Rectal Cancer Adjuvant Chemotherapy: When is More Useful?

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Abstract. *The aim of the study was to evaluate time-to-progression (TTP) of rectal cancer in a group of patients receiving adjuvant chemotherapy (CHT) after combined neoadjuvant treatment. A secondary end-point was to identify the possible influence of clinical TNM (cTNM) or pathological TNM (pTNM) on TTP and overall survival (OS). Patients and Methods: From January 2000 to December 2005, 101 consecutive rectal cancer patients who had been neoadjuvantly treated and had underne adjuvant CHT were retrospectively examined. The variables considered were age, gender and clinical and pathological effect of CHT administration. Results: The mean age was 59 years (29-78 years) and the male:female ratio, 61:40. Forty-two patients had a lower (≤5 cm from the anal verge), 54 a middle (from 6 to 10 cm) and 5 a higher (=10 cm) rectal lesion. All the patients had received the full course of neoadjuvant radiotherapy (RT) while 26.7% patients had received a reduced number of neoadjuvant CHT cycles. All the patients had undergone surgery and had received adjuvant chemotherapy which was completed in only 77.2% of the cases. Tumour down-staging and complete remissions were reported in 75.2% and 14.8% of cases, respectively. TTP and OS at 3 years were 81.2% and 91.1%, respectively. Out of locally recurrent patients, 77.8% were N+ (p=0.0026) at the pathological evaluation. Conclusion: In our series, neither administration of oxaliplatin-based adjuvant chemotherapy (p=0.44) nor age ≥70 years (p=0.51), clinical stage III (p=0.67), tumour down-staging (p=0.44) and achievement of pCR (p=0.66) appeared to have a significant impact on TTP; only pN+ (patients "not responders" to a neoadjuvant CHT-RT) influenced local relapse requiring more accurate postoperative treatment and confirming the literature data about the utility of adjuvant therapy in stage III disease.*

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Postoperative adjuvant combined chemotherapy-radiotherapy (CHT-RT) has long been considered the standard treatment for locally advanced middle to lower rectal cancer (T3-T4 and/or positive lymph nodes) (1). Nowadays, however, preoperative CHT-RT administration has gained popularity and is accepted worldwide as a valid option in the treatment of this neoplasm. Nevertheless, following a radical rectal cancer resection, adjuvant CHT treatment without RT is also usually recommended in order to reduce the incidence of local recurrence and improve survival. Because of the recent local recurrence rate reduction after rectal cancer resection utilizing sharp dissection and total mesorectal excision (TME), especially in T3N0M0 cases, in selected patients with stage II rectal cancer, the standard use of adjuvant therapy for local control cannot be justified except for those patients with a poor prognosis; currently, adjuvant CHT shows a survival improvement of stage III disease (N positive) only (2).

The purpose of this retrospective study was to establish the advantages, in terms of local and distant control of adjuvant CHT after a mesorectal excision in a series of middle to lower rectal cancer, and to evaluate the prognostic impact of clinical TNM (cTNM) and pathological response (pTNM) on the outcome, in terms of overall survival (OS) and time-to-progression (TTP).

Patients and Methods

From January 2000 to December 2005, 101 out of 187 consecutive rectal cancer patients who had been neoadjuvantly treated were retrospectively examined at the Medical Oncology Division, Istituto Oncologico Veneto, Padova, Italy.

Eligibility criteria. Inclusion criteria were: histologically proven rectal cancer located 10 cm or less from the anal verge by rigid proctoscopy, no synchronous colon cancer assessed by colonoscopy; T3-4 with any N or any T with N1-2, M0 (stage II-III) 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; adequate haematological, liver and renal function (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). Each patient gave written consent before starting treatment.

Patients were excluded if they had prior RT to the pelvic region, or previous systemic chemotherapy for any other tumour, or if they had other synchronous carcinomas. Patients suffering from the following conditions were also ineligible: inflammatory bowel disease; malabsorption syndrome; 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 for middle rectal lesions or at the bottom of the obturator foramina for the lower rectal lesions. The lateral borders extended 1.5 cm to the widest bony margins of the pelvic side walls. The field also extended to the posterior aspect of the symphysis pubis or the anterior margin of the symphysis pubis, with shielding of the anterior parts of the bony sacral margin. All the 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 report 50 (ICRU 50, 1999) (3), with daily fractions of 1.8 Gy on 5 consecutive days per 5.5 weeks.

Chemotherapy. 5-Fluorouracil (5-FU) (or capecitabine) was neoadjuvantly and adjuvantly administered by continuous infusion (*c.i.*) or by bolus ± oxaliplatin.

Degree of toxicity. The dose modifications applied for the CHT-RT were reported in according to NCI CTC, version 2.

Surgery. Four to six weeks after the completion of the CHT-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: intended type of operation documented at baseline; total mesorectal excision (4) performed where technically feasible; defunctioning stoma highly recommended for lower rectal lesions with reversal at the surgeon's discretion, but recommended that this took place after completion of adjuvant chemotherapy; post-operative documentation by the surgeon of the type of surgery performed and completeness of the procedure (mesorectal fascia intact, mesorectal fascia breached, or obvious margin involvement) and a pelvic CT scan, endosonography of the rectum and/or rectosigmoidoscopy and carcinoembryonic antigen (CEA) assessment post CHT-RT performed within 2 weeks of the planned surgery date.

Histopathological 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 (5, 6).

Study design, definitions and endpoints. The aim of the study was to evaluate rectal cancer TTP in a group of patients receiving an adjuvant chemotherapy after a combined neoadjuvant treatment. A secondary endpoint was to identify OS and the possible influence of age, gender, cTNM, tumour response to neo-adjuvant chemotherapy and achievement of pathological complete remission (pCR) on local and systemic relapse.

Any pT0N0M0 was defined as pCR, any cT or cN reduction was defined as partial remission (pPR), and any cT or cN increase was defined as disease progression. The median TTP was defined as the time from start neoadjuvant chemotherapy to local or systemic progression, or to death from any cause. OS was computed from the start of chemotherapy to death from any cause. The survival of patients lost at follow-up was checked by phone interview or by consultation of the municipal records and was censored at the latest day they were known to be alive. Chi-square or Fisher's exact tests were used to compare frequencies. The median TTP and OS were estimated using the Kaplan-Meier method (7). Prognostic factors for survival were tested by means of a two-sided log-rank test. All statistics were performed by means of Statistica software, version 6 (Statsoft, Inc., Tulsa, OK, USA).

Results

Patient characteristics. The patients and tumour characteristics at diagnosis are shown in Table I. The mean age was 59 years (range 29-78 years).

All the patients received the full course of neoadjuvant RT, while 26.7% patients received a reduced number of neoadjuvant CHT cycles (Table II). All the patients underwent surgery, 33 (32.7%) low rectal excision (LAR), 48 (47.5%) rectal anterior excision (RAR), 14 (13.9%) abdominal-perineal excision (Miles); 2 Hartmann, 2 left hemicolectomy and 2 transanal excision were also reported.

Fifteen patients had a pCR (14.8%) (no microscopic disease at the histological examination of the primitive site of disease) and tumour down-staging was observed in 76 patients (75.2%) at the time of surgery and sphincter preservation was achieved in 87 cases (86.1%) (Table III).

Except for 23 patients (22.8%), all patients completed the planned number of cycles of adjuvant chemotherapy. Ten (9.9%) patients received the FOLFOX4 regimen (Oxaliplatin plus 5-FU bolus and *c.i.* plus LV), forty six (45.5%) the Machover regimen (5-FU/LV for 5 days out 28), 37 (36.6%) 5-FU bolus, five (4.9%) capecitabine alone and three capecitabine plus oxaliplatin (Table IV). Twenty-three patients precociously interrupted adjuvant chemotherapy because of a secondary neoplasm (4.3%), colostomy closure (8.7%), reactivation of a previous disease (8.7%), lost to follow-up (13%), patient refusal (43.5%) or toxicity (21.8%).

Table I. *Characteristics of the tumour and of 101 mid-low rectal cancer patients.*

Characteristics	No	%
Age (years)		
<70	86	85.1
≥70 to 78	15	14.9
Gender		
Male	61	60.4
Female	40	39.6
Tumour distance from the anal verge		
≤5 cm	42	41.6
6-10 cm	54	53.5
=10 cm	5	4.9
cTNM		
T3N0	16	15.9
T4N0	7	6.9
T2N1	4	3.9
T3N1	38	37.7
T4N1	6	5.9
T2N2	1	0.9
T3N2	21	20.9
T4N2	8	7.9
Stage II	23	22.8
Stage III	78	77.2

CTNM, clinical TNM.

Table II. *Neoadjuvant chemotherapy.*

Characteristics	Regimen doses	n. pts	%
Neoadjuvant	5-FU *c.i.* 225 mg/m^2	44	43.6
	5-FU *c.i.* 225 mg/m^2 + oxaliplatin 60 mg/m^2	31	30.7
	5-FU bolus 450 mg/m^2 weekly	17	16.8
	capecitabine 825 mg/m^2 twice daily	6	5.9
	capecitabine 825 mg/m^2 twice daily + oxaliplatin 50 mg/m^2	3	3.0

5-FU, 5-fluorouracil; LV, leucovorin; *c.i.*, continuous infusion.

Table III. *Tumour down-staging after neoadjuvant therapy.*

cTNM	(n. of pts)	Tumour down-staging (n. of pts)	%
T3N0	16	CR (2)	12.5
		PR (5)	31.3
T4N0	7	CR (1)	14.3
		PR (4)	57.1
T2N1	4	PR (3)	75.0
T3N1	38	CR (3)	7.9
		PR (25)	65.8
T4N1	6	CR (1)	16.7
		PR (4)	66.6
T2N2	1	PR (1)	100.0
T3N2	21	CR (6)	28.7
		PR (13)	61.9
T4N2	8	CR (2)	25.0
		PR (6)	75.0

CR, complete remission; PR, partial remission.

Toxicities after adjuvant therapy. Grade 3 (see Methods) gastrointestinal toxicities after adjuvant therapy with 5-FU/LV by bolus occurred in two (1.9%) out of all the patients and consisted of diarrhoea and mucositis. One patient (0.9%) experienced grade 3 haematological toxicity and another one (0.9%) a grade 2, both had received the FOLFOX4 regimen. Among the oxaliplatin-treated patients, one suffered a lung embolism and another septic shock.

Grade 1 diarrhoea was observed in four patients (3.9%); two of them had been treated with the Machover regimen, one with 5-FU/LV by bolus and one with FOLFOX4.

In view of the paucity of patients experiencing relevant toxicities, the association with age and type of chemotherapy regimen could not be explored.

Time to progression and overall survival. After a median follow-up of 43.1 months, 16 patients had progressed (15.8%), five locally, four locally and distantly, seven only distantly. Seven patients died after disease progression, while another six patients died without documented relapse. TTP and OS at 3 years were 81.2% and 91.1%, respectively. The Kaplan-Meier curve for progression of all 101 patients is shown in Figure 1.

Clinical nodal involvement (stage III) was not found to be prognostic for developing local (p=0.66), systemic (p=0.70), or any type of recurrence (p=0.47). At 3 years, 88.4% of cN+ (stage III) and 78.9% of cN0 (stage II) patients were relapse-free according to Kaplan-Meier estimations (p=0.67) and 100% and 88.6% of them, respectively, were still alive (p=0.54). Persistence of nodal disease after neoadjuvant CHT-RT significantly predicted local relapse considering that 7 out of nine patients with local recurrence were pN+ (77.8%, p=0.0026), but this did not correlate with systemic disease since only three out of seven systemically recurrent patients were pN+ (42.8%, p=0.42). Five out of seven cN+ patients with local recurrence (71.4%) were pPR (they had a partial response on the primitive lesion after surgery), the others had a pathological disease stabilisation (pSD) (neither progression nor partial response on the primitive lesion was achieved after surgery). Among the patients with pPD, only 14.3% progressed locally while among those with pSD, 17.6% relapsed locally and 5.9% systemically. All except one had received 5-FU/LV-based adjuvant chemotherapy. pN+ had a significant impact on local relapse (p=0.0026).

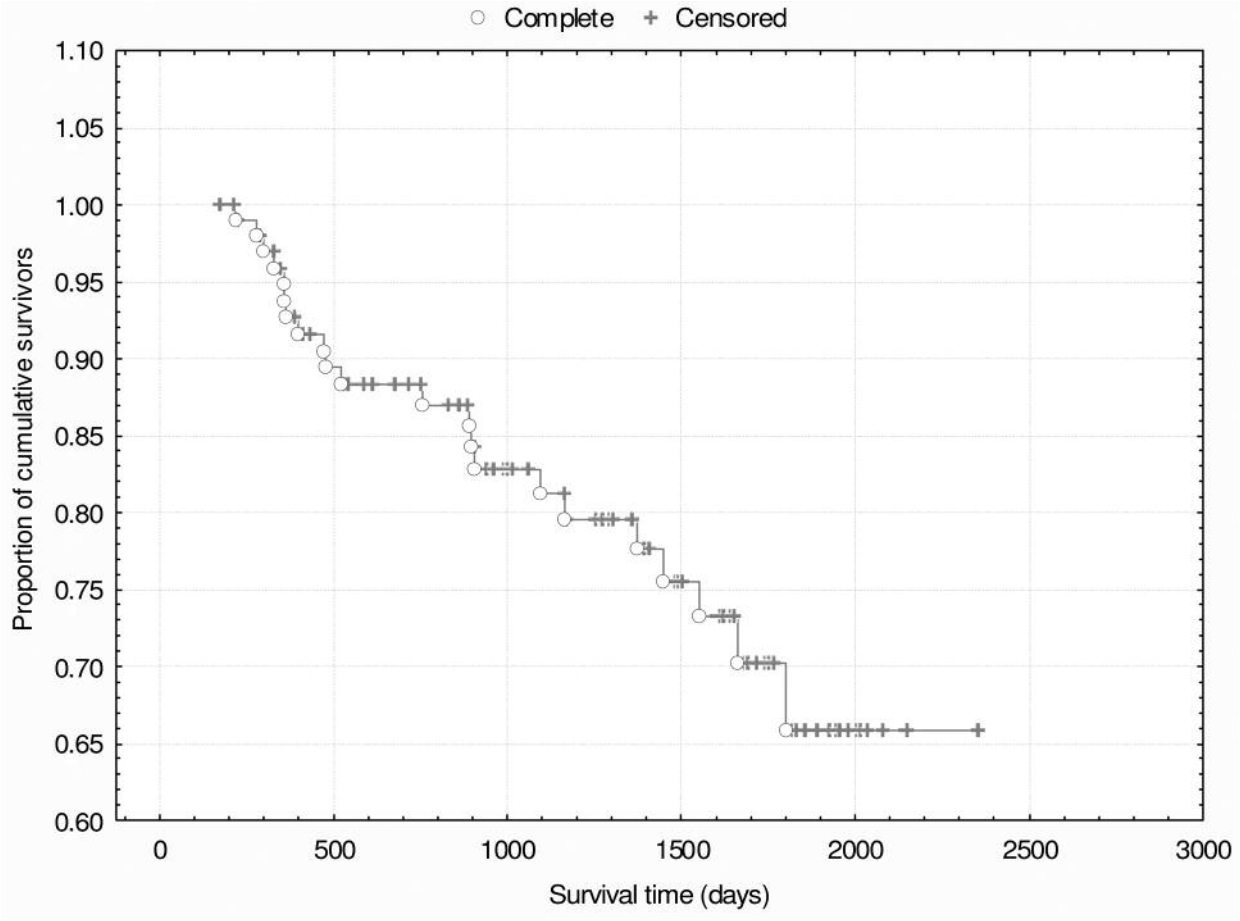

Figure 1. *TTP in the whole group (79 censored, 22 events).*

Only one recurrence was found among 13 patients (7.7%) receiving adjuvant oxaliplatin-based chemotherapy, compared to fifteen patients out of eighty eight (17.0%) treated with 5-FU-LV or capecitabine alone ($p=0.44$) (Table V).

A systemic relapse was observed in two patients adjuvantly treated with 5-FU/LV by bolus (5.4%) and in five patients treated with the Machover regimen (10.9%). A local relapse was observed in one patient adjuvantly treated with capecitabine (20%), in one patient adjuvantly treated with capecitabine and oxaliplatin (33.3%), in four treated with 5-FU/LV by bolus (10.8%) and in three treated with the Machover regimen (6.5%).

Tumour down-staging was found in 48 males patients (62.3%) and 29 females patients (37.7%) ($p=0.47$). All except one had received 5-FU/LV-based adjuvant chemotherapy (5 5-FU/LV by bolus and 5 the Machover regimen). Age under 70 years was not significantly prognostic factor for tumour down-staging (65 out of 86: 75.6%) compared to patients ≥70 years (12 out of 15, 80%), $p=0.51$.

None of the following factors was found to significantly impact on TTP: age ≥70 years ($p=0.51$), clinical stage III ($p=0.67$), down-staging of disease (=chemosensitivity) ($p=0.44$), achievement of pCR (maximum chemosensitivity plus optimal resectability) ($p=0.66$) (Figures 2 and 3) and administration of oxaliplatin-based chemotherapy compared to regimens with 5-FU/LV only ($p=0.44$).

Discussion

In our small series, because too many different schema were adopted, it was not possible to define if pTNM depended on the modality of neoadjuvant treatment used or if the adjuvant chemotherapy influenced the outcome. Excellent treatment response allowed two-thirds of the patients with low rectal cancer lesions to have an anal sphincter-sparing procedure, in agreement with the findings of other authors, reporting 60-90% of sphincter-sparing (8).

Tumour down-staging (pPR + pCR) was observed in 76.2% of cases and pCR (pT0N0) in 14.8% patients

Table IV. *Adjuvant therapy according to cTNM or pTNM.*

cTNM (n. of pts, %)	pTNM (n. of pts,%)	Tumour down-staging (n. of pts)	CHT regimen (n. of pts)
stage II: 8 (21.6%) stage III: 29 (78.4%)	stage 0: 8 (21.7%) stage I: 13 (35.1%) stage II: 9 (24.3%) stage III: 7 (18.9%)	CR 8 PR 22 SD 7	5-FU 450 mg/m^2 bolus + LV 100 mg/m^2 weekly (37)
stage II: 11 (23.9%) stage III: 35 (76.1%)	stage 0: 6 (13.0%) stage I: 16 (34.8%) stage II: 11 (23.9%) stage III:13 (28.3%)	CR 6 PR 30 SD 7 PD 3	Machover (46)
stage II: 2 (20%) stage III: 8 (80%)	stage 0: 1 (10%) stage I: 2 (20%) stage II: 2 (20%) stage III: 5 (50%)	CR 1 PR 5 SD 2 PD 2	FOLFOX4 (10)
stage II: 3 (60%) stage III: 2 (40%)	stage I: 3 (40%) stage III: 2 (60%)	PR 3 SD 1	Capecitabine 825 mg/m^2 twice daily (5) PD 1
stage III: 3 (100%)	stage III: 3 (100%)	SD 3	Oxaliplatin 130 mg/m^2 + capecitabine 825 mg/m^2 twice daily (3)

CTNM, clinical TNM; pTNM, pathological TNM; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; 5-FU, 5-fluorouracil; LV, leucovorin; Machover, 5-FU/LV; FOLFOX4, oxaliplatin+5-FU/LV.

Table V. *Characteristics of disease in progressing patients.*

cTNM (n. of pts)	pTNM (n. of pts)	Tumour down-staging (n. of pts)	CHT regimen (n. of pts)
Local Relapse (9 patients)			
stage II: 2 (22.2%) stage III: 7 (77.8%)	stage 0: 1 (11.1%) stage II: 1 (11.1%) stage III: 7 (77.8%)	CR 1 PR 5 SD 3	5-FU/LV bolus (4)* Machover (3) Capecitabine (1) Capecitabine + oxaliplatin (1)
Systemic Relapse (7 patients)			
stage II: 1 (14.3%) stage III: 6 (85.7%)	stage I: 3 (42.8%) stage II: 1 (14.3%) stage III:3 (42.8%)	PR 4 SD 3	5-FU/LV bolus (2) Machover (5)

cTNM, clinical TNM; pTNM, pathological TNM; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; 5-FU, 5-fluorouracil; LV, leucovorin. *Three of the patients treated with 5-FU/LV by bolus and the patient treated with capecitabine also progressed systemically.

("responders"), also according to literature data (about 4% to 44% of cases) (9-11). In the present study a local and systemic recurrence was found in 7.8% and 6.5% of down-staged patients, respectively (despite all except one patient with recurrence had received an adjuvant fluoropyrimidine-based therapy) but neither clinical N+ stage, down-staging of disease ($p=0.44$) nor the achievement of pCR ($p=0.66$) were found to have a significant impact on TTP (12, 13). The high number of censored patients, the heterogeneity of postoperatively administered therapies (46.8% of down-staged patients had received an adjuvant therapy with Machover regimen, 38.9% with 5-FU bolus, 7.8% with FOLFOX4 and 6.5% with capecitabine; all except one patient with pCR had received 5-FU/LV-based chemotherapy) and the incompleteness of the planned number of adjuvant

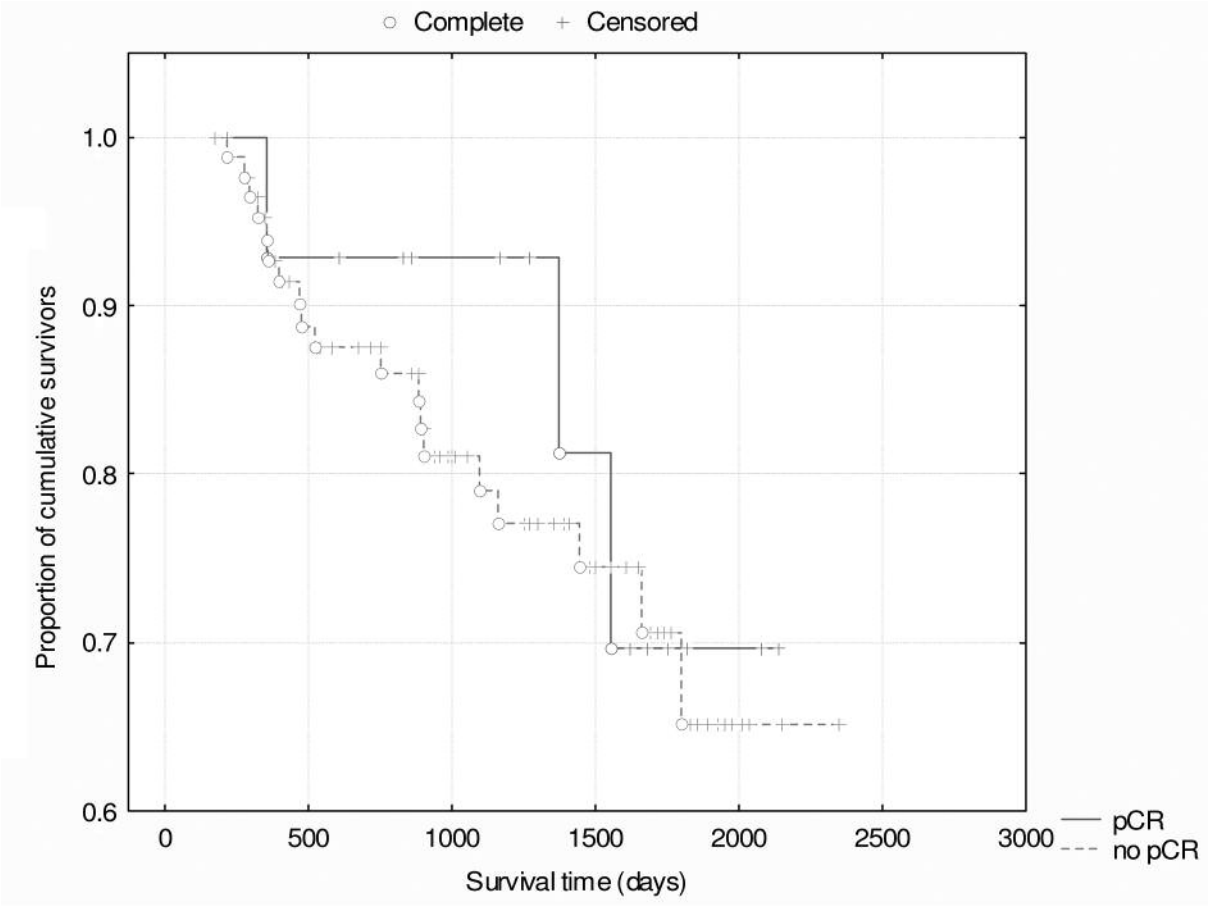

Figure 2. *TTP according to pCR or no-pCR.*

chemotherapy cycles (in total, 83% of the patients had received an adequate number of adjuvant chemotherapy cycles; only few patients experienced relevant toxicities (21.8%) but a high number of them refused chemotherapy (43.5%)) might have influenced the impact of pCR on the outcome (14-18). In our series, the choice of adjuvant chemotherapy in the "responders" patients had been more influenced by pTNM than by cTNM (Table VI). Nevertheless, the type of adjuvant chemotherapy adopted did not influence TTP ($p=0.44$).

Among the 17 patients with pSD (52.9% of them were N+) ("not responders"), 82.3% had received 5-FU/LV-based therapy. A local and systemic recurrence was reported in 23.5% of the patients (75% of them were N+); two of them died after systemic progressive disease (PD); a third patient with systemic PD was still alive, as was the patient with a local recurrence. Also in this case, the choice of postoperative treatment adopted (firstly, fluoropyrimidine-based therapy as in the preoperative setting) did not significantly influence TTP.

To date, among our evaluable patients, 83.3% were still free from progression (in concordance with literature data) after a median follow-up of 43.1 months (11) while 13.5% had died.

Conclusion

A significant correlation between pTNM and local relapse was found here despite the shortness of follow-up, and tumour down-staging was high. The practical dilemma is, given these results, how do we manage the postoperative patient who has received preoperative combined-modality therapy? Although there was no survival benefit to postoperative chemotherapy for those with pT3-4 disease it should be emphasized that this does not mean that chemotherapy is not necessary but rather, in this single trial, bolus 5-FU/LV chemotherapy was not helpful for those patients who received this regimen preoperatively. In the Authors opinion, 4 months of postoperative adjuvant chemotherapy are still appropriate. However, in

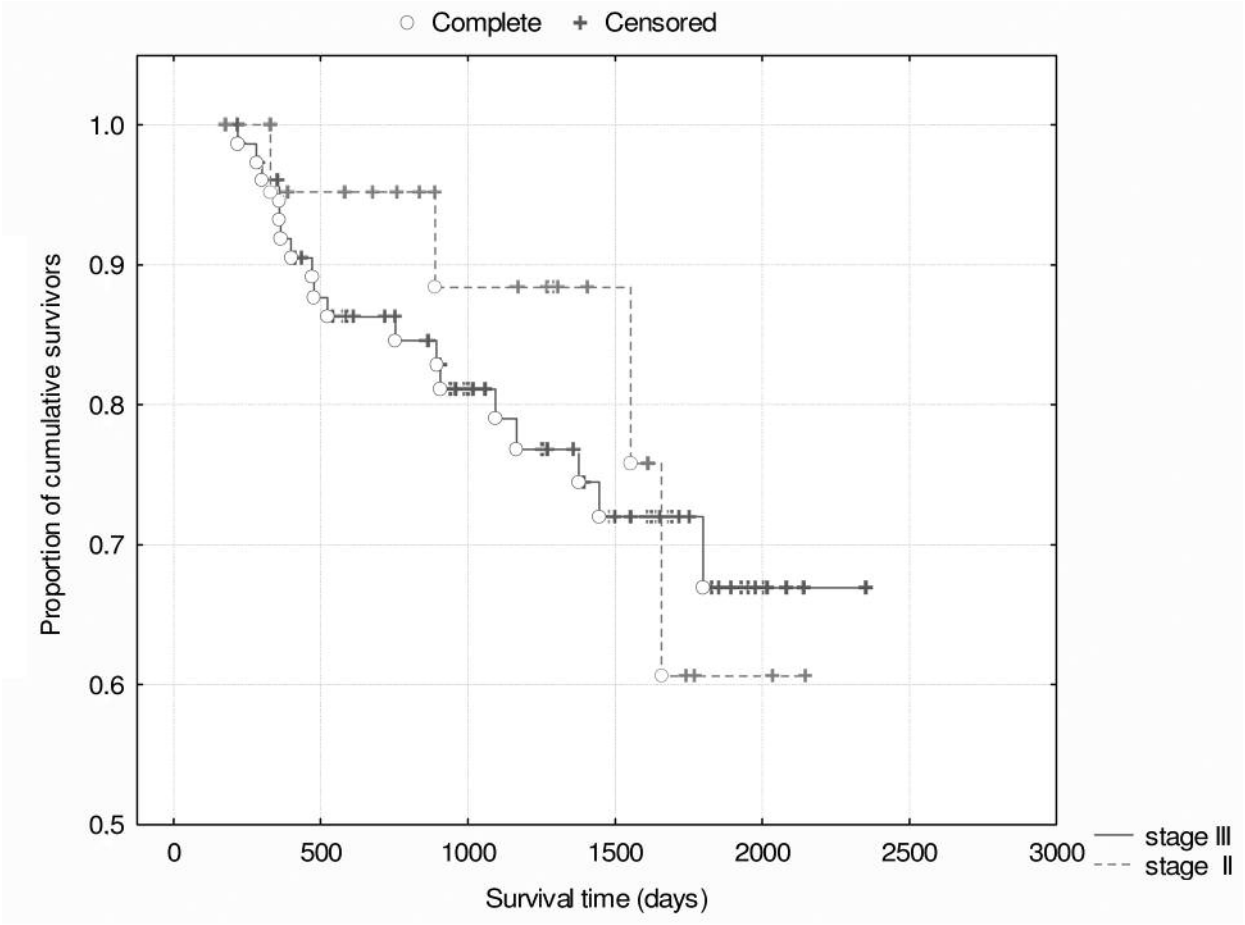

Figure 3. *Comparison between stage II and III (cN+) of disease (p=0.67).*

Table VI. *Adjuvant therapy according to cTNM or pTNM in 77 down-staged patients.*

	cTNM (n. of pts)	pTNM (n. of pts)	CHT regimen (n. of pts)
stage 0-I	0	15+34	Machover (31)
stage II	11		5-FU/LV bolus (13)
stage III	38		Capecitabine (3)
			FOLFOX4 (2)
stage 0-I	0		Machover (7)
stage II	1	12	5-FU/LV bolus (2)
stage III	11		FOLFOX4 (1)
stage 0-I	0		Machover (7)
stage II	1		5-FU/LV bolus (2)
stage III	15	16	Capecitabine + oxaliplatin (2)
			FOLFOX4 (2)

cTNM, clinical TNM; pTNM, pathological TNM; pts, patients; 5-FU, 5-fluorouracil; LV, leucovorin; Machover, 5-FU/LV; FOLFOX4, oxaliplatin+5-FU/LV. Not all patients were treated with adjuvant chemotherapy (see text).

those patients with tumors that did not respond to preoperative treatment, Authors recommend using an alternative chemotherapeutic regimen in the postoperative setting such as FOLFOX4 (infusional 5-FU, LV and oxaliplatin).

Neither down-staging ($p=0.44$), pCR ($p=0.66$), nor adjuvant therapy ($p=0.44$) had a significant impact on TTP. A better selection of patients to treat after a preoperative therapy and an adequate choice of postoperative treatment, might improve in the future the TTP also within "responders" patients. The identification of pathologic and molecular predictive markers needs to be an integral component in the design of future clinical trials. Molecular markers such as gene expression profiling to predict tumour response (19) and thymidylate synthase expression to determine who may benefit from 5-FU-based chemotherapy (20) may help us understand the underlying molecular mechanisms and provide a rationale for selection of the appropriate therapies.

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