Primary Rectal Carcinoma in Patients with Stage IV Resectable Disease at Diagnosis

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Abstract. *Background: Rectal cancer is commonly diagnosed at a precocious stage, but for patients presenting at diagnosis with stage IV disease the best treatment is still undefined. The purpose of this study was to review the feasibility and outcome of multimodality treatment of rectal cancer patients metastatic at diagnosis. Patients and Methods: From January 2000 to December 2005, 40 patients with histologically proven stage IV rectal adenocarcinoma (<12 cm from the anal verge) were examined. Variables considered were age (under or over 65 years), tumour grade, presence of peritoneal carcinomatosis, type of surgery (palliative versus resection). Results: The median age was 61 years (range, 32-83) and 27 were male and 13 female. Seventeen patients with unresectable or potentially resectable metastatic disease received neoadjuvant chemoradiotherapy (CHT-RT) with 5-fluorouracil (5FU) (plus oxaliplatin in 11 cases), radical surgery was performed in almost half of the cases; only in two patients were metastases also resected. If the patient is a candidate for radical surgical resection, the primary tumour should initially be treated as in a patient without metastatic disease and subsequently the primary tumour and metastases should be treated surgically. If the metastases are unresectable, the treatment of the primary lesion, according to the patient's symptoms, should be by palliative CHT. It is still not determined whether RT should be reserved for the symptomatic cases as an alternative to local surgery. In five patients treated with neoadjuvant CHT alone, radical local surgery was performed in two cases. Eighteen symptomatic patients were resected primarily; all of them received a postoperative CHT but only five of them also received postoperative RT. Nevertheless, after a multimodality treatment (neoadjuvant CHT ± RT) 22.5% achieved a response rate (RR) (one complete remission (CR) and eight partial remission (PR)). Considering that all except two of the patients were locally radically resected and two of them also underwent metastases surgery, the overall RR was 17.5% (four CR and three PR). All of the CR were disease-free and alive after a median follow-up of 19.3 months. Age ≥65 years had no impact on overall survival (OS), but the presence of peritoneal carcinosis in five patients showed a trend towards diminished survival, although it was not statistically significant (p=0.08). Conclusion: The best treatment on diagnosis of metastatic rectal cancer is a multimodality CHT-RT approach. New prospective studies should evaluate non cross-resistant regimens as additional therapy for those patients with a systemic residual disease after common CHT-RT.*

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Rectal cancer is commonly diagnosed at a precocious stage, but because of local relapse and/or metastatic disease, only half of radically resected patients can be considered free of disease. In patients with rectal cancer and metachronous metastatic disease, a mean survival time (MST) of 25 months in patients with solitary hepatic metastases, compared to three months for patients with extensive bilobar disease has been demonstrated (1); in patients with synchronous metastatic disease, resection of the hepatic metastases achieved a survival advantage over patients with unresectable liver lesions with a MST of 29.6 *versus* 10.2 months, respectively. Common agreement is now that in patients with resectable synchronous metastatic disease, the primary tumour should be treated with neoadjuvant CHT-

RT (45-50.4 Gy in 25-28 fractions) and concomitant 5FU continuous infusion (*c.i.*). Metastases can or may not be resected simultaneously with the primary tumour depending on their site (2, 3).

Data suggest that the primary tumour in patients with rectal cancer will cause obstruction of the large bowel in 15 to 20% of cases (4). Perforation is the presenting symptom in fewer than 10% of patients and a clinically significant haemorrhage from the primary is also rare, with an incidence of less than 10% (5). The presence of any of these symptoms at the time of diagnosis should mandate tumour-directed therapy, usually in the form of tumour resection. However, the benefit of resecting asymptomatic primary rectal cancer in the setting of incurable metastatic disease has to be defined (6, 7). In a retrospective study of 955 patients who had initially undergone a resection or nonoperative management of their primary lesion, no differences in OS were reported between the two groups (8). In addition, the rate of eventual complications attributable to an unresected primary lesion was low with only 9% of cases with bowel obstruction. Patients presenting with stage IV rectal carcinoma not amenable to metastasectomy therefore require careful evaluation for primary tumour-related symptoms. In the presence of symptoms, primary tumour-directed therapy is warranted, usually in the form of surgical resection or RT (8). External beam RT, with or without radiosensitizing CHT, is the usual non-surgical therapy for locally advanced rectal diseases. Although few data are available regarding the utility of pelvic radiation with or without CHT, considerable experience with radiation in the setting of locally advanced, unresectable, or recurrent rectal cancer has been obtained and an MST of 17-18 months reported (9-11).

If however, there are no symptoms associated with the primary lesion, patients may undergo nonoperative management, which allows prompt initiation of systemic disease-directed therapy without delay (12-14). In the presence of widespread metastatic disease no curative CHT is known, but trials with palliative 5FU and leucovorin (LV) compared with the best supportive care have demonstrated an increased number of PR and prolongation of time to disease progression (TTP), as well as improved OS and quality of life in the first arm (15-17). In recent years, adding irinotecan (CPT11) or oxaliplatin to 5FU/LV, has increased RR, TTP and OS (18, 19).

In our study the efficacy of different treatments, in terms of local and metastatic resectability, OS and disease-free survival (DFS), in a group of 40 consecutive stage IV potentially resectable metastatic rectal cancer patients was analysed. The primary objective of the study was to determine the RR achieved by CHT-RT, followed by surgery with curative intent. Secondary end-points were to assess the DFS and OS with this type of CHT-RT combination *versus* those observed in patients who had been surgically treated from the beginning.

Patients and Methods

From January 2000 to December 2005, 40 patients with histologically proven stage IV rectal adenocarcinoma (≤12 cm from the anal verge) were retrospectively examined at the Medical Oncology Division, Istituto Oncologico Veneto, of Padova.

Eligibility criteria. Inclusion criteria were: age ≥18 years; histologically proven rectal cancer located up to 12 cm from the anal verge by rigid proctoscopy; no synchronous colon cancer assessed by colonoscopy; clinical stage IV (metastasis (M) following transrectal ultrasonography and/or pelvic computed tomography (CT) scan, with distant metastases assessed by abdominal and thoracic CT scan; Eastern Cooperative Oncology Group performance status ≤1, and adequate haematologic, liver and renal function (neutrophils $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, creatinine <140 μmol/L, creatinine clearance ≥60 mL/min, total bilirubin concentration ≤1.5 times the upper normal limit (UNL), and liver transaminase or alkaline phosphatase concentrations ≤2.5 times the UNL). Each patient gave written consent before starting treatment.

Patients suffering from the following conditions were ineligible: active inflammatory bowel disease, malabsorption syndrome, congestive heart failure, recent ischemic heart disease, peripheral neuropathy, serious uncontrolled active infection and psychiatric disorders or psychological disabilities thought to adversely affect treatment compliance, pregnant or lactating patients and women with child-bearing potential who lacked effective contraception.

Radiotherapy. RT was delivered with a linear accelerator using 6 MV photons and a three- or four-field box technique with the patient in the prone position. The 3D planning target volume was designed to include all macroscopically identified disease, the entire mesorectum with margin, and the internal iliac and presacral nodes up to the level of the fifth lumbar vertebra (superior border: L5/S1 junction). The distal border was 3 cm below the distal extent of the primary tumour or at the bottom of the obturator foramina. The lateral borders extended 1.5 cm lateral to the widest bony margins of the true pelvic side walls. The field also extended to the posterior aspect of the symphysis pubis or anterior margin of the symphysis pubis, with shielding of the anterior parts of the bone sacral margin. All patients received a total dose of 50.4 Gy (45 Gy/25 fractions to the posterior pelvis followed by 5.4 Gy/3 fractions boost to the tumour over 5.5 weeks with daily fractions of 1.8 Gy on five consecutive days), as specified according to the International Commission on Radiation Units and Measurements 50 report.

Chemotherapy. Whenever it was possible, neoadjuvant 5FU was delivered by *c.i.* at a fixed dose of 225 mg/m^2 daily (or by bolus at a fixed dose of 450 mg/m^2 weekly) ± oxaliplatin by two hour infusion 60 mg/m^2 weekly, continuously for approximately 5.5 weeks, from the first to the last day of RT. When RT was not administered CPT11 or oxaliplatin-based regimens were administered postoperatively.

In some cases 5FU was delivered neoadjuvantly without RT, by bolus at a fixed dose of 400 mg/m^2 on days 1 and 2 followed by 22

hour *c.i.* at a fixed dose of 600 mg/m^2 daily on days 1 and 2 plus LV 100 mg/m^2 by 2 hour infusion on days 1 and 2 and oxaliplatin by 2 hour infusion 85 mg/m^2 on day 1, every two weeks.

Dose modification. The following recommendations for CHT dose reductions were applied. In patients who experienced grade 3 toxicity, according to the National Cancer Institute Common Terminology Criteria, Version 2 (NCI-CTC) (20), 5FU and oxaliplatin treatment was interrupted until the toxicity resolved to grade 0-1, and appropriate symptomatic and prophylactic treatment was administered. When the toxicity resolved to grade 0 or 1, treatment was continued at 75% of the original dose at the first appearance of the respective toxicity.

The RT schedule for ≤grade 2 toxicities was not modified unless the severity worsened. If grade 4 toxicities developed, CHT-RT was discontinued, unless the investigating committee considered it to be in the best interest of the patient to continue at 50% of original 5FU dose, once toxicity had resolved to grade 0-1.

The patients were monitored weekly by ECOG performance status, clinical examination, full haematology, blood biochemistry and liver function tests.

Surgery. Four to six weeks after completion of the CHT-RT, the same surgeon reassessed resectability by clinical examination and thoracic-abdomen CT scan. In those cases in which metastatic disease was reduced or stabilised, surgical treatment was immediately scheduled. In resectable tumours, the possibility of sphincter preservation was determined by the surgeon at the time of surgery. The general guidelines were applied: a pelvic CT scan, endosonography of the rectum and/or rectosigmoidoscopy and CEA post CHT-RT within two weeks of the planned surgery date; radical resection of the primary tumour and simultaneously (when possible) of the metastatic disease; total mesorectal excision (21) where technically feasible except for upper rectal lesions where partial total mesorectal excision (TME) was more appropriate; stoma highly recommended for lower rectal lesions with reversal at the surgeon's discretion after completion of adjuvant CHT and post-operative documentation of the type of surgery performed and completeness of the procedure (mesorectal fascia intact, mesorectal fascia breached, or obvious margin involvement).

In symptomatic patients, surgery of the primary tumour or a stoma was performed (independent of resectability of the metastases) and four to six weeks later, some of them received postoperative CHT ± RT.

Histopathological assessment of response to chemoradiotherapy. Surgical specimens were reviewed by two pathologists who were unaware of the patients' outcome and reported according to the American Joint Committee on Cancer TNM classification (2).

Response of the primary tumour was considered as a down-staging of T and/or N compared to the status at diagnosis, while response of the metastases was registered according to WHO criteria (22).

Statistical analysis. The median time to progression (TTP) was defined as the time from the start of therapy to local or systemic progression or to death for any cause. The OS was counted from the start of treatment to death from any cause. Survival of patients lost at follow-up was checked by phone interview or by consultation of the municipal records. The median TTP and OS were estimated using the Kaplan-Meier method (23). Prognostic factors for survival (age <65 *versus* ≥65 years, histological grade 3 *versus* 2 or 1, surgical removal of primary tumour *versus* palliative measures and the presence of peritoneal carcinomatosis) were tested by means of a two-sided log-rank test .

Results

Twenty two out of the 40 (55%) patients with primary adenocarcinoma of the middle and low rectum and synchronous metastases underwent neoadjuvant CHT with 5FU ± oxaliplatin (all patients had unresectable metastatic disease and all of them were asymptomatic) and 17 of them (77.3%) also received concomitant RT (these patients had potentially resectable metastatic disease). The other 18 patients received surgery (in five of them, 27.8%, a stoma was introduced) (all of them had synchronous metastatic disease and symptomatic primary disease) but only five of them (27.8%) underwent postoperative CHT-RT (four with 5FU *c.i.* + oxaliplatin and one with 5FU *c.i.* alone) (Tables I-III). Surgery on metastases was performed on seven patients, before (two patients), concomitantly (four patients) or after (one patient) the removal of the primary tumour.

At the end of the multimodality treatment (neoadjuvant CHT ± RT and surgery), which was well tolerated, four patients were rendered free of all macroscopically assessable disease and were therefore considered in CR.

Toxicities. Gastrointestinal toxicities occurred in seven out of 11 patients treated with neoadjuvant CHT-RT with 5FU *c.i.* and oxaliplatin and consisted primarily of diarrhoea up to grade 4 (one patient) and constipation (grade 2); other grade 2 toxicities included haematological in two cases, asthenia in two cases, neurological in one case and cutaneous in one case (Table IV).

Gastrointestinal toxicities occurred in three out of six patients treated with a postoperative CPT11-based regimen and consisted primarily of grade 2 diarrhoea and grade 3 vomiting or mucositis (one patient in each case); only two out of six patients treated with a postoperative oxaliplatin-based regimen, experienced grade 2 gastrointestinal toxicity (one diarrhoea and one nausea).

The incidence and severity of effects after CHT alone are shown in Table V.

Compliance and dose modifications. Chemotherapy was prematurely interrupted in four out of 21 patients preoperatively treated and in eight out of 32 patients postoperatively treated, due to toxicity (eleven patients), disease progression (five patients) or refusal (one patient). All 17 patients treated with preoperative CHT-RT and all five patients treated with postoperative CHT-RT received the full course of RT, with a total dose of 50.4 Gy.

Table I. *Tumour characteristics of 40 patients affected by metastatic mid-low rectal cancer.*

Characteristics	No	%
Age		
Median (range) yrs		
32-65	27	67.5
≥65	13	32.5
Gender		
Male	27	67.5
Female	13	32.5
Tumour distance from the anal verge		
na	5	12.5
≤7 cm	19	47.5
>7 cm	16	40.0
Pretreatment T stage		
T2	1	2.50
T3	23	57.5
T4	11	27.5
Tx	5	12.5
Pretreatment N stage		
N0	6	15.0
N1	19	47.5
N2	10	25.0
Nx	5	12.5

Tx, Nx=data not available.

Table II. *Type of treatment.*

	Neoadjuvant CHT alone	Neoadjuvant CHT-RT	Surgery
No. of pts	5	17	18
Type of therapy	Folfox4 5	5FU c.i. + Oxa 11 5FU c.i. 4 5FU bolo 2	RAR 8 (44.4) Miles 3 Colectomy 1 Colostomy 5

Pts=patients; c.i.=continuous infusion; Oxa=oxaliplatin; CHT=chemotherapy; RT=radiotherapy; RAR=rectal anterior resection; Miles=abdominal perineal resection.

Table III. *Treatment sequence.*

	Surgery* (after neoadjuvant therapy)		Postoperative (after surgery as first approach)	
	post CHT	post CHT-RT	CHT	CHT-RT
No. of pts	2	9	13	5
Type of therapy	RAR 2	RAR 3	Folfox4 5	5Fu c.i. + Oxa 4
		LAR 2	Muggia 1	5Fu c.i. 1
		Miles 2	Folfiri 5	
		Left colectomy 1	Folfiri + Folfox4 1	
		Colostomy 1	Machover	1
			Folfox4 5	-
			Folfiri 1	
			Machover 1	

Pts=patients; c.i.=continuous infusion; Oxa=oxaliplatin; CHT=chemotherapy; RT=radiotherapy; RAR=rectal anterior resection; LAR=low anterior resection; Miles=abdominal perineal resection. *after surgery: 11 pts.

Pathological response. A nodal status downstaging (cN+ to pN0) was observed at surgery in five out of eleven patients after CHT-RT with 5FU *c.i.* plus oxaliplatin and in one out of four patients after 5FU *c.i.* ($p=0.46$); a tumour downstaging (cT to pT) was observed in six out of eleven patients after CHT-RT with 5FU *c.i.* plus oxaliplatin and in one out of four patients after 5FU *c.i.* ($p=0.33$). The cytoreduction obtained by the addition of oxaliplatin therefore appeared to be increased compared to 5FU c.i alone, although not reaching statistical significance in this small sample (Table VI).

Associations between the tumour and the systemic responses are shown in Table VII.

Progression-free and overall survival. After a median follow-up of 15 months, 11 patients had progressed and 15 had died. The median time to progression and survival were 19.7 and 28.3 months, respectively. After progression, 10/11 patients had a second line of CHT (Table VIII).

Subgroup analysis. Because of the differences in the regimens, with or without RT, in the neoadjuvant or postoperative setting, it was not possible to compare DFS and OS according to type of CHT. Age ≥65 years had no impact on survival ($p=0.76$), conversely, the presence of peritoneal carcinomatosis in five patients showed a trend towards diminished survival ($p=0.08$). No difference according to tumour grade was found in terms of survival

Table IV. *Incidence and maximum severity of adverse events after the full dose of RT.*

RT (50.4 Gy)	Toxicity	NCI-CTC Grade			
		G1	G2	G3	G4
Pre-surgery	Haematological	10	2	0	0
+ 5FU c.i.	Neurotoxicity	1	2	0	0
(15 pts)	Diarrhoea	6	2	0	1
	Constipation	0	1	0	0
	Nausea	3	0	0	0
	Mucositis	1	0	0	0
	Asthenia	4	2	0	0
	Cutaneous	1	1	1	0
	Urological	4	0	0	0
Pre-surgery	Haematological	1	1	0	0
+ 5FU bolus	Diarrhoea	0	1	1	0
(2 pts)	Urological	1	0	0	0
Post-surgery	Haematological	2	0	0	0
+ 5FU + Oxa	Neurotoxicity	1	1	0	0
(4 pts)	Diarrhoea	0	0	1	0
	Constipation	1	0	0	0
	Nausea	0	1	0	0
	Mucositis	1	0	0	0
	Asthenia	0	1	0	0
Post-surgery	Nausea	1	0	0	0
+ 5FU c.i.	Vomiting	1	0	0	0
(1 pt)	Asthenia	1	0	0	0

Pts=patients; c.i.=continuous infusion; Oxa=oxaliplatin; 5FU=5fluorouracil; RT=radiotherapy; G=grade.

Table V. *Incidence and maximum severity of adverse events after CHT alone.*

CHT regimen	Toxicity	NCI-CTC Grade			
		G1	G2	G3	G4
Pre-surgery					
Folfox	Haematological	2	1	2	0
(5 pts)	Diarrhoea	0	2	0	0
	Constipation	1	0	0	0
	Mucositis	2	0	0	0
	Neurotoxicity	0	2	2	0
	Asthenia	0	2	0	0
	Cutaneous	0	2	0	0
Post-surgery					
Folfiri	Haematological	3	0	0	0
(5 pts)	Alopecia	2	0	0	0
	Diarrhoea	2	1	0	0
	Vomiting	0	0	1	0
	Mucositis	0	0	1	0
Folfox	Haematological	2	2	1	0
(5 pts)	Alopecia	0	1	0	0
	Diarrhoea	1	1	0	0
	Constipation	1	1	0	0
	Mucositis	1	0	0	0
	Urological	1	0	0	0
	Neurotoxicity	3	1	0	0
Folfiri → Folfox (1 pt)	Diarrhoea	1	0	0	0
Machover (1 pt)	---				
Muggia (1 pt)	----				

pts=patients; CHT=chemotherapy; G=grade.

(p=0.32), but information on grade was missing for 18 patients. The type of surgery (radical *versus* palliative) did not heavily impact on survival (p=0.1).

All four of the patients achieving CR after multimodality treatment were still disease-free and alive after a median follow-up of 19.3 months.

Discussion

At presentation, about 25% of patients with rectal cancer have synchronous distant metastases and a substantial proportion of them have minimal or no symptoms related to the primary tumour. In the presence of distant disease, the decision about the primary tumour treatment is complex and requires careful consideration. The critical point is whether the patient is a potential candidate for a curative resection of metastases or not. If the patient is a candidate, the primary tumour should be staged and treated as in a patient without metastatic disease with neoadjuvant CHT-RT and locoregional resection. The resection of metastases could then be carried out simultaneously with the primary tumour resection, depending on the number and the site of the lesions (24). If technical considerations, performance status (PS) or the presence of unresectable extrahepatic disease preclude liver resection, the focus of management should be palliative. In this situation, management of the primary tumour is controversial.

Palliative CHT increases the number of PR and prolongs the TTP, as well as improving OS and quality of life (25-27). According to some authors (28, 29), early resection of the primary lesion may prevent the need for urgent surgical resections at a later time, when the patient might be less fit and the disease more widespread or in extremis. However, others (30) affirm that the rate of eventual complications attributable to an unresected primary lesion is low and most

Table VI. *Local pathological response.*

Neoadjuvant therapy (no. patients)	Pathological local response				
	CR	PR	SD	PD	NA
Folfox 4 (5 pts)	1	1	3	0	0
5FU c.i. + oxaliplatin + RT (11 pts)	0	6	1	3	1*
5FU c.i. alone + RT (4 pts)	0	1	2	0	1*
5FU bolus + RT (2 pts)	0	0	0	2	0

c.i.=continuous infusion; RT=radiotherapy; CR=complete remission; PR=partial remission; SD=stable disease; PD=progressive disease; NA=not available. *Patient died at the end of CHT-RT so a re-evaluation was not performed.

Table VII. *Association between tumour and systemic response.*

Tumour response after neo CHT	No. of patients	Systemic response	
		CR	PR
5FU-oxaliplatin			
CR	0	0	0
PR	6	2	3
SD	0	0	0
5FU c.i./bolus			
CR	0	0	0
PR	1	0	1
SD	2	1	0
FOLFOX4			
CR	1	1	0
PR	1	1	0
SD	3	0	1

neo=neoadjuvant; CHT=chemotherapy; 5FU=5-fluorouracil; c.i.=continuous infusion; CR=complete remission; PR=partial remission; SD=stable disease.

of the patients with stage IV disease succumb to systemic disease before the development of a major complication related to an intact primary lesion. Thus, if there are no symptoms associated with the primary lesion, patients may undergo systemic disease-directed therapy without delay. These patients require ongoing careful observation with special attention to their intact primary lesions and the low, but measurable, risk of eventual obstruction, at which point prompt surgical therapy is mandatory.

Table VIII. *Association between treatment and state of disease.*

Treatment (no. of patients)	Response after treatment			State of patient
	After Neo CHT±RT (systemic response)	After surgery (local response)	After p.o. CHT or CHT-RT	
Neo CHT or CHT-RT and p.o. CHT (10 pts)	4 CR 3 PR	1 CR 6 PR	4 CR 3 PR 2 SD 1 PD	4 CR 6 alive with disease 0 dead
Radical surgery and p.o. CHT or CHT-RT (9 + 4 pts)	na	13 PR	13 PR	0 CR 7 alive with disease 6 dead
Only CHT-RT and then CHT (not surgery) (8 pts)	0 CR 2 PR	Na	1 PR 1 SD 2 PD 4 na	0 CR 4 alive with disease 4 dead

neo=neoadjuvant; p.o.=postoperative; CHT=chemotherapy; RT=radiotherapy; PD=progressive disease; CR=complete remission; PR=partial remission; SD=stable disease; na=not available.

In the present study (even if it was small), in asymptomatic patients with unresectable liver metastases, the best treatment was a CHT approach. At present, the introduction of concomitant RT is debated, nevertheless, in the present study, after a multimodality treatment 10% patients achieved CR and all of them were still disease-free and alive after a median follow-up of 19.3 months. In the future, to improve DFS and OS, prospective studies should evaluate the best non cross-resistant secondary regimens to add to the neoadjuvant CHT-RT and surgery in those patients with a local or systemic residual disease.

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