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Multicentre study of short-course radiotherapy, systemic therapy and resection/ablation for stage IV rectal cancer

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Background: The optimal treatment sequence for patients with rectal cancer and synchronous liver metastases remains unclear. The aim of this study was to evaluate the feasibility and effectiveness of short-course pelvic radiotherapy (5 × 5 Gy) followed by systemic therapy and local treatment of all tumour sites in patients with potentially curable stage IV rectal cancer in daily practice.

Methods: This was a retrospective study performed in eight tertiary referral centres in the Netherlands. Patients aged 18 years or above with rectal cancer and potentially resectable liver ± extrahepatic metastases, treated between 2010 and 2015, were eligible. Main outcomes included full completion of treatment schedule, symptom control and survival.

Results: In total, 169 patients were included with a median follow-up of 49.5 (95 per cent c.i. 43.6 to 55.6) months. The completion rate for the entire treatment schedule was 65.7 per cent. Three-year progression-free survival and overall survival (OS) rates were 24.2 (95 per cent c.i. 16.6 to 31.6) and 48.8 (40.4 to 57.2) per cent respectively. Median OS of patients who responded well and completed the treatment schedule was 51.5 months, compared with 15.1 months for patients who did not complete the treatment ($P < 0.001$). Adequate symptom control of the primary tumour was achieved in 87.0 per cent of all patients.

Conclusion: Multimodal treatment leads to relief of symptoms in most patients, and is associated with good survival rates in those able to complete the schedule.

[Correction added on 12 February 2020, after first online publication: the Conclusion has been reworded for clarity]

*Other members of the Dutch Stage IV Rectal Cancer Group are co-authors of this article and can be found under the heading Collaborators

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Introduction

Curative treatment of stage IV rectal cancer is challenging and up to 80 per cent of patients have unresectable liver metastases at diagnosis¹. Previous studies^{2,3} have shown that systemic therapy can downsize the metastases with subsequent conversion to resectable or ablatable disease. Nevertheless, radical resection of multiple tumour sites remains challenging in patients with metastatic disease⁴. In the setting of synchronous metastases, the rectal tumour is often locally advanced. Traditionally, the preferred treatment is long-course chemoradiotherapy including 5-fluorouracil or capecitabine as radiation sensitizer, with

limited effect on distant metastases^{5,6}. Consequently, the metastatic disease is left untreated for a significant period of time.

To minimize treatment delay, a new treatment schedule was introduced that combined radiotherapy of the primary tumour with a timely and adequate dose of systemic therapy to address the distant disease. This schedule consisted of preoperative short-course radiotherapy (5 × 5 Gy), followed by six cycles of capecitabine–oxaliplatin–bevacizumab (CAPOX-B), with the intention of subsequent surgical resection or ablation of all tumour sites⁷. In a phase II single-arm study⁷, 50 patients with rectal cancer and resectable or ablatable liver and/or lung

metastases underwent this treatment schedule. Eventually, 36 patients (72 per cent) underwent radical surgical treatment with 2-year recurrence-free and overall survival rates of 64 and 80 per cent respectively.

After completion of this so-called M1 study, multiple centres in the Netherlands implemented this treatment schedule in routine daily practice, as it effectively combines local control of the rectal tumour with a timely start of systemic therapy. Although the original study⁷ only included patients with treatable and limited metastatic disease, less strict eligibility criteria are used in daily practice. The aim of the present study was to evaluate the feasibility and effectiveness of this treatment schedule in stage IV rectal cancer patients in daily practice.

Methods

This was a retrospective study in eight centres in the Netherlands: Amsterdam University Medical Centre, Catharina Hospital Eindhoven, University Medical Centre Groningen, Leiden University Medical Centre, Maastricht University Medical Centre, Netherlands Cancer Institute (Amsterdam), Radboud University Medical Centre (Nijmegen) and University Medical Centre Utrecht. Patients with a diagnosis of synchronous metastasized rectal cancer were identified from institutional databases and registrations between January 2010 and December 2015.

Patients were eligible if rectal cancer with (potentially) curable liver \pm extrahepatic metastases was confirmed histologically and they were scheduled for the multimodality treatment, consisting of 5×5 Gy pelvic radiotherapy followed by systemic therapy and subsequent surgery, with or without other local treatment modalities. Simultaneous lung or distant lymph node metastases were accepted as long as treatment with curative intent was deemed possible after systemic therapy. Standard diagnostic investigation consisted of pelvic MRI for local staging of the rectal tumour and CT of the chest, abdomen and pelvis to detect distant metastases. All patients were discussed in a multidisciplinary meeting with (intervention) radiologists, and medical, radiation and surgical oncologists. Clinical data of eligible patients were collected from medical records and anonymized.

This study was approved by the institutional review board (METC17.1695/M17CRM).

Neoadjuvant treatment and reassessment

Patients with significant signs of obstruction at diagnosis received a diverting stoma. Neoadjuvant short-course

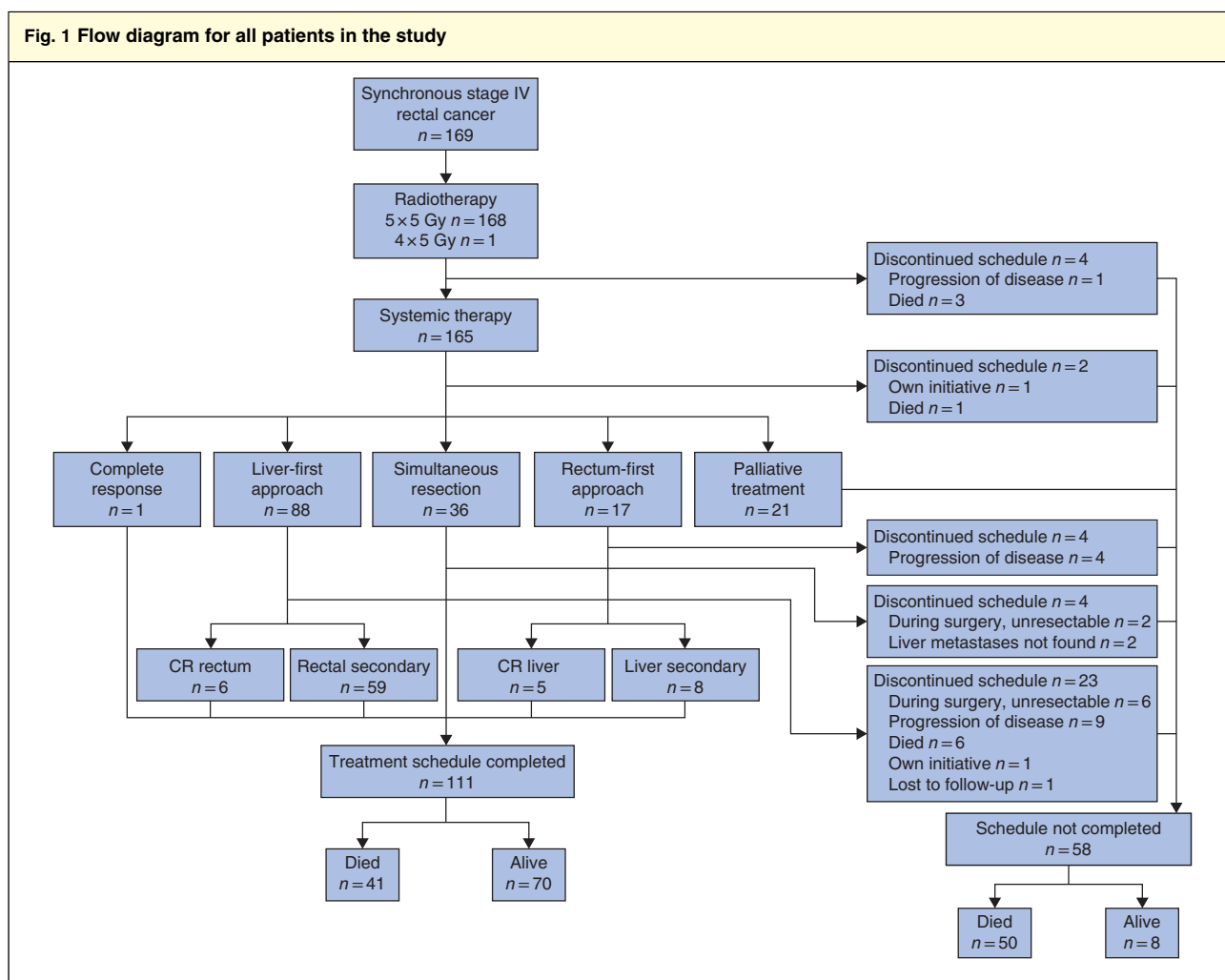
radiotherapy (5×5 Gy) was given to the primary tumour, mesorectum and regional lymph nodes. Systemic therapy started approximately 2 weeks after the last fraction of radiation. The choice of systemic therapy regimen was at the discretion of the local team. After three cycles of systemic therapy, radiological evaluation of response was performed using CT and MRI. In each participating centre a multidisciplinary team decided on the next optimal treatment step: continuation of systemic treatment, staged or simultaneous local treatment of primary tumour and/or distant metastases, or palliative treatment.

Surgery and histopathology

After completion of neoadjuvant treatment, the multidisciplinary team reviewed the resectability of the primary tumour and metastases. The optimal sequence of surgical treatment and type of surgical procedure with or without other local treatment modalities were tailored to the individual patient. Other local treatment modalities included radiofrequency ablation (RFA) and stereotactic radiotherapy. Primary tumour resection was performed by partial or total mesorectal excision⁸. The choice of surgical procedure and the use of a diverting stoma were at the discretion of the local surgeon. Treatment of extrahepatic metastases included pulmonary metastasectomy, pulmonary RFA, stereotactic radiotherapy of the lung and lymph node resection. In patients with complete response of the primary tumour and/or the metastases to neoadjuvant treatment, a watch-and-wait approach was sometimes chosen⁹. After surgical resection of all tumour sites, no adjuvant therapy was given. Histopathological evaluation of the specimen was performed by the local pathologist. Downstaging of the primary tumour was evaluated, comparing the baseline cT status with the (y)pT status.

Outcomes

The main outcomes were completion of the entire treatment schedule, pathological response and overall survival (OS). Ancillary outcomes were treatment-related toxicity, surgical complications, symptom control of the primary tumour and progression-free survival (PFS). Completion of the treatment schedule was defined as neoadjuvant short-course radiotherapy, at least two cycles of systemic therapy and subsequent local treatment of all tumour sites. Treatment-related toxicity was registered using the US National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0¹⁰. Radiotherapy-related toxicity was classified as acute and late toxicity, defined as toxicities within or after 3 months. Surgical complications for both liver and rectal surgery were graded using



CR, complete response.

the Dindo–Clavien classification¹¹. Tumour response evaluation was assessed using the RECIST (Response Evaluation Criteria In Solid Tumours) criteria version 1.0¹². PFS was calculated from the first day of radiotherapy to the first evidence of recurrence (local, regional or metastatic) or until death. OS was calculated from the first day of radiotherapy until death or last documented follow-up.

Statistical analysis

All analyses were performed using SPSS® version 24.0 (IBM, Armonk, New York, USA). Patients and treatment characteristics are presented as percentages, medians with ranges or medians with 95 per cent confidence intervals. Categorical variables were compared using the χ^2 test, and continuous variables with the Mann–Whitney U test. OS and PFS were calculated using Kaplan–Meier curves. The

association of completing the treatment schedule with OS was analysed using an extended Cox proportional hazards model, in which treatment completion was used as the time-dependent co-variable to avoid immortal time bias. The log rank test was used to compare survival probabilities between subgroups. Univariable and multivariable Cox regression analyses were performed to identify predictors of survival. A binary logistic regression model was used to identify prognostic factors of treatment completion. All variables with significance of $P \leq 0.200$ in univariable analysis were entered in the multivariable analysis. $P < 0.050$ (two-sided) was regarded as statistically significant.

Results

Between January 2010 and December 2015, 169 patients with potentially resectable or ablatable stage IV rectal

Table 1 Patient characteristics	
	No. of patients* (n = 169)
Age at start of treatment (years)†	63 (32–83)
Sex ratio (M : F)	109 : 60
WHO performance status	
0	128 (75.7)
1	33 (19.5)
2	8 (4.7)
Clinical tumour and node status	
T2 N0	2 (1.2)
T2 N1–2	11 (6.5)
T3 N0	10 (5.9)
T3 N1–2	117 (69.2)
T4 N1–2	29 (17.2)
Mesorectal fascia involvement	
	75 (44.4)
Location of primary rectal cancer	
Low (0–5 cm)	67 (39.6)
Middle (5–10 cm)	76 (45.0)
High (10–15 cm)	24 (14.2)
Unknown	2 (1.2)
Metastatic site	
Liver only	130 (76.9)
Liver and lung	19 (11.2)
Liver and distant lymph nodes	19 (11.2)
Liver, lung and distant lymph nodes	1 (0.6)
No. of liver metastases†	
	3 (1–20)
Location of liver metastases	
Unilobar	95 (56.2)
Bilobar	74 (43.8)
Diameter of largest metastasis (cm)†	
	3.0 (0.8–22.1)

*With percentages in parentheses unless indicated otherwise; †values are median (range).

cancer fulfilled the criteria and started the treatment schedule (Fig. 1). Patient and treatment characteristics are shown in Tables 1 and 2 respectively. In 70 patients (41.4 per cent), all tumour sites were considered surgically amenable for local treatment before any neoadjuvant treatment. Neoadjuvant 5 × 5 Gy radiotherapy was completed in 168 patients; the other patient received only four fractions of 5 Gy owing to bowel toxicity (perforation). Overall, 94.1 per cent of all patients received between three and eight cycles of systemic therapy. Systemic therapy consisted of capecitabine and oxaliplatin (CAPOX); capecitabine, oxaliplatin and bevacizumab (CAPOX-B); capecitabine and bevacizumab (CAP-B); fluorouracil, oxaliplatin and folinic acid (FOLFOX), fluorouracil, oxaliplatin, folinic acid and bevacizumab (FOLFOX-B) or capecitabine monotherapy. Median follow-up was 49.5 (95 per cent c.i. 43.6 to 55.6) months.

Table 2 Treatment details	
	No. of patients* (n = 169)
Diverting stoma	
Before all treatment	26 (15.4)
During neoadjuvant treatment	14 (8.3)
Radiotherapy	
5 × 5 Gy	168 (99.4)
4 × 5 Gy	1 (0.6)
Chemotherapy	
	n = 165
CAPOX	41 (24.9)
CAPOX-B	109 (66.1)
FOLFOX	5 (3.0)
FOLFOX-B	5 (3.0)
CAP	4 (2.4)
CAP-B	1 (0.6)
Total no. of administered cycles†	
1–3	48 (29.1)
4–6	102 (61.8)
≥ 7	15 (9.1)
Rectal resection‡	
	n = 112
Low anterior resection	74 (66.1)
Hartmann procedure	13 (11.6)
Abdominoperineal resection	25 (22.3)
Liver treatment‡	
	n = 132
Liver resection	83 (62.9)
RFA alone	13 (9.8)
Resection + RFA	34 (25.8)
Radiotherapy	2 (1.5)
Treatment of extrahepatic metastases	
Lung	
Metastasectomy	6 (3.6)
Pulmonary RFA	3 (1.8)
Radiotherapy	2 (1.2)
Lymph node resection	
Combined lymph node and rectal resection	4 (2.4)
Rectal radiotherapy expanded for lymph node	2 (1.2)
Length of hospital stay (days)†	
Rectal resection	8 (3–29)
Liver resection	7 (1–62)
Simultaneous resection	14 (5–57)

*With percentages in parentheses unless indicated otherwise; †values are median (range). ‡Includes 36 local treatment procedures performed during simultaneous resections. CAP, capecitabine; OX, oxaliplatin; B, bevacizumab; FOLFOX, 5-fluorouracil, folinic acid and oxaliplatin; RFA, radiofrequency ablation.

Completion of entire treatment schedule

In total, 111 patients (65.7 per cent) completed the entire treatment schedule. After neoadjuvant treatment, 88 patients received a liver-first approach, and in 17 primary tumour resection was performed first. Simultaneous

Table 3 Anatomical location of progression of disease during and after completing the treatment schedule

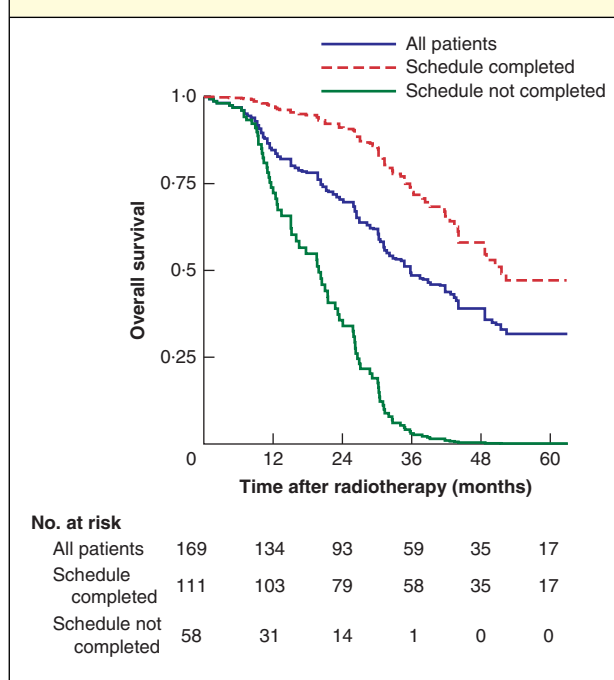
Anatomical location	During treatment schedule	After treatment schedule
Liver	25	23
Lung	3	13
Liver and lung	8	15
Liver and rectum (local recurrence)	3	2
Lung and rectum (local recurrence)	0	2
Other	9	14

surgery of the primary tumour and liver metastases was performed in 36 patients. A complete response at all tumour sites after neoadjuvant treatment was seen in one patient, and a watch-and-wait approach was applied (Fig. 1).

In multivariable logistic regression, the number of liver metastases (hazard ratio 0.82, 95 per cent c.i. 0.66 to 0.94; $P = 0.004$) was the only significant predictor for completion of the entire treatment schedule. Of the 58 patients who were not able to complete the treatment schedule, 24 (41 per cent) received palliative systemic treatment, 19 (33 per cent) refrained from active treatment, four (7 per cent) received palliative radiotherapy, ten (17 per cent) died and one (2 per cent) was lost to follow up.

Progression-free and overall survival

Forty-eight patients had progressive disease during treatment and 69 after completing the entire treatment schedule. Progression of disease was observed most frequently in the liver (Table 3). Seven patients developed local recurrence after rectal surgery. Of the

Fig. 2 Kaplan–Meier analysis of overall survival for the whole cohort, patients who completed the treatment schedule, and those who did not

$P < 0.001$ (log rank test).

48 patients who showed progression during the treatment schedule, seven were able to complete the entire schedule and 41 were not. The 1-, 3- and 5-year PFS rates for all patients were 59.3 (95 per cent c.i. 51.6 to 66.9), 24.2 (16.6 to 31.6) and 17.1 (9.6 to 24.5) per cent respectively.

Median OS for all patients was 35.7 (range 1.0–88.4) months. The 1-, 3- and 5-year OS rates were 85.2 (95 per cent c.i. 79.7 to 90.7), 48.8 (40.4 to 57.2) and 31.1 (22.8 to

Table 4 Univariable and multivariable analyses for overall survival

	Univariable analysis		Multivariable analysis	
	Hazard ratio	<i>P</i>	Hazard ratio	<i>P</i>
Age at diagnosis (continuous)	0.99 (0.97, 1.01)	0.351		
Sex (M versus F)	1.18 (0.76, 1.84)	0.453		
WHO performance status (2 versus 0–1)	1.06 (0.72, 1.55)	0.782		
No. of liver metastases				
Continuous	1.12 (1.04, 1.21)	0.003	1.11 (1.02, 1.20)	0.011
> 4 versus ≤ 4	1.76 (1.13, 2.76)	0.013		
cT category (IV versus II–III)	1.47 (0.95, 2.27)	0.086	1.30 (0.83, 2.03)	0.252
cN category (II versus 0–I)	1.23 (0.86, 1.75)	0.253		
Extrahepatic disease (yes versus no)	1.37 (0.85, 2.20)	0.200	1.24 (0.77, 2.01)	0.379

Table 5 Neoadjuvant treatment toxicity and local treatment complications

	No. of events	No. of patients with events	Total no. of patients
Radiotherapy-related toxicity			
Grade 3–4		11	169
Acute	9		
Late	2		
Grade 5		1	169
Acute	1		
Late	0		
Chemotherapy-related toxicity*			
Grade 3–4		45	165
Gastrointestinal	31		
Vascular	12		
Neurological	7		
Dermatological	7		
Haematological	5		
Cardiological	2		
Infection	2		
Grade 5	0	0	165
Unknown toxicity		22	165
Surgical complications			
Grade III–IV, staged rectal resection†		14	112
Ileus/gastroparesis	4		
Anastomotic leakage	4		
Presacral abscess	3		
Wound dehiscence	2		
Other	3		
Grade III–IV, staged liver treatment†		16	132
Infection/abscess			
Abdominal	6		
Thorax	4		
Wound	2		
Bleeding	3		
Bile duct perforation or stenosis	3		
Other	4		
Grade V, liver treatment		3	132
Acute coronary syndrome	3		
Grade III–IV, simultaneous resection†		16	36
Infection/abscess			
Abdominal	6		
Thorax	6		
Wound	3		
Ileus/gastroparesis	4		
Wound dehiscence	3		
Other	4		

*Some patients had more than one toxicity; †some patients had more than one complication.

39.9) per cent respectively (*Fig. 2*). The median OS for the 111 patients who completed the entire treatment schedule was 51.5 months, compared with 15.1 months in patients who did not complete the treatment ($P < 0.001$). The 3- and 5-year OS rates for patients who completed the entire

treatment schedule were 73.6 (64.1 to 83.1) and 46.8 (34.8 to 58.7) respectively.

In multivariable analysis, the number of liver metastases (hazard ratio 1.11; 95 per cent c.i. 1.02 to 1.20; $P = 0.011$) was associated with decreased OS (*Table 4*).

Evaluation of radiological and pathological responses

Complete radiological and endoscopic response of the rectal tumour was observed in 11 of 165 patients (6.7 per cent), allowing a watch-and-wait approach. Five of these patients had recurrence of the rectal tumour within 6 months and underwent rectal resection. In six patients, no recurrence was observed during follow-up (median follow-up 26.6 months). A partial response was observed in 49.1 per cent of patients. A radiological complete response of the liver was observed in five patients (3.0 per cent).

Clear margins at rectal surgery (R0) were accomplished in 99 (88.4 per cent) of the 112 patients who had a rectal resection, including 14 patients (12.5 per cent) with a pathological complete response. Pathological downstaging of the primary tumour was seen in 38 patients (33.9 per cent). Resection margins of the liver specimen were involved (R1) in 11 (10.3 per cent) of the 107 patients undergoing surgical resection of liver metastases. A pathological complete response of the liver was reported in 15 patients (14.0 per cent).

Toxicity and morbidity

Grade 3–4 radiotherapy-related toxicity was observed in 11 of the 169 patients (6.5 per cent) (Table 5). One patient died within 1 month after radiotherapy from rectal bleeding. Chemotherapy-related grade 3–4 toxicity was observed in 45 patients (27.3 per cent). Gastrointestinal complaints and pulmonary embolism were reported most frequently.

Severe surgical complications (grade III–IV) were observed after rectal resection in 14 patients (12.5 per cent). The most frequent complications were ileus and anastomotic leakage. Grade III–IV complications after liver treatment occurred in 16 of 132 patients (13.7 per cent). Twelve of the 16 patients suffered from infection in the abdomen/thorax or of the wound. Within 30 days of liver surgery, three patients (2.3 per cent) died from acute coronary syndrome. After simultaneous resection, 16 of the 36 patients (44 per cent) experienced grade III–IV complications. The most common complications were abdominal, pulmonary and wound infection.

Control of symptoms from the primary tumour

Despite short-course radiotherapy, 35 patients experienced rectal complaints during the treatment schedule. The most reported complaints were pain, obstruction and rectal bleeding. Of all patients, 16 (8.5 per cent) received pharmacological treatment, 14 (8.2 per cent) required a diverting stoma during systemic treatment, and in four

patients (2.4 per cent) rectal surgery was performed earlier than planned. In the remaining 131 patients (79.4 per cent), the treatment schedule provided local symptom control during follow-up in both curative and palliative settings.

Discussion

This evaluation of clinical practice shows that subsequent local treatment of all tumour sites after multimodal neoadjuvant therapy was achieved in the majority of patients, with tolerable morbidity and mortality. The number of liver metastases at diagnosis appeared to be the only predictor of treatment completion and survival. In the initial prospective M1 study^{7,13}, 80 per cent of patients received local treatment at all tumour sites, with a 5-year OS rate of 38 per cent, whereas in the present study these numbers were lower. In the initial trial, only patients with limited metastatic disease, who were considered treatable with curative intent at baseline, were included. In the present study, less than half of the patients had resectable metastases at baseline and the resectability of the metastases in most patients was highly dependent on the response of the systemic treatment.

In locally advanced rectal cancer, short-course radiotherapy with subsequent systemic therapy can be an alternative for long-course chemoradiotherapy. A large randomized study¹⁴ compared short-course radiotherapy combined with three cycles of FOLFOX4 with long-course chemoradiotherapy in patients with locally advanced rectal cancer (cT4 or fixed cT3). No significant difference was observed in local efficacy between the treatments. A different study¹⁵ with a similar design found improved pathological tumour downstaging and better disease-free and metastasis-free survival in patients treated with short-course radiotherapy plus chemotherapy. In the present study, complete pathological response of the primary tumour was observed in 12.5 per cent, omitting surgical treatment in six patients, and a partial response in 49.1 per cent.

Symptom control is important in patients with rectal cancer. Short-course pelvic radiotherapy has been shown to be an effective palliative treatment modality in patients with symptomatic rectal cancer^{16,17}. Many clinicians, however, are hesitant to use short-course radiotherapy in patients with locally advanced disease because of the perceived risk of providing less optimal local control compared with that obtained with chemoradiotherapy. In the present study, adequate symptomatic local control of the primary tumour was achieved in the majority of the patients. This confirms that short-course radiotherapy followed by systemic chemotherapy is an effective and safe treatment in stage IV rectal cancer, in both the curative and palliative setting.

Systemic chemotherapy plays a significant role in downstaging liver metastases and eradication of microscopic disease. Earlier studies^{18,19} showed that induction chemotherapy can convert initially unresectable liver metastases to resectable disease. In the present study, 99 patients (58.6 per cent) had potentially or borderline resectable/ablative liver metastases at the time of diagnosis. Of these patients, 60.1 per cent had a partial response after systemic treatment, enabling curative liver treatment. This confirms that systemic treatment can downsize metastases to resectable disease, yet the optimal regimen has not been defined. Currently, a Dutch multicentre randomized phase 3 trial (CAIRO5) is underway that compares multiple systemic treatment regimens in patients with colorectal cancer and initially unresectable liver-only metastases (NCT02162563)²⁰. The estimated study completion date is the end of 2020.

An alternative treatment for stage IV rectal cancer has been published previously^{21–23}. Patients received chemotherapy followed by a liver-first approach. After liver surgery, (chemo)radiotherapy was administered with subsequent primary tumour resection. Ninety of the 129 patients (69.8 per cent) completed the protocol, of whom ten had a (near) complete response of the primary tumour. A disadvantage of this approach is that the duration of treatment is longer compared with the schedule in the present study. Moreover, with this approach a simultaneous resection is not feasible because of the treatment sequence.

Collaborators

Members of the Dutch Stage IV Rectal Cancer Group include: G. L. Beets, A. G. J. Aalbers, N. F. M. Kok, T. J. M. Ruers, C. B. H. A. Kobus, S. V. Siemons, C. Grootsholten, L. G. H. Dewit, J. G. van den Berg and I. Zavrakidis (Netherlands Cancer Institute); K. P. de Jong, G. A. P. Hospers and A. Karrenbeld (University Medical Centre Groningen, University of Groningen); E. D. Geijsen and C. J. A. Punt (Amsterdam UMC, University of Amsterdam); H. Rutten and S. Radema (Radboud University Medical Centre, Nijmegen); M. P. W. Intven and J. M. L. Roodhart (University Medical Centre Utrecht); F. Holman and E. Kapiteijn (Leiden University Medical Centre); J. Melenhorst (Maastricht University Medical Centre); J. S. Cnossen and G.-J. M. Creemers (Catharina Hospital, Eindhoven).

Disclosure

The authors declare no conflict of interest.

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