Rectal Cancer Neoadjuvant Treatment in Elderly Patients

LARA MARIA PASETTO[1], MARIA LUISA FRISO[2], SALVATORE PUCCIARELLI[3], UMBERTO BASSO[1], CRISTINA FALCI[1], ALBERTO BORTOLAMI[1], PAOLA TOPPAN[3], MARCO AGOSTINI[3], MASSIMO RUGGE[4], SAMANTHA SERPENTINI[3], DONATO NITTI[3] and SILVIO MONFARDINI[1]

[1]Medical Oncology Department, [2]Radiotherapy, [3]Second Surgical Clinic and [4]Pathology, Istituto Oncologico Veneto, Padova, Italy

Abstract. *Background: The aim of the study was to evaluate the differences in terms of toxicity and feasibility of neoadjuvant 5-fluorouracil (5FU) continuous infusion (c.i.) or bolus in combination with pelvic radiotherapy (RT) in locally advanced rectal cancer "fit" or "vulnerable" elderly patients. A secondary endpoint was to identify any specific comorbidity that affected either effectiveness or morbidity of treatment. Patients and Methods: From June 2000 to June 2005, 36 patients over 70 years of age out of a total of 88 consecutive elderly cases were retrospectively examined. Variables considered were age, gender, modality of 5FU administration and comorbidities (evaluated according to Cumulative Illness Rating Scale-Geriatric, CIRS-G). Results: Median age was 74 years (range, 70–82) years and the male:female ratio, 22:14. Fourteen % of the patients healthy and 25% with slight comorbidities were considered "fit" and 61% "vulnerable". All the patients received the full course of RT. The mean number of chemotherapy weeks was 5.34 (range, 2-6); "vulnerable" patients did not experience higher toxicity compared to "fit" patients (p=0.69). Eighty-nine % of the patients were operated without relevant postoperative complications. Thirteen out of 20 "vulnerable" and 10 out of 12 "fit" patients had a pathological downstaging of disease (p=0.24). Conclusion: Selected elderly "vulnerable" patients with rectal cancer can receive the same neoadjuvant 5FU-based chemoradiotherapy (either bolus or c.i.) and undergo surgery as well as "fit" elderly patients, since tolerability and response rate seem to be similar in both categories of patients.*

The incidence of colorectal cancer is approximately 650,000 cases per year worldwide and 30,000 in Italy (1). In patients over 85 years of age, colorectal cancer constitutes one third of all neoplasms. Of the 65-71% of all patients with rectal cancer aged 65 years or older (2), only 24% receive additional therapy (RT or chemotherapy) following an operation, compared to 44% of those under 60 years of age. Moreover, for those over 80 years of age, chemo-radiotherapy (CHT-RT) is administered in only 8% of the cases (3, 4). Concerning preoperative CHT-RT there are sufficient data supporting the use of chemotherapy in "fit" elderly patients (patients with no functional dependence in activity of daily living [ADL] and instrumental ADL [IADL], no relevant comorbidities, no geriatric syndromes) who can tolerate cytotoxic treatment, but there are few data about prospective studies in "vulnerable" elderly patients (5-9).

In the few randomised studies, in which neoadjuvant CHT-RT with 5FU resulted in higher response rate (RR) than to RT alone (10-12) and to postoperatory CHT-RT (13-15), data on elderly patients were retrospectively extrapolated. Up to now, 5FU (bolus, infusional or peroral, unmodulated or biochemically modulated) has been the drug more studied in all age groups (13, 16-19). Changes in its schedule have shown that continuous infusion (*c.i.)* administration is associated with a RR, but not an overall survival (OS), better than bolus administration (pCR of 67% *versus* 10%) (20-22). *C.i.* significantly increases the time of cancer exposure; this permits the achievement of a maximum tolerated dose (MTD) higher than that obtained with bolus administration and it also modifies the type of toxicity (from neutropenia to palmar-plantar erythrodysesthesia) being used less in cardiological patients (the majority of which are elderly patients). Disadvantages of 5FU *c.i.* include inconvenience because of technical requirements, such as central venous access, portable pump and cost, and the 15% to 20% incidence of significant complications such as infections, bleeding, thrombosis and pneumothorax, which have a negative impact on quality of life of elderly patients.

Less than 20% of patients aged 65 years, affected by colorectal cancer or other tumours, are usually included in clinical trials and they represent the minority of the very "fit" patients (23). Commonly, major barriers excluding participation in clinical trials are aggressive therapies with

Correspondence to: Lara Maria Pasetto, Istituto Oncologico Veneto, Divisione di Oncologia Medica, Via Gattamelata 64, 35128 Padova, Italy. Tel: +39-049-8215931, Fax: +39-049-8215932, e-mail: laramary@libero.it

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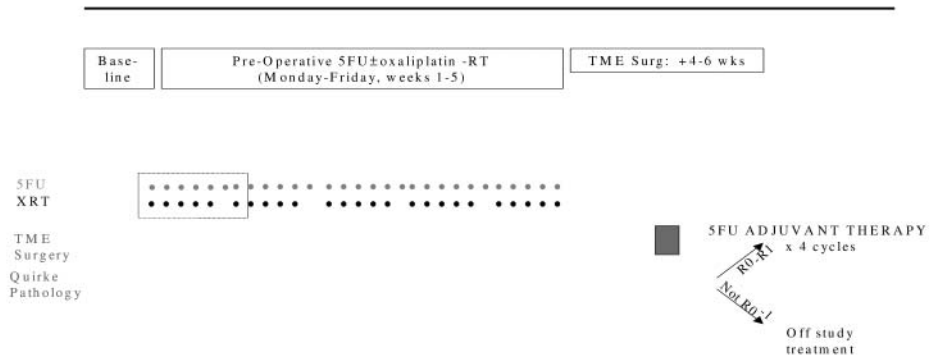

Scheme 1. *Study treatment program.*

substantial toxicity, the large number of coexisting illnesses, the small number of trials designed for older patients, the patients' limited expectations of long-term benefits and the lack of financial, logistic and social support (24). In addition, age-related differences in the metabolism of chemotherapeutic agents exist, but these differences may not be clinically significant if older patients are in good health (25).

In our retrospective study we analysed the toxicity and efficacy of 5FU bolus or *c.i.* plus standard RT administration, in a group of patients older than 70, that we divided into the "fit" or "vulnerable" groups according to their morbidities, and we tried to observe how and if comorbidities could affect these results.

Patients and Methods

Eligibility criteria. From June 2000 to June 2005, 36 patients over 70 years of age out of a total of 88 consecutive elderly cases (from a group of 300 locally advanced low and middle rectal cancer patients of all age) were retrospectively examined at the Medical Oncology Division, Istituto Oncologico Veneto, Padova, Italy.

Inclusion criteria were: age ≥70 years, histologically proven rectal tumour located up to 12 cm from the anal verge by rigid proctoscopy, no synchronous colon cancer assessed by colonoscopy, clinical stage II-III (cT3-4/ and or N positive) following transrectal ultrasonography and/or pelvic computed tomography (CT) scan, no distant metastases assessed by abdominal and thoracic CT scan, Eastern Cooperative Oncology Group performance status 1, and adequate haematologic, liver and renal functions (neutrophils $1.5x10^9$/L, platelet count $100x10^9$/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).

A complete multidimensional geriatric assessment (MGA) was not possible in all patients so, comorbidities were evaluated according to Cumulative Illness Rating Scale-Geriatric (CIRS-G) (26) or Charlson's score and patients were retrospectively deemed "fit" if they were otherwise healthy or had one or more comorbidities of only grade 1; "vulnerable" if they had one or more comorbidities of grade 2 or 3. Each patient gave written consent before starting treatment.

Patients were excluded if they had prior RT to the pelvic region or previous cytotoxic chemotherapy or if they had other synchronous cancers. Patients suffering from the following conditions were also ineligible: inflammatory bowel disease, malabsorption syndrome, congestive heart failure, angina pectoris not medically controlled, recent ischemic heart disease, peripheral neuropathy, serious uncontrolled active infection and psychiatric disorders or psychological disabilities thought to adversely affect treatment compliance.

RT. 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 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 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.

Chemotherapy. 5FU was delivered by *c.i.* at a fixed dose of 225 mg/m^2 daily ± oxaliplatin 85 mg/m^2 weekly (in 7 cases) or by bolus 450 mg/m^2 weekly (in 4 cases), continuously for approximately 5.5 weeks, from the first to the last day of RT. In some cases capecitabine substituted 5FU and it was delivered at 825 mg/m^2 twice daily Monday-Friday of weeks 1-5 (a total of 25 days dosing) in combination with oxaliplatin 50 mg/m^2 weekly for 5 weeks.

Dose modification. The following recommendations for chemotherapy dose reductions were applied. In patients who experienced grade 3 toxicity, according to the National Cancer Institute Common Terminology Criteria, Version 3 (NCI-CTC) (27), 5FU 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 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 investigators' committee considered it to be in the best interest of the patient to continue at 50% of the original 5FU dose, once toxicity had resolved to grade 0-1. Patients were monitored by weekly history, ECOG performance status, clinical examination, full haematology, blood biochemistry and liver function tests.

Surgery. Four to six weeks after completion of CHT-RT, resectability was assessed by clinical examination and CT scan of the pelvis. In low-lying tumors, the possibility of sphincter preservation was determined by the surgeon at the time of surgery. The following general guidelines were followed:

- A pelvic CT scan, endosonography of the rectum and/or rectosigmoidoscopy and CEA post CHT-RT were performed within 2 weeks of the planned surgery date.
- Radical resection; intended type of operation was documented at baseline.
- Total mesorectal excision (28) was performed, where technically feasible except for upper rectal lesions, where partial total mesorectal excision might be more appropriate.
- Defunctioning stoma was highly recommended for lower rectal lesions with reversal at the surgeon's discretion, but it was recommended that this should take place after completion of adjuvant chemotherapy.
- Surgeon had to document post-operatively the type of surgery performed and the completeness of the procedure (mesorectal fascia intact, mesorectal fascia breached, or obvious margin involvement).

Histopathologic assessment of response to chemoradiotherapy. Surgical specimens were reviewed by two pathologists who were unaware of the patients' outcome and reported findings following the American Joint Committee on Cancer TNM classification.

Study design, definitions and end points. The primary objective of the study was to evaluate the safety and tolerability of neoadjuvant chemoradiotherapy in "fit" and "vulnerable" patients over 70 years of age. Secondary end points were to evaluate the differences in terms of safety and tolerability of 5FU *c.i.* or by bolus in elderly patients (assessing the clinical tumour and lymph node response and the pCR rate, according to the UICC 2002 criteria); to identify any specific comorbidity that affected either effectiveness or morbidity of treatment.

Any pT0N0M0 was defined as pCR; any cT or cN reduction was defined as partial remission (PR); any cT or cN increase or any M1 was defined as progressive disease (PD).

Chi-squared or Fisher's exact tests were used to evaluate prognostic factors for response and for toxicity (aged more or less than 75 years, gender, Charlson's score of 0 *versus* 1 or more, *c.i. vs.* bolus chemotherapy). Median time to progression (TTP) was defined as the time from start of neoadjuvant chemotherapy to local or systemic progression or to death for any cause. OS was computed from start of chemotherapy to death for any cause. Survival of patients lost at follow-up was checked by phone interview or by consultation of municipal registries and was censored at the latest day they were known to be alive. Median TTP and OS were estimated using the Kaplan-Meier method (29). Prognostic factors for survival were tested by means of a two-sided log-rank test.

Table I. *Characteristics of 36 elderly patients who underwent preoperative CT-RT for mid-low rectal cancer.*

Characteristics	No	%
Age median (range) yrs		
≥70 to 75	13	63.9
>75 to 82	23	36.1
Gender		
male	22	61.1
female	14	38.9
Tumor distance from the anal verge		
≤7 cm	23	63.9
>7 cm	13	36.1
Preoperative T stage		
T2	5	13.9
T3	25	69.4
T4	6	16.7
Preoperative N stage		
N0	16	44.4
N1	17	47.2
N2	3	8.4

Results

Patients characteristics. From June 2000 to June 2005, 32 (also evaluable for pCR rate) out of 36 (88.9%) consecutive enrolled patients (all evaluable for toxicity and survival) ≥70 years of age with primary adenocarcinoma of the middle and low rectum underwent surgery following CHT-RT (Tables I, II). Twenty three patients (71.9%) received an adjuvant chemotherapy because of clinical and pathological stage, while 10 (43.5%) did not (2 for metastatic disease, 6 for refusal, 2 for the long time lapsed from surgery). Excluding the 3 out of 32 patients with metastatic disease at the re-evaluation, only 1 out of 29 (3.4%) locally progressed (without metastatic disease) and is still alive.

Fourteen patients (5 healthy, 13.8%, and 9 with slight comorbidities, 25%) were "fit" and 22 (61.2%) were "vulnerable". Thirty one patients had one (19.4%) or more (69.6%) comorbidities, with a mean number of 2.1 comorbidities per patient. Nineteen patients had a Charlson's score of 0, 14 of 1 and the remaining 3 of 2.

Toxicities. Gastrointestinal toxicities occurred in 22 (61.1%) out of all patients and consisted primarily of grade 1 (25%) or 2 (13.9%) diarrhea; only 2 out of 4 patients (50%)

Table II. *Patient comorbidities.*

Pts	Age	Comorbidities	Charlson score
1	70	Hypertension G1, diabetes G1, ischemic cardiopathy G2	2
2	70	Prostatic hypertrophy G1	0
3	70	Hypertension G1, C hepatitis G2	0
4	71	Hypertension G1, duodenal ulcer G2, hiatus hernia G1, lung embolism G2	2
5	71	Hypertension G1, rettocolite G1, B hepatitis G2, bronchopneumopathy G2	1
6	71	Hypertension G2, diabetes G1, gastritis G1, urolithiasis G1	1
7	71	Hypertension G1	0
8	71	Diverticolosis G1, colloids struma G1, hypercolesterolemy G1	0
9	71	-	0
10	71	Diabetes G1	1
11	71	Carotid stenosis G2, duodenal ulcer G1	1
12	72	-	0
13	72	Hypercolesterolemy G1	0
14	72	Hypertension G1	0
15	72	Hypertension G1, diabetes G1, atrial fibrillation G2	1
16	73	-	0
17	73	Hypertension G2	0
18	73	Hypertension G1, C hepatitis G2	0
19	74	Prostatic hypertrophy G1	0
20	75	Transitory ischemic attack G2	1
21	75	Gastritis G1, duodenal ulcer G1, prostatic hypertrophy G1	1
22	75	Hypertension G1 , mitralic prolapse G2	1
23	75	Hypertension G1, diabetes G1, diverticolosis G1	1
24	77	Hypertension G2, hypercolesterolemy G1	0
25	77	Ischemic cardiopathy G2	1
26	78	Hypertension G2, diabetes G1	1
27	78	Hypertension G2, gastric ulcer G1, prostatic hypertrophy G1	1
28	78	-	0
29	79	Hypertension G1, hypercolesterolemy G1, transitory ischemic attack G2	1
30	79	Hypertension G2	0
31	79	Hypertension G1, diabetes G1, cardiopathy G2	2
32	80	Hypertension G2, B hepatitis G1	0
33	80	-	0
34	80	Emphysema G2, atrial fibrillation G2	1
35	81	Hypertension G1, hyperglycaemia G1	0
36	82	Prostatic hypertrophy G2, urolythiasis G1	0

G=grade according to the CIRS-G score.

treated with 5FU and oxaliplatin, experimented grade 4 diarrhea and stopped chemotherapy for 3 weeks. Nausea, vomiting, mucositis or constipation were less frequent (27.8%) and of low grade. Grade 3 cutaneous toxicity was restricted to 3 (8.3%) patients. Haematological toxicity did not exceed grade 1 except 1 case of grade 2 anaemia (2.8%) after 5FU *c.i.* and another of grade 2 leucopenia (2.8%) after 5FU bolus (Table III).

"Vulnerable" patients did not experience higher toxicity compared to "fit" patients (8 out of 22 "vulnerable" and 6 out of 14 "fit" patients developed toxicities ≥2 , $p=0.69$) even with the different 5FU regimen administration within both groups (72.7% "vulnerable" patients *versus* 14.3% of "fit" patients were treated with 5FU bolus). Also patients with Charlson's score of 1 or more compared to those with a score of 0 (36.8 and 41.2%, respectively, $p=0.79$), as well as patients ≥75 years compared to 70-75 years old patients (30.7 and 43.5%, respectively, $p=0.34$), did not experience toxicity ≥ grade 2. Conversely, females displayed an increased incidence of toxicities ≥ grade 2 (64.3%) compared to males (22.7%, $p=0.16$).

Eight patients out of 18 (44.4%) receiving 5FU bolus chemotherapy experienced toxicities ≥ grade 2 compared to 5 out of 18 treated with *c.i.* 5FU (27.8%), but the difference was not statistically significant ($p=0.29$).

Compliance and dose modifications. All patients received the full course of RT, with a total dose of 50.4 Gy while a total of 6 weeks of chemotherapy was only administered to 23 patients (63.9%). The mean number of weeks was 5.34 (comparable in "fit" and "vulnerable" patients: 5.4 *versus* 5.28, respectively), ranging from 2 to 6 weeks. Four out of 14

Table III. *Incidence and maximum severity of adverse events.*

Toxicity	NCI-CTC Grade							
	1		2		3		4	
	N° pts	%	N° pts	%	N° pts	%	N° pts	%
Diarrhea	9	25	5	13.9	1	2.8	2	5.5
Nausea	3	8.3	0	0	0	0	0	0
Vomiting	1	2.8	0	0	0	0	0	0
Stomatitis	3	8.3	1	2.8	0	0	0	0
Proctitis	7	19.4	1	2.8	3	8.3	0	0
Fatigue/asthenia	6	16.7	1	2.8	0	0	0	0
Anaemia	11	30.5	1	2.8	0	0	0	0
Leucopoenia	7	19.4	1	2.8	0	0	0	0
Thrombocytopenia	6	16.7	0	0	0	0	0	0

(28.6%) "fit" patients and 9 out of 22 (40.9%) "vulnerable" patients had to interrupt chemotherapy prematurely because of toxicity ($p=0.26$). One "vulnerable" patient treated with capecitabine and oxaliplatin received 5 weeks of therapy according to the protocol. One "fit" patient (2.8%) required dose reduction for grade 4 diarrhea and one "vulnerable" patient (2.8%) for grade 3 cutaneous toxicity; both patients had been treated with 5FU and oxaliplatin.

Surgical morbidity. Six weeks after completion of CHT-RT, patients were reassessed for surgery.

With the exception of 2 "fit" and 2 "vulnerable" patients who were lost from follow-up before surgery, 32 patients (88.9%) were operated. Thirty cases (12 out of 14 "fit" patients – 85.7% - and 18 out of 22 – 81.8% - "vulnerable" patients) were radically resected without postoperative complications. Thirteen out of 20 "vulnerable" and 10 out of 12 "fit" patients had a pathological downstaging of disease ($p=0.24$).

Within the 3 cases of PD, 2 (66.6%) received an anterior rectal resection (RAR), the third was unresectable so a colostomy was performed. In total, 32 patients (88.9%) underwent surgery; 2 of them (6.2%) experienced perioperative complications (anastomosis dehiscence and haemorrhage).

Within the 29 patients with locally advanced resectable rectal cancer, 4 patients (13.8%) underwent abdominal perineal excision (Miles), 20 (69%) RAR, 2 (7%) low anterior resection (LAR), 1 (3.4%) Hartman, 1 (3.4%) local excision and 1 (3.4%) left colectomy.

Pathological response. Within the 32 evaluable patients (1 patient died before surgery for a not-disease related cause, 3 patients were followed by another centre and information about surgery or following treatments was unavailable), 7 pCR (21.8%) and 16 PR (50%) were obtained, for an overall RR of 71.8%. Five patients had stable disease (SD) (15.6%), while 4 (12.5%) progressed locally (1 patient) or at distance (3 patients) during neo-adjuvant CHT-RT (PD).

Comparing the clinical stage with the pathological stage, tumour downstaging with respect to the T category was observed in 10 patients (31.2%) with cT3 and in 6 patients (18.7%) with cT4, respectively. Nodal status downstaging was detected in 16 (84.2%) (including 1 metastatic case) of 19 N+ patients (Table IV).

Table IV. *Distribution of pTNM compared with cTNM among 32 patients who underwent surgery.*

cTNM	pTNM
cT2N0, n=3	pT2N0, n=3*
cT2N1, n=2	pT1N0, n=1
	pT3N0, n=1
cT3N0, n=9	pT0N0, n=3
	pT1N0, n=1
	pT2N0, n=2
	pT3N0, n=2
	pT3N1, n=1
cT3N1, n=10**	pT0N0, n=1
	pT2N0, n=2
	pT3N0, n=5
	pT3N1, n=1
cT3N2, n=2	pT0N0, n=1
	pT3N1, n=1
cT4N0, n=1	pT0N0, n=1
cT4N1, n=4	pT0N0, n=1
	pT2N0, n=2
	pT2N1, n=1
cT4N2, n=1***	pT3N0

n: number of patients.
*1 patient progressed but the stage of the primitive tumour did not change.
**1 patient progressed so the tumour was not locally evaluated.
***1 patient progressed so the tumour was not locally evaluated.

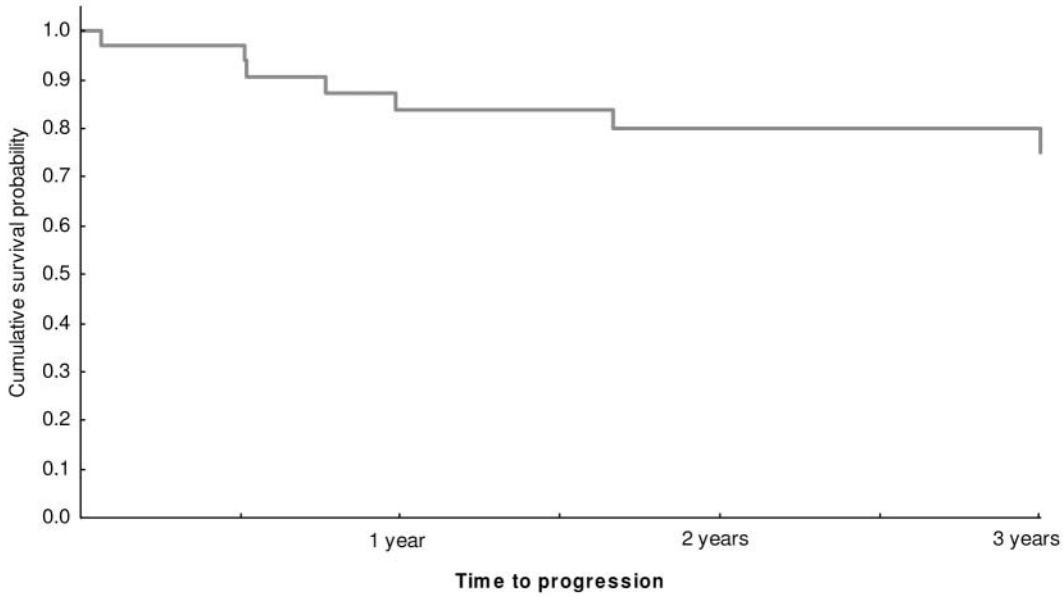

Figure 1. *TTP of the whole population (10 events, 26 censored patients).*

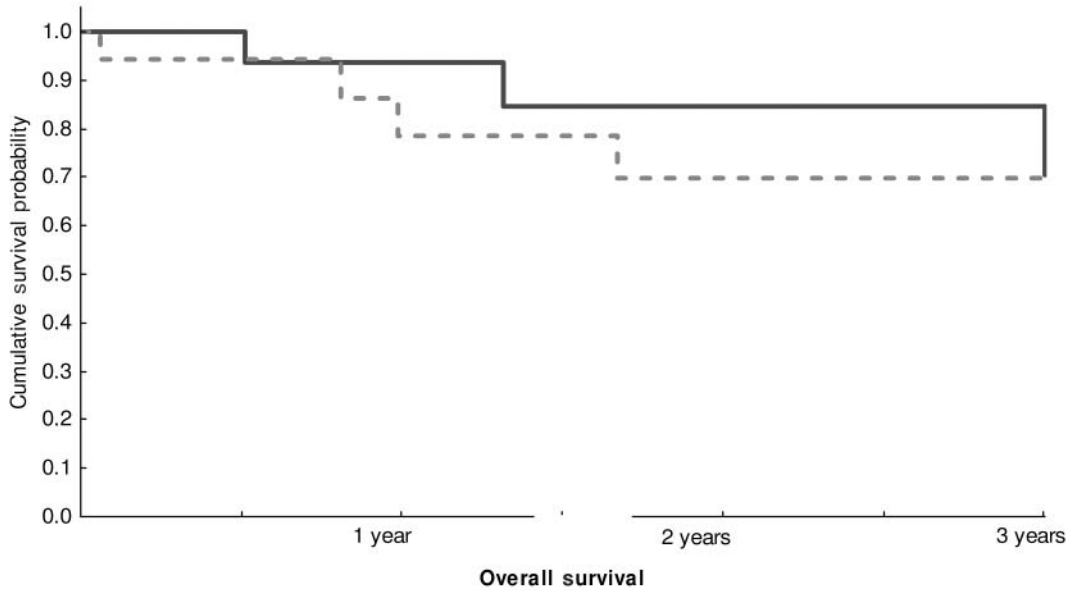

Figure 2. *Survival according to Charlson's score of 0 (3 events, 16 censored) or of 1 or more (5 events, 12 censored).*

Time to progression and overall survival. Twenty-six out of 36 patients (72.2%) were still free from progression after a median follow-up of 37.2 months. Median TTP was not been reached at the time of this analysis. The Kaplan-Meier curve for all patients is shown in Figure 1. The neoadjuvant CHT-RT response was not statistically significant for progression ($p=0.178$).

Eight patients (22.2%) have died (3 from disease-related causes). Median survival has not been reached yet.

Subgroup analysis. Males and females had comparable RR of 69.23% and 73.68%, respectively ($p=0.54$).

Age 70 to 75 years was not significantly prognostic for tumour response (77.27%) compared to patients ≥75 years (60%, $p=0.27$).

Response was not influenced by comorbidity since 67.7% of patients with Charlson's score of 0 responded, compared to 80% of those with a score of 1 or more ($p=0.24$).

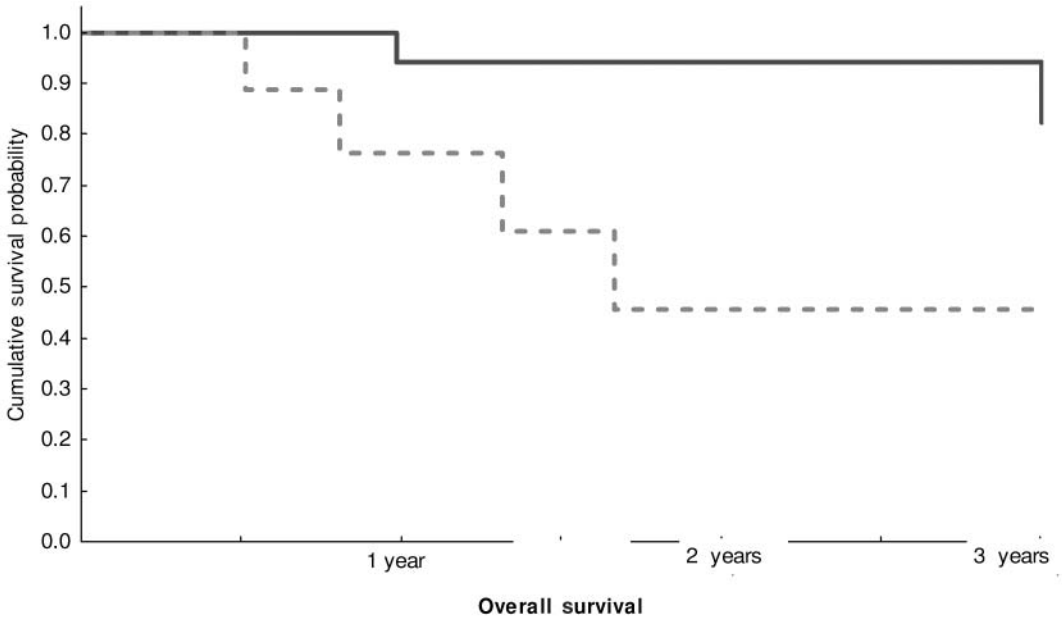

Figure 3. *Overall survival in responsive (3 events, 20 censored patients) or non-responsive (4 events, 5 censored patients) to neo-adjuvant CHT-RT.*

Eighteen patients who received 5FU-bolus chemotherapy had a lower percentage of response (56.25%) compared to those who received 5FU *c.i.* or capecitabine (87.5%) with borderline statistical significance ($p=0.056$).

Comparing patient survival with a Charlson's score of 0 with that of patients with 1 or more, we did not observe any difference ($p=0.49$) (Figure 2). Otherwise, the response to neoadjuvant CHT-RT almost reached a prognostic significance ($p=0.058$) (Figure 3 and Table V).

Table V. *Subgroup analysis.*

Variable	*P*	
	RR	OS
Age		
≥75 years		
<75 years	$p=0.27$	na
Gender		
male	$p=0.54$	na
female		
Modality of 5FU administration		
5FU bolus	$p=0.056$	$p=0.058$
5FU *c.i.*		
Charlson's score		
0	$p=0.24$	$p=0.49$
≥1		

c.i.=continuous infusion; 5FU=5-fluorouracil; na=not available.

Discussion

The elderly are the largest group of oncological patients for a medical doctor, but they are often under-treated and excluded from clinical trials; when included they represent the minority of "fit" elderly (30-32). Data obtained from the few clinical trials should be interpreted with caution as the results only apply to patients that fulfilled the protocol requirements (33). Age alone is not a sufficient reason to withhold adjuvant, neoadjuvant or palliative treatment or to reduce the dose of a cytotoxic drug, even though old age is often associated with an increased haematological toxicity (34-38). Observing the 36 out of 88 consecutive elderly patients with stage II-III rectal cancer, treated with combined neoadjuvant CHT-RT, we obtained a nodal status downstaging in 84.2% of cases and a pCR (pT0N0) in 21.8% patients (85.7% of them were treated with 5FU *c.i.*, the other one with 5FU bolus) (39); similar data have also been observed in other trials (40-51) (Tables VI, VII). A trend for increased response with the *c.i.* regimen was noted, though with a borderline statistical significance ($p=0.056$) (13, 14, 20-22, 52). No significant differences were observed between "fit" and "vulnerable" patients, independent of the way 5FU was administered.

Gastrointestinal toxicity (diarrhea) occurred in 47.2% of patients but consisted primarily of grade 1-2 toxicity; 29.4% of these patients were treated with 5FU *c.i.*, the other 53% with 5FU bolus (in the same period, similar toxicities were reported in our Institution in a group of adult patients neoadjuvantly treated with the same schedules) (51); the only 3 cases of grade 3-4 gastrointestinal toxicity were treated with

Table VI. *Neoadjuvant 5FU bolus regimens in adult patients (< 70 years old).*

Authors	No. of patients	CT regimen	RT (Gy)	Results	DFS	OS
Grann *et al.* (1997) (40)	32 (T3 only)	5FU+LD-LV (1° and 5° wks of RT)	50.4	Resectability: 85% pCR: 9%	3-y 60%	NR
Pucciarelli *et al.* (2000) (41)	51 (locally advanced)	5FU+LV (1° and 5° wks of RT)	45	Resectability: 100% pCR: 16%	5-y 86%	5-y 85%
Minsky *et al.* (1993) (42)	21 (unresectable, 7 of which local relapses)	5FU+HD-LV (pre-RT and 4° wk of RT)	50.4	Resectability: 89% pCR: 29%	3-y 64%	3-y 69%
Bosset *et al.* (1993) (18)	85 (locally advanced)	5FU+LD-LV (1° and 5° wks of RT)	45	Resectability: 51% pCR: 15%	NR	NR
Marsh *et al.* (1996) (19)	18 (locally advanced + unresectable)	5FU chronomodulated (concomitant)	45-55.8	Resectability: 94% pCR: 28%	NR	NR

DFS = disease free survival; OS = overall survival; wks = weeks; y = years; nr = not reported; 5FU = 5-fluorouracil; LD-LV = low dose leucovorin; HD-LV = high dose leucovorin; RT = radiotherapy; CT = chemotherapy; pCR = pathological complete remission
The first trials used 5FU bolus concurrently with the 1st and 5th week of radiation therapy. The different doses of radiotherapy employed and the different stages of treated disease made the trial results difficult to be analysed.

5FU *c.i.* and oxaliplatin (17.6%) (53-55). In our previous study (56), only 4.4% adult patients with locally advanced rectal cancer treated with 5FU *c.i.* and oxaliplatin did not complete the chemotherapy program because of toxicity, only 2.2% patients experienced grade 4 toxicity and less than 10% grade 3 diarrhea. Grade 3 cutaneous toxicity (proctitis) was restricted to 8.3% elderly patients; only 1 of them was treated with 5FU bolus and, according to the literature data on adults, proctitis was due more to the local effect of radiotherapy than to the systemic effect of chemotherapy (20). Haematological toxicity did not exceed grade 1; 41.7% patients received 5FU *c.i.* while the others received 5FU bolus (6, 41) (Table IV). Grade 1-2 (haematological) toxicity and the mean number of treatment weeks (30.5% skipped some weeks of therapy and 5.5% had to definitively stop it) did not differ from the usual toxicity found in the adult patients treated with 5FU neoadjuvant chemoradiotherapy (6, 20, 29, 40-42). In this small cohort, 5FU bolus appeared to cause more toxicities compared to 5FU *c.i.*, but this was not statistically significant. Clearly there was not adequate number of patients to allow a meaningful comparison. Inclusion of a higher number of patients as they become available might correct this.

Comorbidity and age were not related with toxicity, while females experienced higher toxicities.

Only 15 out of 30 eligible patients (50%) underwent adjuvant chemotherapy and 20% interrupted it prematurely, for refusal (66.6%) or for colostomy closeness (33.4%). Of these 15 patients, 3 died and 12 (80%) are still alive and disease free. Only 2.7% patients (cT3N0M0, pT0N0M0) reported a local relapse but they were not treated because of inadequate physical condition.

72.2% of patients are still free from progression after a median follow-up of 37.2 months; 22.2% if the patients have died. Median TTP and median survival have not been reached yet. The neoadjuvant CHT-RT response was not statistically relevant for progression ($p=0.178$), but it reached a prognostic significance ($p=0.058$) for survival probably because of the low number of analysed patients. Also in this case, data did not seem different from those observed in adults but they need to be confirmed by a larger study (5, 6, 18, 22, 40-50). Charlson's score was not statistically relevant for survival ($p=0.49$) probably because of the selected population.

Conclusion

Elderly "vulnerable" patients with rectal cancer can receive the same neoadjuvant CHI-R and undergo surgery as well as "fit" elderly patients since tolerability and RR seem to be similar in both categories of patients, independent of the form of 5FU administration. Less is known for the category of "frail" patients that are usually excluded from more aggressive treatments. Geriatric functional assessment with an evaluation of comorbidities with the Charlson or CIRS-G scale should always recognize potentially treatable conditions, assess functional reserve and estimate life expectancy. Its use should help to specify populations that actually may or may not benefit from various therapeutic approaches (especially the "vulnerable" group of patients that is more often under-treated). Moreover, only prospective trials on a high number of cases could confirm these results.

Table VII. *Neoadjuvant 5FU c.i. regimens in adult patients (<70 years old).*

Authors	No. Patients	CT regimen	RT (Gy)	Results	DFS	OS
Rodel *et al.* (2000) (5)	31 (T4 only)	5FU *c.i.* (1° and 5° wks of RT)	55.8	Resectability: 94% pCR: 13%	NR	5-y 51%
Schaffer *et al.* (2002) (43)	50 (locally advanced)	5FU *c.i.* (1° and 5° wks of RT)	45	Resectability: 86% pCR: 8%	NR	NR
Videtic *et al.* (1998) (6)	29 (T4 only)	5FU *c.i.* (concomitant)	54	Resectability: 79% pCR: 13%	3-y 83%	3-y 94%
Chen *et al.* (1994) (44)	31 (locally advanced)	5FU *c.i.* (concomitant)	55.8	Resectability: 100% pCR: 10%	NR	3-y 68%
Janjan *et al.* (1999) (45)	117 (locally advanced)	5FU *c.i.* (concomitant)	45	Resectability: 100% pCR: 27%	NR	NR
Ngan *et al.* (2001) (46)	82 (locally advanced)	5FU *c.i.* (concomitant)	54	Resectability: 100% pCR: 16%	NR	NR
Mehta *et al.* (2002) (47)	30 (locally advanced)	5FU *c.i.* (concomitant)	54	Resectability: 100% pCR: 33%	NR	NR
Pucciarelli *et al.* (2004) (51)	106 (locally advanced)	5FU *c.i.* (concomitant)	50.4	Resectability: 100% pCR: 17.9%	5-y 83.6%	5-y 83.6%

DFS = disease free survival; OS = overall survival; wks = weeks; y = years; nr = not reported; 5FU = 5-fluorouracil; *c.i.* = continuous infusion; RT = radiotherapy; CT = chemotherapy; pCR = pathological complete remission.
5FU *c.i.* significantly increases the time of cancer exposition since it is a drug phase-dependent and with a brief half-life. This has permitted the achievement of a maximum tolerated dose higher than that obtained with bolus administration and it has modified the type of toxicity.

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