Original article

Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases

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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.

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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, extrahepatic 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

Table 1 Neoadjuvant treatment

Neoadjuvant treatment	Group 1 ($n = 29$)	Group 2 ($n = 8$)	Group 3 ($n = 20$)
Primary tumour			
Chemoradiotherapy*	8	6	18
Radiotherapy†	3	1	2
Liver metastases			
Chemotherapy‡	13	2	19

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

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 survival 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).

Table 2 Rectal and liver surgery

	No. of patients ($n = 57$)
Rectal surgery	
Low anterior resection	43 (75)
(Sub)total colectomy	2 (4)
Abdominoperineal resection	9 (16)
Pelvic exenteration	3 (5)
ypT	
T0	7 (12)
T1	1 (2)
T2	5 (9)
T3	37 (65)
T4	7 (12)
ypN	
Negative	25 (44)
Positive	32 (56)
Liver treatment	
Right hemihepatectomy	17 (30)
Left hemihepatectomy	3 (5)
Extra-anatomic resection	36 (63)
Radiofrequency ablation	1 (2)

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

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 1*). Type of rectal surgery is shown in *Table 2*. One patient was treated with intraoperative radiotherapy because the resection margin was less than 2 mm[16].

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 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 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 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 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 3*). There were no in-hospital deaths. Median (range) length 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 ($P < 0·001$).

Table 3 Complications

Complications	Group 1 ($n = 29$)	Group 2 ($n = 8$)	Group 3 ($n = 20$)
Primary tumour			
None	20	6	16
Mild*	6	2	3
Severe†	3	0	1
Liver metastases			
None	24	6	14
Mild*	4	2	6
Severe†	1	0	0

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

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. 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 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.

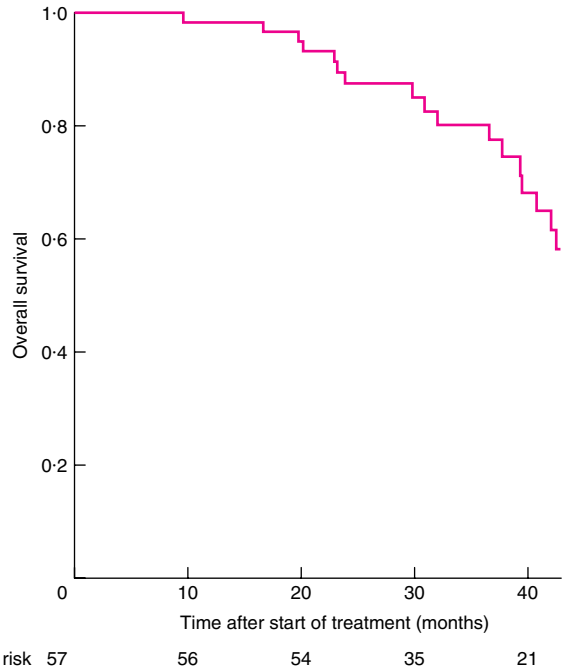

Fig. 1 Kaplan–Meier overall survival curve for the whole study group

Table 4 Univariable analysis of risk factors associated with overall survival following resection of rectal synchronous liver metastases in 57 patients

	No. of patients	5-year survival (%)	Median survival (months)	*P**
Age (years)				0·959
≤ 60	25	36	58	
> 60	32	39	45	
Sex				0·119
F	17	31	40	
M	40	42	58	
pT, primary tumour				0·111
T0–2	13	50	58	
T3–4	44	36	43	
pN, primary tumour				0·288
Negative	25	39	43	
Positive	32	35	47	
CEA level (ng/ml)				0·051
≤ 200	53	40	47	
> 200	4	0	39	
No. of hepatic metastases				0·151
≤ 3	36	41	58	
> 3	21	35	42	
Distribution of liver metastases				0·299
Unilobar	31	48	46	
Bilobar	26	29	47	
Neoadjuvant chemotherapy				0·391
No	23	21	46	
Yes	34	51	81	
Extrahepatic disease				0·189
No	51	44	47	
Yes	6	0	46	
Resection margin				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.

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 ($P = 0{\cdot}051$) (*Table 4*).

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 who 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 (three or fewer segments) in one session is an attractive option. In patients with early-stage rectal cancer and extensive liver disease (more than three 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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Commentary

Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases (*Br J Surg* 2010; 97: 383–390)

This paper addresses the treatment of rectal cancer presenting with synchronous (potentially) operable liver metastases. Because of the increasing use of (neo)adjuvant treatment and the different treatment options, deciding on the best combination can be difficult. Some help and guidance with this would be helpful, and this is the authors' main 'selling point' of the manuscript. Rectal cancer with synchronous metastases is a bad thing to have. In the present paper, the authors report a 5-year survival rate of 38 per cent in a selected group of patients who have completed an aggressive multimodal treatment. This is quite an achievement and these unfortunate patients definitely deserve a chance. Their best chance is probably referral to a centre with expertise, where they don't give up easily. The authors try to make a case for tackling the metastatic disease first, challenging the classical approach of dealing with the primary tumour first. They start with systemic therapy and then resect the metastases. Whether the primary tumour is resected simultaneously or at a later stage is dictated by the anticipated morbidity of the procedure. I think this is a good approach, not because the results in this paper are particularly convincing but because it makes a good deal of sense. The thing with rectal cancer is that there are many variations within this approach: the duration and type of systemic therapy, short-course radiotherapy with a long or short interval, long-course chemoradiation or no radiotherapy at all, resection of liver metastases before or after radiotherapy or during the interval, etc. It will take some time before we get a good feel for the merits of these combinations, and we therefore welcome reports on the subject.

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