Neoadjuvant Chemoradiotherapy with 5-Fluorouracil by Bolus

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Abstract. *Background: Neoadjuvant chemoradiotherapy (CT-RT) with continuous infusion (c.i.) 5-fluorouracil (5-FU) before resection of high-risk rectal cancer improves overall survival (OS) and pelvic control. Since the presence of cardiomiopathy may contraindicate c.i. of 5-FU, an alternative regimen of 5-FU CT-RT was prospectively studied in these patients. Patients and Methods: From October 2000 to December 2006, patients with clinical stage T3 or T4, or node-positive disease were assigned according to their cardiological status to receive weekly 5-FU bolus administration during radiotherapy (RT). The preoperative treatment consisted of 5,040 cGy, delivered in fractions of 180 cGy per day, five days per week, and 5-FU, given in 15 minutes at a dose of 450 mg/m^2 of body surface area weekly during all radiotherapy. Surgery was performed six weeks after the completion of CT-RT. The primary endpoint was disease-free survival (DFS). Results: Fifty-one patients received preoperative CH-RT. The 2-year OS rate was 92.3% and the 3-year DFS was 87.5%. The five-year cumulative incidence of local relapse was 3.9%. Grade 3 acute toxic effects occurred in 19.6% of the patients; worsening of patient's cardiopathy was never reported. Conclusion: Patients with cardiopathy developed similar local control and DFS, toxicity and OS with 5-FU administered weekly by bolus as those reported by literature data.*

Postoperative chemoradiotherapy (CT-RT) for rectal cancer has improved overall survival (OS) and pelvic control (1-4) but only recently, have preoperative trials addressed chemotherapy radiosensitization to reduce locoregional failure. In fact, protracted venous infusion (PVI) of 5-fluorouracil (5-FU) is the more common treatment. Seven phase III trials comparing PVI *versus* bolus indicated improved response rates (RR) in metastatic disease (5-12); this improvement has raised the possibility that PVI might eradicate subclinical distant metastasis more effectively in the adjuvant and neoadjuvant setting too, improving radiosensitization (13-17). In the Intergroup (INT) 864751 trial, where PVI *versus* bolus 5-FU were compared, bolus 5-FU was administered before, during and after pelvic radiotherapy (RT) *versus* the same pre- and post-CT-RT schedule, but with PVI administered with RT. Improved OS and disease-free survival (DFS) were observed with the latter schedule (4).

When Chau *et al.* (18) randomly administered resected colorectal cancer patients 6 months of bolus 5-FU/leucovorin (LV) *versus* 12 weeks of PVI 5-FU, PVI 5-FU improved DFS and OS (although without statistical significance) with less toxicity. Biochemical modulation of 5-FU also generated interest. Improvement in OS was observed in several adjuvant extrapelvic colon trials using 5-FU modulated by LV (19-21) or levamisole (22-24). In addition, reports suggested that biochemically modulated 5-FU improved survival in advanced disease (25-27).

The INT 0114 trial tested bolus 5-FU alone, 5-FU plus LV, 5-FU plus levamisole and 5-FU plus LV plus levamisole, all with pelvic RT (28, 29). No OS or DFS difference was observed. Outcome was similar to the PVI arm of INT 864751, raising the possibility that a bolus-alone 5-FU schedule might obviate the requirement for a central venous catheter. Toxicity was different however.

PVI 5-FU is associated with an incidence of cardiotoxicity of 7.6-18% *versus* 1.6-3% reported after bolus 5-FU (30-32). In fact, cardiotoxicity is more frequent after prolonged (more than 5 days) and/or high doses of PVI 5-FU (more than 800 mg/m^2) (33-35) than after 2 or 3 days' infusion (*i.e.* De Gramont regimen); in these cases cardiotoxicity is about 4% (36, 37). Cardiotoxicity pathogenesis is still unknown; some authors have reported direct damage to myocardiocytes (38,

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39), an autoimmune phenomenon (40), fluoracetaldehyde-mediated damage (41) and damage to the vascular endothelium with consequent coronary vasospasm (42, 43). The most frequently described events are angina, acute myocardial infarction, rhythm alterations (44), congestive cardiac failure or sudden death (37). Symptoms usually disappeared after therapy interruption and specific cardiological therapy. Cardiotoxicity may be acute (45, 46) or can appear after some cycles (47, 48).

The purpose of this study was to determine whether administration of weekly bolus 5-FU plus RT in patients with cardiomyopathy could give the same outcome (OS and DFS) with less toxicity than in those patients undergoing PVI 5-FU.

Patients and Methods

Eligibility criteria. Patients were required to have locally advanced non-metastatic rectal adenocarcinoma. Extension through the muscularis propria and/or nodal spread (T3-4, N0 or T1-4, N1-3) following transrectal ultrasonography and/or pelvic computed tomography scan was necessary. Rectal cancer was defined as the presence of a tumor below the peritoneal reflection or ≤11 cm from the anal verge. Patients with dentate involvement were eligible. Patients were older than 18 years, with 0 to 2 performance score and were not pregnant or lactating. No prior chemotherapy or radiation therapy for rectal cancer or prior history of rectal cancer (with the exception of previously resected T1-2, N0, M0 tumours) was allowed. Satisfactory pretreatment laboratory parameters and the absence of serious illness (with the exception of those involving the cardiovascular system) were required; only cardiopathic patients (*e.g.* those with arrhythmia, ischemic heart disease, previous heart failure) or those with uncontrolled blood pressure (with hypertensive peaks despite ongoing treatment) were considered (Table I). Chest x-ray and abdominopelvic computed tomography scans were required within 56 days of treatment start. Each patient gave written consent before starting treatment.

Chemotherapy. Patients received a bolus neoadjuvant CT-RT regimen. The following treatment was used: bolus 5-FU at 450 mg/m^2/weekly for 6 weeks during RT. Appropriate dose modifications (by 20, 25 or 50%) were applied after grade 2 or 3 toxicities prolonged for more than 2 weeks.

Adjuvant chemotherapy was administered according to the clinical TNM to all patients with positive lymph nodes.

Radiotherapy. Radiotherapy 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 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 bony sacral margin. All patients received a total dose of 50.4 Gy (45 Gy/25 fractions in 5 weeks to the posterior pelvis followed by a 5.4 Gy/3 fractions boost to the tumour), as specified according to the International Commission on Radiation Units and Measurements 50 report with daily fractions of 1.8 Gy on 5 consecutive days per 5.5 weeks.

Surgery. Four to six weeks after completion of CT-RT, resectability was assessed by clinical examination and a CT scan of the pelvis. In low-lying tumours, the possibility of sphincter preservation was determined by the surgeon at the time of surgery. The following general guidelines were followed: i) A pelvic CT scan, endosonography of the rectum and/or rectosigmoidoscopy and CEA post CT-RT were performed within 2 weeks of the planned surgery date. ii) Intended type of operation was documented at baseline. iii) Total mesorectal excision was performed where technically feasible. iv) Defunctioning stoma was highly recommended for lower rectal lesions with reversal at the surgeon's discretion but it was recommended that this take place after completion of adjuvant chemotherapy. v) Postoperatively, the surgeon had to document the type of surgery performed and the completeness of the procedure (mesorectal fascia intact, mesorectal fascia breached, or obvious margin involvement).

Histopathological assessment of response to CT-RT. Surgical specimens were classified according to the American Joint Committee on Cancer TNM classification (49).

Response of the primitive tumour was considered a downstaging of either T or N, when compared to baseline parameters (50).

Study design, definitions and endpoints. All eligible and consenting patients (the full analysis population) were included in the analyses of OS and DFS and the cumulative incidence rates of local and distant recurrences, according to the intention-to-treat principle. Endpoints were measured beginning at the start of treatment.

The aim of the study was to evaluate rectal cancer DFS in a group of patients receiving a combined neoadjuvant treatment. Secondary endpoints were OS, local and distant recurrences, postoperative complications, acute and long-term toxic effects, and sphincter preservation. Patients who received neoadjuvant radiotherapy were assessed for acute and delayed toxic effects. Patients who refused treatment were not included in toxicity analyses.

OS was computed from the start of chemotherapy to death of any cause. Survival of patients lost at follow-up was confirmed by phone interview or by consultation of municipal records and was censored at the latest day they were known to be alive. Median DFS was defined as the time from the end of neoadjuvant chemotherapy to local or systemic progression, or to death attributable to rectal cancer or treatment toxicity. Patients dying of other causes were censored for progression at their date of death. Median DFS and OS were estimated using the Kaplan-Meier method (51). Prognostic factors for survival such as age (more or less than 70 years), T stage (T3 *versus* T4), N stage (cN+ *versus* N) and response to neoadjuvant CT-RT (= downstaging) were tested by means of a two-sided log-rank test. Data from patients who were alive and free of recurrence or who died without having had a recurrence were censored in the analyses of disease-free survival and recurrence. Any pT0N0M0 was defined as pCR; any cT or cN reduction was defined as partial remission (PR); any cT or cN increase was defined as progressive disease (PD).

Chi-squared and Fisher's exact tests were used to compare patient frequencies.

All statistics were performed by means of Statistica software, version 6 (Statsoft, Inc., Tulsa, OK, USA).

Table I. *Cardiomyopathy definition according to Common Toxicity Criteria v 3 (55).*

Conduction abnormality/atrioventricular heart block
– Asystole
– AV Block-First degree
– AV Block-Second degree Mobitz Type I (Wenckebach)
– AV Block-Second degree Mobitz Type II
– AV Block-Third degree (Complete AV block)
– Conduction abnormality NOS
– Sick sinus syndrome
– Stokes-Adams syndrome
– Wolff-Parkinson-White syndrome
Palpitations
Prolonged QTc interval
Supraventricular and nodal arrhythmia
– Atrial fibrillation
– Atrial flutter
– Atrial tachycardia/paroxysmal atrial tachycardia
– Nodal/junctional
– Sinus arrhythmia
– Sinus bradycardia
– Sinus tachycardia
– Supraventricular arrhythmia NOS
– Supraventricular extrasystoles (premature atrial contractions; premature nodal/junctional contractions)
– Supraventricular tachycardia
Vasovagal episode
Ventricular arrhythmia
– Select
– Bigeminy
– Idioventricular rhythm
– PVCs
– Torsade de pointes
– Trigeminy
– Ventricular arrhythmia NOS
– Ventricular fibrillation
– Ventricular flutter
– Ventricular tachycardia

Results

Patient characteristics. From October 2000 to December 2006, 51 consecutive rectal cancer patients were enrolled. Their median age was 69 years (range, 69-84 years). Patient characteristics are listed in Table II.

All patients received the prescribed radiotherapy but 88.2% only completed preoperative CT as planned. Major protocol deviations occurred in 3 (5.9%) patients, mainly due to toxic effects; only 1 patient had a dose reduction.

All except 6 patients were operated on (3 are still waiting for surgery) and nobody reported any relevant postoperative complications. Nine patients underwent low rectal excision (LAR) (17.6%), 24 underwent rectal anterior excision (RAR) (47%), 5 abdominal-perineal excision (Miles) (9.8%); 1 Hartmann, 3 hemicolectomy, 3 transanal excision and 1 explorative laparotomy were also reported.

Nineteen patients underwent adjuvant chemotherapy with 5-FU.

Table II. *Characteristics of the tumour and of 51 mid-low rectal cancer patients.*

Characteristic	
Age, years	
Median	69
Range	49-84
Gender	
Male	34
Female	17
Cardiac disease	
Chronic atrial fibrillation	8
Myocardial infarction	8
Angina	2
Badly controlled hypertension	33
Tumour distance from the anal verge	
≤5 cm	21
6-11 cm	30
N stage (%)	
0	23
1	20
2	8
T stage (%)	
2	1
3	43
4	7

Histopathological tumour staging and surgical procedures. Within 45 evaluable patients, there was a significant shift toward earlier TNM stages: 2 patients had a pCR (4.4%) according to histopathological examination of the tumor specimen and only 24.4% (as compared with 60% in the preoperative-treatment group) had positive lymph nodes (TNM stage III). Tumour downstaging was reported for 33 patients [73.3%; 95% confidence interval (CI), 60.4 to 86.3%) (Table III). A sphincter-sparing surgery, in those patients with tumors that were determined by the surgeon before randomization to require an abdominoperineal excision (≤7 cm from the anal line), was obtained in 26 cases (89.6%).

Postoperative morbidity and toxicity of CT-RT. No in-hospital mortality occurred. The overall rate of postoperative complications (with consequently more than 13 days of hospitalization) was 33.3%: the rate of anastomotic leakage of any grade was 11.1%, delayed sacral-wound healing 11.1%, postoperative bleeding 2.2% and ileus 8.7%.

Grade 3 or 4 acute and long-term toxic effects that occurred among patients who received preoperative CT-RT are summarized in Table IV. The overall rate of toxic effects was about 19.6%. Nobody reported acute cardiological problems for the rest of the entire follow-up period. Annual electrocardiogram, echocardiogram and cardiological assessment never reported a cardiological worsening.

Table III. *Tumour downstaging after neoadjuvant therapy within 45 resected patents.*

cTNM	No. of patients (no. CR + PR)	Tumour downstaging	%
T2N1	1	0 + 1	2.2
T3N0	18	2 + 9	24.4
T3N1	13	0 + 9	20.0
T3N2	7	0 + 6	13.3
T4N1	5	0 + 5	11.2
T4N2	1	0 + 1	2.2

CR, complete remission; PR, partial remission.

Table IV. *Toxic effects of CT-RT, according to treatment received.*

Toxicity	Grade 1-2 (%)	Grade 3-4 (%)
Cutaneous	16 (31.4%)	6 (11.8%)
Gastrointestinal		
Diarrhoea	23 (45.1%)	4 (7.8%)
Vomiting	5 (9.8%)	0
Mucositis	2 (3.9%)	0
Cardiological	0	0
Haematological	25 (49.0%)	0

Events during follow-up. As of April 2007, surviving patients had been followed for a median of 36.7 months (range, 4 to 78 months). Of the 9 deaths (17.6%) that occurred during follow-up, 7 were related to rectal cancer and 2 to other causes. Thirteen patients have relapsed (25.5%), either locally (2 patients), or at distance (10 patients), or both (1 patient). Ten patients experienced metastasis and underwent palliative chemotherapy.

Overall and disease-free survival. Disease-free and OS at 2 years were 87.5% and 92.3%, respectively. The Kaplan-Meier curve for progression and OS of all 51 patients is shown in Figure 1.

Age over 70 years (p=0.71), clinical T4 disease (p=0.51), nodal involvement (p=0.16) and administration of adjuvant chemotherapy (p=0.56) did not impact on DFS, while downstaging after neoadjuvant CT-RT had a marginal trend towards delayed relapse (p=0.09).

The same prognostic factors were tested for significance on OS and none of them appeared to have any impact on survival (age, p=0.77; clinical T stage, p=0.92; clinical N stage, p=0.31; downstaging after neoadjuvant CT-RT, p=0.22; administration of adjuvant chemotherapy, p=0.31).

Two patients achieving CR after neoadjuvant chemotherapy did not receive adjuvant chemotherapy. They are still alive and disease free after 30.7 and 51 months, respectively.

At 3 years, 64.3% of cN+ (stage III) and 86.9% of cN0 (stage II) patients were relapse free according to Kaplan-Meier estimations (p=n.s.) and 75% and 91.3% of them, respectively, were still alive.

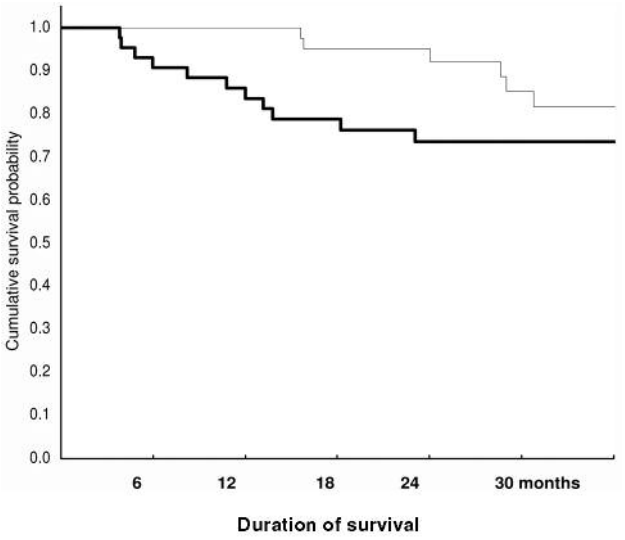

Figure 1. *Disease-free survival (bold line) and overall survival (thin line) of 51 patients.*

Yet, persistence of nodal disease after neoadjuvant CT-RT significantly predicted local relapse considering that 2 out of 3 locally recurrent patients were pN+ (66.7%), but this did not correlate with systemic disease since only 5 out of 11 systemically recurrent patients were pN+ (45.4%). Two out of 3 locally recurrent patients (66.7%) were pPR; the other was pSD.

Discussion

Interest in preoperative CT-RT for patients with resectable rectal cancer is based not only on the expected survival benefit achieved with this treatment, but also on the potential advantages of delivering both agents preoperatively. These advantages include improved compliance with the CT-RT regimen if it is given before major surgery, as well as downstaging, which may enhance the rate of curative surgery and permit sphincter preservation in patients with low-lying tumours. In addition, because tumour oxygenation is better with preoperative treatment than with postoperative treatment, irradiation seems to be more effective with the former approach (52). Retrospective, nonrandomised studies have also found reduced toxicity with preoperative treatment (53). Prospective, randomised trials comparing the efficacy of preoperative CT-RT with that of standard, postoperative CT-RT for rectal cancer were initiated in the United States by the Radiation Therapy Oncology Group (RTOG) (trial 94-01) and the National Surgical Adjuvant Breast and Bowel Project (protocol R-03) (54). Unfortunately, both studies suffered from low enrolment and were closed prematurely.

In our study, we confirmed that preoperative CT-RT, given as planned (*i.e.* without any modification or dose reduction), significantly reduced rates of local failure and acute and

long-term toxic effects, as in literature data reported with PVI 5-FU, with the advantage of a total absence of cardiotoxicity also in those patients with the worst cardiac failure. Among patients with tumours judged by the surgeon to require an abdominoperineal excision, the rate of sphincter-preserving surgery was more than doubled after preoperative CT-RT. Postponing surgery for a six-week course of neoadjuvant treatment plus a six-week interval to allow tumour shrinkage and recovery from side-effects did not result in an increased rate of surgical complications or an increased incidence of tumour progression.

Given that the rate of local recurrence with preoperative CT-RT and total mesorectal excision was only 6%, satisfactory results in cardiopathic patients or those with uncontrolled blood pressure were achieved even if without the standard PVI 5-FU and independently of age (the mean age was 69 years).

Conclusion

Preoperative CT-RT would appear to be the preferred treatment for patients with locally advanced rectal cancer, given that it is associated with a superior overall compliance rate, an improved rate of local control, reduced toxicity and an increased rate of sphincter preservation in patients with low-lying tumours. No cardiological toxicity was observed even in those patients who had reported cardiomiopathy or hypertension in their medical history. This means of administration is a good opportunity for those patients who, due to their physical condition, otherwise would not have been treated, depriving them of the possibility of a better survival.

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