoadjuvant chemotherapy*
- *Ayez N, Lalmahomed ZS,* **van der Pool AE,** *Vergouwe Y, van Montfort K, de Jonge J, Eggermont AMM, IJzermans JNM, Verhoef C. The clinical risk score for patients with colorectal liver metastases in the era of effective neoadjuvant chemotherapy*

Award

- ESSO winning abstract, World Congress on gastrointestinal cancer 2009

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Geluk is als een vlinder:
hoe meer je er op jaagt,
hoe verder hij zich van jou verwijdert.
Maar als je rustig gaat zitten
en je aandacht aan andere dingen besteedt,
komt hij vanzelf op je schouder zitten.

CURRICULUM VITAE

Anne Elisabeth Maria van der Pool was born on June 5th 1981 in Nijmegen, the Netherlands. She graduated from the gymnasium at the Nijmeegse Scholen Gemeenschap in 1999. She decided to go abroad and worked a year as au-pair in Nevers, France. In 2000, she started medical school at the Erasmus University Medical Centre. During medical school, she spent six months in Cape Town, South Africa, for her masterthesis about peritoneal dialysis at the Groote Schuur/Red Cross Children Hospital. In 2005 she started internships; the interest for general surgery was born. After completing her medical degree she spent 2 months at the department of colorectal surgery at the Boxhill Hospital, Melbourne, Australia. In November 2007 she started as a PhD student at the department of surgical oncology at the Daniel den Hoed Cancer Centre. This research was focused on the treatment of synchronous colorectal liver metastases. After two years of research she started working as a surgical resident at the Maasstad Ziekenhuis. In October 2010 she started her general surgery residency. She will follow the program in the Maasstad Ziekenhuis under the supervision of Dr. van der Harst and at the Erasmus MC under the supervision of Prof. IJzermans.