Role of Neoadjuvant Treatment in cT3N0M0 Rectal Cancer

LARA MARIA PASETTO[1], MARIA LUISA FRISO[2], SALVATORE PUCCIARELLI[3], UMBERTO BASSO[1], MASSIMO RUGGE[4], GIULIETTA SINIGAGLIA[5], ELENA ROSSI[1], ALESSIA COMPOSTELLA[1], PAOLA TOPPAN[3], MARCO AGOSTINI[3] and SILVIO MONFARDINI[1]

Istituto Oncologico Veneto, IRCCS: [1]Medical Oncology 2nd, 35128 Padova; [2]Radiotherapy; Azienda Ospedale-Università, [3]IInd Surgical Clinic, 35128 Padova; [4]Pathology Unit; CRO, [5]UO Farmacologia Sperimentale e Clinica, 33081 Aviano (PN), Italy

Abstract. *Background: The aim of the study was to evaluate the pathological response (pTNM), local relapse and overall survival (OS) in clinical T3N0M0 (cT3N0M0) rectal cancer after a neoadjuvant chemoradiotherapy (CHT-RT) with 5-fluorouracil (5-FU) continuous infusion (c.i.) (± oxaliplatin) or bolus or capecitabine (an oral fluorpyrimidine). A secondary endpoint was to identify the local relapse rate and OS in those patients also receiving an adjuvant chemotherapy. Patients and Methods: From January 2000 to January 2006, 48 consecutive cT3N0M0 rectal cancer cases neoadjuvantly treated were retrospectively examined. Variables considered were age, gender, modality of 5-FU administration and tumour site. Results: Median age was 64 years (range, 22-84 years) and the male:female ratio was 28:20. All the patients received the full course of CHT-RT. Twenty-eight patients received c.i. 5-FU neoadjuvant chemotherapy, 17 received bolus 5-FU administration and 3 patients received capecitabine-based therapy. The mean number of chemotherapy weeks was 4.9 (range, 2-6). A total of 85.4% of patients were operated on without relevant postoperative complications but another 4 are awaiting surgery. Twenty-one patients had a lower (≤5 cm from the anal verge) and 27 had a middle rectal lesion (from 6 to 10 cm). In those patients with the lower site of lesion, a sphincter-saving (SS) procedure was achieved in 88.9%. Downstaging was reported in 66.7%. Ninety percent of cases are still free from progression after a median follow-up of 22.1 months; 7.5% are dead. Conclusion: The down-staging, the good level of SS and the disease-free survival (DFS) obtained here suggests that a neoadjuvant therapy may also be useful for stage II rectal cancer at diagnosis. The use of a postoperative chemotherapy should probably be outlined better.*

Correspondence to: Lara Maria Pasetto, Istituto Oncologico Veneto, IRCCS, Oncologia Medica 2, Via Gattamelata 64, 35128 Padova, Italy. Tel: +39 0498215931, Fax: +39 0498215932, e-mail: laramary@libero.it

Key Words: cT3N0M0, neoadjuvant chemotherapy, rectal cancer.

Postoperative adjuvant combined chemoradiotherapy (CHT-RT) has long been considered standard treatment for locally advanced rectal cancer (T3-T4 and/or positive lymph nodes) (1). Nowadays, however, combined preoperative CHT-RT has gained popularity and is accepted worldwide as a valid option in the treatment of locally advanced, middle to lower rectal cancer. This approach allows high rates of tumour resectability (2, 3), sphincter-saving procedures (4, 5) and down-staging (3, 6, 7); it has also been reported to improve local control and 5-year survival rates (3, 6, 8-10). To date, 5-fluorouracil (5-FU) (bolus, infusional or peroral, unmodulated or biochemically modulated) has been studied most (11-15). Continuous infusion (c.i.) of 5-FU was shown to be associated with a different type of toxicity (from neutropenia to palmar-plantar erythrodysesthesia) and a better response rate (RR), but not overall survival (OS), than bolus administration (pathological complete remission, pCR, of 67% *versus* 10%) (16-18). 5-FU is the most utilised drug in the neoadjuvant setting. However, its usefulness as preoperative therapy in T3N0M0 disease is not known.

Following rectal cancer resection, adjuvant CHT-RT is usually recommended in order to reduce the incidence of local recurrence and improve survival. However, recent experience with rectal cancer resection utilizing sharp dissection and total mesorectal excision has resulted in a reduction in local recurrence rates, especially in T3N0M0 cases, to as low as 5% without adjuvant treatment. For this reason, in selected patients with stage II rectal cancer, the standard use of adjuvant therapy for local control is not justified. Nowadays, in fact, adjuvant chemotherapy for colorectal carcinoma has been found to improve survival of patients with stage III disease (N-positive). Yet, the usefulness of chemotherapy in patients with stage II (any TN0M0) continues to be debated and it is likely that only those patients with a poor prognosis will receive adjuvant chemotherapy. Biological prognostic factors may allow further insight into the optimal treatment strategy for these patients.

The purpose of this retrospective study was to determine the usefulness of CHT-RT followed by a mesorectal excision of middle or lower T3N0M0 rectal cancer in terms of local control and OS and the role of adjuvant therapy.

Patients and Methods

From January 2000 to January 2006, 48 consecutive cT3N0M0 rectal cancer cases out of all neoadjuvantly treated cases were retrospectively examined at the Medical Oncology Division, Istituto Oncologico Veneto, Padova.

Eligibility criteria. Inclusion criteria were: histologically proven rectal carcinoma located up to 10 cm from the anal verge by rigid proctoscopy, no synchronous colon cancer as assessed by colonoscopy, clinical stage II (cT3N0M0) following transrectal ultrasonography and/or pelvic computed tomography (CT) scan, no distant metastases as assessed by abdominal and thoracic CT scan, Eastern Cooperative Oncology Group performance status 1, adequate haematological, liver and renal function [neutrophils $\geq 1.5\times10^9$/l, platelet count $\geq 100\times10^9$/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 their written consent before starting treatment.

Patients were excluded if they had had prior RT to the pelvic region or previous cytotoxic chemotherapy, or if they had other synchronous cancer. Patients suffering from the following conditions were also ineligible: inflammatory bowel disease, malabsorption syndrome, serious uncontrolled active infection, 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. 5-FU was delivered by c.i. at a fixed dose of 225 mg/m^2 daily ± oxaliplatin 60 mg/m^2 weekly or by bolus 450 mg/m^2 weekly, continuously for approximately 5.5 weeks, from the first to the last day of RT. In some cases, capecitabine was substituted for 5-FU and it was delivered at 825 mg/m^2 twice daily Monday-Friday of weeks 1-5 (a total of 25 days' dosing).

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) (19), 5-FU 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 ≤2 grade 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 5-FU dose, once toxicity had resolved to grade 0-1. Patients were monitored by weekly history, ECOG performance status, clinical examination, full hematology, blood biochemistry and liver function tests.

Surgery. Four to six weeks after completion of CHT-RT, resectability was assessed by clinical examination and a 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; intended type of operation was documented at baseline; total mesorectal excision (20) (TME) was performed where technically feasible; 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; surgeon had to document the type of surgery performed and completeness of the procedure (mesorectal fascia intact, mesorectal fascia breached, or obvious margin involvement) postoperatively.

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 (21).

Response of the primitive tumor was considered a down-staging or either T and/or N compared to baseline parameters, while response of metastases was registered according to WHO criteria (22).

Study design, definitions and end points. The primary objective of the study was to evaluate the pTNM, local relapse and OS in cT3N0M0 rectal cancer after a neoadjuvant 5FU-based CHT-RT. A secondary endpoint was to identify the local relapse rate and OS in the group of those patients also receiving adjuvant chemotherapy.

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. Median time to progression (TTP) was defined as the time from the start of 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. Survival of patients lost at follow-up was checked by phone interview or by consultation of municipal records and was censored at the latest date they were known to be alive.

Median TTP and OS were estimated using the Kaplan-Meier method (23). Prognostic factors for survival were tested by means of a two-sided log-rank test.

Table I. *Characteristics of 48 cT3N0M0 mid-low rectal cancer patients and their tumors.*

Characteristics	No.	%
Age (years)		
Median 64 (range 22-84)		
<70	32	66.7
≥70 to 84	16	33.3
Gender		
Male	28	58.3
Female	20	41.7
Tumour distance from the anal verge		
≤ 5 cm	21	43.7
5-10 cm	27	56.3

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

Toxicity	NCI-CTC Grade							
	1		2		3		4	
	No. pts	%	No. pts	%	No. pts	%	No. pts	%
Diarrhea	18	37.5	7	14.6	3	6.2	1	2.1
Nausea	5	10.4	0	0	0	0	0	0
Vomiting	48.3	1	2.1	0	0	0	0	
Stomatitis	3	6.2	2	4.2	0	0	0	0
Proctitis	12	25.0	1	2.1	3	6.2	0	0
Dysuria	6	12.5	0	0	1	2.1	0	0
Fatigue/asthenia	9	18.8	1	2.1	1	2.1	0	0
Anemia	15	31.2	0	0	0	0	0	0
Leukopenia	14	29.2	3	6.2	0	0	0	0
Thrombocytopenia	4	8.3	0	0	0	0	0	0

Results

Patients characteristics. From January 2000 to January 2006, 48 consecutive cT3N0M0 rectal cancer patients out of all those neoadjuvantly treated were retrospectively examined at the Medical Oncology Division, Istituto Oncologico Veneto, in Padova (Table I). The median age was 64 years (range 22-84 years). Within these 48 patients, 3 (6.25%) patients received a neoadjuvant chemotherapy with capecitabine, 6 (12.5%) with c.i. 5-FU and oxaliplatin, 17 with bolus 5-FU (35.4%) and 22 (45.8%) with c.i. 5-FU alone. In total, 41 patients (85.4%) underwent surgery and 4 are still awaiting surgery, 2 were lost from follow-up and 1 died during treatment for a cause not disease-related. Thirty-two patients (78% of those operated) underwent TME. An SS was observed in 88.9% of the operated patients with low rectal cancer.

Only 17 out of 41 patients (41.5%) who underwent surgery received an adjuvant treatment: 4 patients received 5-FU/leucovorin (LV) by bolus, 8 had a Machover regimen, 3 a FOLFOX 4 regimen and 2 a capecitabine-based therapy.

Toxicities. Grade 3-4 gastrointestinal toxicities after neoadjuvant therapy occurred in 4 (8.3%) of all patients and consisted primarily of diarrhea; only 3 patients (6.25%) experienced grade 4 cutaneous toxicity. Nausea, vomiting, mucositis, asthenia and hematological toxicity were more frequent but of low grade (Table II).

Seven out of 16 elderly patients *versus* 12 out of 32 younger patients developed some toxicity of grade 2 or more, but with no significant difference in frequences (p=0.67).

Ten out of 17 patients receiving bolus 5-FU developed significant toxicities of grade 2-4 compared to 9 out of 31 patients treated with c.i. 5-FU or with capecitabine (p=0.043). One patient died during CT/RT, but this death was due to causes other than treatment toxicity.

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 34 patients (75%). The mean number of weeks was 4.9, ranging from 2 to 6 weeks. Eight patients had to interrupt chemotherapy prematurely because of toxicity, 3 because of refusal and 1 because of death not disease-related. Two patients treated with capecitabine (an oral fluoropyrimidine) received 5 weeks of therapy according to the protocol.

Surgical morbidity. Six weeks after completion of CHT-RT, patients were reassessed for surgery. With the exception of the four patients who are still awaiting surgery, the two who were lost from follow-up before surgery and one who died during treatment for a cause not disease-related, 41 patients (85.4%) were operated on. All tumors were radically resected without relevant postoperative complications.

Twenty-one patients (43.7%) underwent rectal anterior resection (RAR), 11 (22.9%) low anterior resection (LAR) (1 progressed patient also underwent liver metastases resection), 4 (8.3%) left colectomy, 2 (4.2%) abdominal perineal excision (Miles), 1 (2.1%) Hartman, 1 (2.1%) local excision and 1 proctocolectomy (2.1%).

Pathological response. Within the 39 evaluable patients, 10 patients had pCR (25.6%; 8 of whom had undergone TME) and 16 PR (41.1%; 13 of whom had undergone TME), for an overall response rate (RR) of 66.7%. Seven patients reported stable disease (SD) (17.9%; 6 of them had undergone TME). Four cases locally progressed (PD) (10.2%) and 2 locally and systemically progressed (5.2%); in total, 3 out of these 6 patients were found to have positive nodes at the re-evaluation. One patient underwent nonradical surgery and another was operated on in another country (Table III).

Table III. *Pathological local response among the 39 valuable patients.*

pTNM	No. patients (%)
CR	10 (25.6)
PR	16 (41.1)
SD	7 (17.9)
PD	6 (15.4)
Total 39 evaluable patients	

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; NA, not available. [One patient was not radically resected (the histological exam was lost); two other patients systemically progressed].

Table IV. *Adjuvant treatment according to pathological local response.*

pTNM (No. patients)	Type of chemotherapy	No. patients (%)
CR (10)	FOLFOX 4	2 (20%)
	Machover	1 (10%)
	Total	30 %
PR (16)	Machover	2 (12.5%)
	Capecitabine	2 (12.5%)
	5-FU/LV by bolus	1 (6.2%)
	Total	31.2 %
SD (7)	Machover	5 (71.4%)
	5-FU/LV by bolus	2 (28.6%)
	Total	100 %
Local PD (4)	FOLFOX 4	1 (25%)
	5-FU/LV by bolus	1 (25%)
	Total	50 %

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; 5-FU, 5-fluorouracil; LV, leucovorin.

Progression-free and overall survival. Thirty-six out of 40 patients evaluable for progression (90%) are still free from progression after a median follow-up of 22.1 months. The Kaplan-Meier survival curves for all 48 patients is shown in Figures 1 and 2. One of the patients with a pPD, also systemically progressed 2 months after the end of the adjuvant therapy; he is still alive. One of the patients with a pPR developed systemic disease 5 years after the end of the adjuvant therapy; he is also still alive. The only patient not undergoing radical resection progressed 2 months after surgery but did not undergo chemotherapy because of their poor general condition; all information was lost because the patient transferred to another Institution. Median TTP was not evaluable.

Due to the low number of progressions registered, the prognostic role of the response to neoadjuvant CHT-RT could not be assessed. All pCR and SD patients are still alive and disease free, independently of adjuvant chemotherapy administration. One out of 16 patients with PR (6.25%) progressed after 5 years; he had received 5-FU + oxaliplatin as neoadjuvant and Machover regimen as adjuvant therapy and is still alive. One of two patients adjuvantly treated (5-FU/LV by bolus administration) for a local PD was also found to have a systemic disease 2 months after the end of adjuvant chemotherapy; he has been neoadjuvantly treated with bolus 5-FU and he is still alive (Table IV).

Three patients (7.5%) have died: one of them died before the end of neoadjuvant treatment for a cause not disease-related; another (82 years old) died 3 months after surgery (at the histological exam local PD was observed) and the third died 9 months after surgery (at the histological exam local and systemic PD was observed). At the time of writing, 93.7% of patients are still alive.

Subgroup analysis. Males and females had a RR of 69.2% and 61.5%, respectively (p=0.44). Being under 70 years of age was not significantly prognostic for tumour response (69%) compared to patients ≥70 years of age (60%, p=0.44). Patients with middle and low lesions had RR of 65.2% and 73.3%, respectively (p=0.43).

Fourteen patients who received neoadjuvant 5-FU-bolus chemotherapy had a lower percentage of response (57.1%) compared to those who received c.i. 5-FU (alone or with oxaliplatin), or capecitabine (72%), without statistical significance (p=0.28).

Due to the small number of events, the prognostic role of the type and response to neoadjuvant chemotherapy as well as administration of adjuvant chemotherapy could not be assessed.

Adjuvant treatment administered to 30% pCRs, 31.2% pPRs, 100% SD and 50% PD patients could not be assessed for a prognostic role in progression and OS.

Discussion

Preoperative CHT-RT is a well-established treatment for locally advanced mid-low rectal cancer. One of the potential advantages of this approach is the down-staging of the tumor and SS, a local relapse reduction and an increased OS (2, 8, 16, 24, 25). An open question is the utility of neoadjuvantly treating stage II of disease or not (independently of the site of the lesion being middle or low) and the utility of an adjuvant therapy for all these patients or only for those patients with a worse pTNM. In fact, patients with cT3N0M0 usually have a 2% risk of mesorectal nodal metastases at surgery even if they are yT0 at the reevaluation after a CHT-RT treatment; the risk is about 15% if yT1, 17% if yT2 and 38% if yT3 (24).

This retrospective study was undertaken to evaluate the impact of preoperative CHT-RT followed by adjuvant chemotherapy or not on the outcome (DFS and OS) and SS in only cT3N0M0 mid-low rectal cancer.

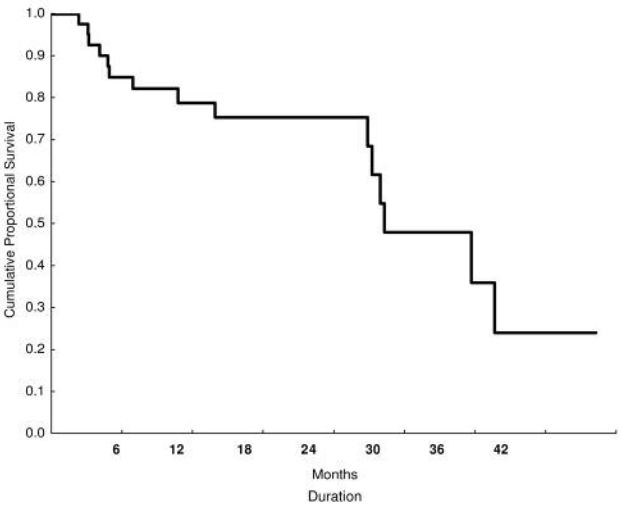

Figure 1. *Cumulative survival of 48 patients (25 censored).*

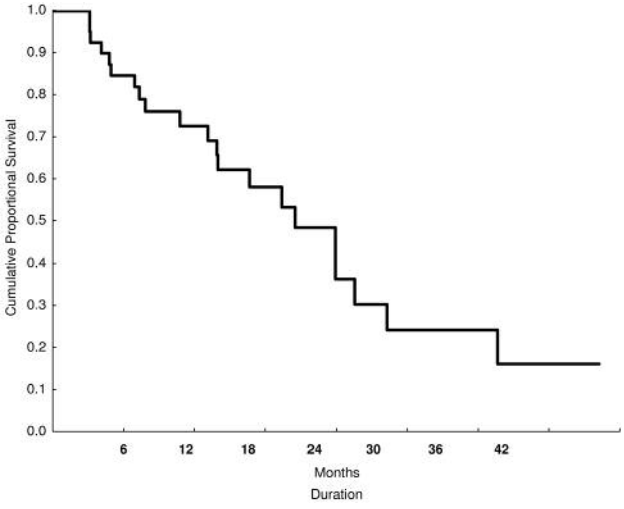

Figure 2. *Time to progression in 40 patients (19 censored).*

Our findings showed a trend (though not statistically significant) of the tumor response following preoperative CHT-RT depending on the modality of treatment used: a better tumor response was achieved after CHT-RT with c.i. 5-FU or capecitabine than with bolus 5-FU (p=0.27) (24). A tumor status down-staging was observed in 63.4% of cases and a pCR (pT0N0) in 24.4% patients (46.1% of all responder patients were treated with c.i. 5-FU, 30.8% with bolus 5-FU; 15.4% with c.i. 5-FU and oxaliplatin and 7.7% with capecitabine) (in concordance with literature data) (16-18, 26-28). Moreover, grade 2 or more toxicities were less frequent with c.i. 5-FU compared to bolus (p=0.043), therefore the c.i. regimen as neoadjuvant treatment is preferrable. An SS was observed in 88.9% of the operated patients with low rectal cancer lesions.

Since being over 70 years of age did not negatively influence the incidence of toxicities (p=0.67), age should not be considered a barrier for neoadjuvant CHT-RT for rectal cancer.

Only 17 out of 41 surgically treated patients (41.5%) received an adjuvant treatment (independently of the pTNM) and 11.8% interrupted it prematurely for refusal. Among all these 17 patients, complete responders and patients with an SD after CHT-RT are still alive and disease free; literature data commonly report a 5-year local control and OS of 100% and 81% for pT0N0M0 patients and of 79% and 66%, respectively, for pT3N0M0 patients (6). A total of 6.25% of those who achieved pPR systemically progressed at 5 years; literature data report a 5-year local control and OS of 88% and 91% for pT1-2N0M0 patients (6) (Table IV). Unlike literature data which report a local relapse rate of about 22-35% in cT3N0M0 patients, in our study we observed only 9.7% cases of local relapse and 4.9% cases of local and systemic progression. The only relapsing patient was neoadjuvantly treated with bolus 5-FU, was not radically resected and did not receive any adjuvant therapy; he is still alive.

At present, 90% of our patients are still free from progression after a median follow-up of 22.1 months, while 7.5% have died. Contradictory to other authors (26-28), neoadjuvant CHT-RT response was not assessed as a prognostic factor for survival probably because of the low number of analysed patients and short follow-up (24).

Depending on features of the cancer, approximately 60% of patients with T3N0M0 rectal cancer are cured without evidence of cancer recurrence following treatment with surgery alone. Despite undergoing complete surgical removal of tumour, 25-40% of patients with stage II rectal carcinoma experience recurrence of their disease with a 5-year survival of 43-71% . It is important to realize that many patients with stage II disease already had small amounts of cancer that had spread away from the rectum and were not removed by surgery. These cancer cells are referred to as micrometastases and cannot be detected with any of the currently available tests. The presence of these microscopic areas of cancer causes the relapses that follow treatment with surgery alone. An effective treatment is needed to clean the body of micrometastases in order to improve the cure rate achieved with surgical removal of the cancer. The administration of cancer treatment following local treatment with surgery is referred to as “adjuvant” therapy.

Actually, in our small 6-year study we reported 90% of cases as still being free from progression after a median follow-up of 22.1 months. Tumor down-staging and resectability rates were high. Moreover, excellent treatment response allowed two-thirds of the patients with low rectal

cancer lesions to have an anal sphincter-sparing procedure. We did not find any influence on local relapse regarding the type of neoadjuvant or adjuvant treatment but the results were more optimistic than those observed in the literature data. We conclude (despite the small number of patients homogenously treated, the retrospective character of collected data and the very short follow-up) that a neoadjuvant therapy may also be useful for stage II rectal cancer at diagnosis, especially for those patients with low lesions. The use of a postoperative chemotherapy should probably be outlined better. A previous trial in our Institution reported, in fact, that the pretreatment T stage and not the pTNM stage was a significant prognostic factor for outcome (8) but, because the number of events (recurrences and deaths) was low and so as to enable statistical analyses, preoperative stage cT2 patients were considered together with cT3 stage patients, postoperative stage pT0 patients were considered together with pT1 stage patients, and pT3 stage patients were considered together with pT4 stage patients. This fact could have influenced the results in these subcategories of patients in some way.

The number of T3N0M0 patients is not so high but, with the introduction of chemoprevention with fecal occult blood and colonoscopy, it could increase in the following years becoming a crucial problem. In the future, only by unifying results from different institutions in prospective studies will it actually be possible to get better insight not only into the role of neoadjuvant therapy in cT3N0M0 mid-low rectal cancer patients, but also into the utility of adjuvant chemotherapy in the same patients.

References

1 NIH Consensus Conference 'Adjuvant therapy for patients with colon and rectal cancer' JAMA *264*: 1444-1450, 1990.

2 Minsky BD, Cohen AM, Kemeny N, Enker WE, Kelsen DP, Reichman B *et al*: Combined modality therapy of rectal cancer: decreased acute toxicity with the preoperative approach. J Clin Oncol *10*: 1218-1224, 1992.

3 Minsky BD, Cohen AM, Enker WE, Saltz L, Guillem JG, Paty PB *et al*: Preoperative 5-FU, low-dose leucovorin, and radiation therapy for locally advanced and unresectable rectal cancer. Int J Radiat Oncol Biol Phys *37*: 289-295, 1997.

4 Minsky BD, Cohen AM, Enker WE and Paty P: Sphincter preservation with preoperative radiation therapy and coloanal anastomosis. Int J Radiat Oncol Biol Phys *31*: 553-559, 1995.

5 Janjan NA, Khoo VS, Abbruzzese J, Pazdur R, Dubrow R, Cleary KR *et al*: Tumour down-staging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: the M.D. Anderson Cancer Center Experience. Int J Radiat Oncol Biol Phys *44*: 1027-1038, 1999.

6 Valentini V, Coco C, Picciocchi A, Morganti AG, Trodella L, Ciabattoni A *et al*: Does down-staging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys *53*: 664-674, 2002.

7 Janjan NA, Crane CN, Feig BW, Cleary K, Dubrow R, Curley SA *et al*: Prospective trial of preoperative concomitant boost radiotherapy with continuous infusion 5-fluorouracil for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys *47*: 713-718, 2000.

8 Pucciarelli S, Friso ML, Toppan P, Fornasiero A, Carnio S, Marchiori E and Lise M: Preoperative combined radiotherapy and chemotherapy for middle and lower rectal cancer: preliminary results. Ann Surg Oncol *7*: 38-44, 2000.

9 Chan AK, Wong AO, Langevin J, Jenken D, Heine J, Buie D and Johnson DR: Preoperative chemotherapy and pelvic radiation therapy for tethered or fixed rectal cancer: a phase II dose escalation study. Int J Radiat Oncol Biol Phys *48*: 843-856, 2000.

10 Desch CE, Benson AB, Smith TJ, Flynn PJ, Krause C, Loprinzi CL *et al*: Recommended colorectal cancer surveillance guidelines by the American Society of Clinical Oncology. J Clin Oncol *17(4)*: 1312-1316, 1999.

11 Paty PB, Enker WE, Cohen AM, Minsky BD and Friedlander-Klar H: Long-term functional results of coloanal anastomosis for rectal cancer. Am J Surg *167*: 90-95, 1994.

12 Minsky BD, Cohen AM, Kemeny N, Enker WE, Kelsen DP, Saltz L and Frankel J: The efficacy of preoperative 5-fluorouracil, high-dose leucovorin, and sequential radiation therapy for unresectable rectal cancer. Cancer *71(11)*: 3486-3492, 1993.

13 Merchant NB, Guillem JG, Paty PB, Enker WE, Minsky BD, Quan SH *et al*: T3N0 rectal cancer: results following sharp mesorectal excision and no adjuvant therapy. J Gastrointest Surg *3(6)*: 642-647, 1999.

14 Bosset JF, Pavy JJ, Hamers HP, Horiot JC, Fabri MC, Rougier P *et al*: Determination of the optimal dose of 5-fluorouracil when combined with low dose D,L-leucovorin and irradiation in rectal cancer: results of three consecutive phase II studies. EORTC Radiotherapy Group. Eur J Cancer *29(10)*: 1406-1410, 1993.

15 Marsh RD, Chu NM, Vauthey JN, Mendenhall WM, Lauwers GY, Bewsher C and Copeland EM: Preoperative treatment of patients with locally advanced unresectable rectal adenocarcinoma utilizing continuous chronobiologically shaped 5fluorouracil infusion and radiation therapy. Cancer *78(2)*: 217-225, 1996.

16 Mohiuddin M, Regine Wf, John WJ, Hagihara PF, McGrath PC, Kenady DE and Marks G: Preoperative chemoradiation in fixed distal rectal cancer: dose time factors for pathological complete response. Int Radiat Oncol Biol Phys *46(4)*: 883-888, 2000.

17 Streit M, Jaehde U, Stremetzne S, Ridwelski K, Kerz H, Strohbach F *et al*: Five days continuous infusion of 5-fluorouracil and pulsed folinic acid in patients with metastatic colorectal carcinoma: an effective second-line regimen. Ann Oncol *8(11)*: 163-165, 1997.

18 Hartmann JT, Kohne CH, Schmoll HJ, Daikeler T, Kanz L and Bokemeyer C: Is continuous 24-hour infusion of 5-fluorouracil plus high dose folinic-acid effective in patients with progressive or recurrent colorectal cancer? A phase II study. Oncology *55(4)*: 320-325, 1998.

19 Chiara S, Nobile MT, Vincenti M, Lionetto R, Gozza A, Barzacchi MC *et al*: Advanced colorectal cancer in the elderly: results of consecutive trials with 5-fluorouracil-based chemotherapy. Cancer Chemother Pharmacol *42(4)*: 336-340, 1998.

20 Stein BN, Petrelli NJ, Douglass HO, Driscoll DL, Arcangeli G and Meropol NJ: Age and sex are independent predictors of 5-FU toxicity. Analysis of a large scale phase III trial. Cancer *75*: 11-17, 1995.

21 AJCC American Joint Committee on Cancer. Fleming DI, Cooper SJ, Henson ED, Hutter VR, Kennedy JB, Murphy PG, O'Sullivan B, Sobin HL and Yarbro WJ (eds.). AJCC Cancer Staging Manual, 5th ed. Philadelphia, Lippincott-Raven pp. 83-90, 1997.

22 Park JO, Lee Sl, Song SY, Kim K, Kim WS, Jung CW *et al*: Measuring response in solid tumours: comparison of RECIST and WHO response criteria. Jpn J Clin Oncol *33(10)*: 533-537, 2003.

23 Kaplan EL and Meier P: Non-parametric estimation for incomplete observation. J Am Stat Assoc *53*: 457-481, 1958.

24 Pucciarelli S, Toppan P, Friso ML, Russo V, Pasetto L, Urso E, Marino F, Ambrosi A and Lise M: Complete pathologic response following preoperative chemoradiation therapy for middle to lower rectal cancer is not a prognostic factor for a better outcome. Dis Colon Rectum *47(11)*: 1798-1807, 2004.

25 Valentini V, Glimelius B, Minsky BD, Van Cutsem E, Bartelink H, Beets-Tan RG *et al*: The multidisciplinary rectal cancer treatment: main convergences, controversial aspects and investigational areas which support the need for an European Consensus. Radiother Oncol *76(3)*: 241-250, 2005.

26 Desch CE, Benson AB, Smith TJ, Flynn PJ, Krause C, Loprinzi CL *et al*: Recommended colorectal cancer surveillance guidelines by the American Society of Clinical Oncology. J Clin Oncol *17(4)*: 1312, 1999.

27 Roh M, Petrelli N, Wieand S *et al*: Phase III randomized trial of preoperative *versus* postoperative multimodality therapy in patients with carcinoma of the rectum. Proc Am Soc Clin Oncol *20*: 123a (abs 490), 2001.

28 Sauer R, Fietkau R, Wittekind C, Rödel C, Martus P, Hohenberger W *et al*: Adjuvant *versus* neoadjuvant radiochemotherapy for locally advanced rectal cancer: the German trial CAO/ARO/AIO-94. Colorectal Dis *5(5)*: 406-415, 2003.

Received May 26, 2008
Revised July 30, 2008
Accepted August 11, 2008