

## Retrospective long-term results and prognostic factors of postoperative treatment for UICC stages II and III rectal cancer

Domenico Genovesi<sup>1</sup>, Giampiero Ausili Cèfaro<sup>1</sup>, Annamaria Vinciguerra<sup>1</sup>, Antonietta Augurio<sup>1</sup>, Marco D'Alessandro<sup>1</sup>, Valentina Borzillo<sup>1</sup>, Rita Marchese<sup>1</sup>, and Marta Di Nicola<sup>2</sup>

<sup>1</sup>Radiation Oncology Department, and <sup>2</sup>Laboratory of Biostatistics, Department of Biomedical Science, "G. d'Annunzio University", Chieti, Italy

---

### ABSTRACT

---

**Aims.** To retrospectively evaluate 5-year local control, disease-free survival, cancer-specific survival and overall survival rates in patients with UICC stages II and III rectal cancer treated with adjuvant therapy and especially to analyze the impact of some prognostic factors on clinical outcome at univariate and multivariate analyses.

**Methods and materials.** We retrospectively reviewed 306 patients treated with postoperative 5-fluorouracil-based chemoradiation (278 patients) or radiotherapy alone (28 patients) after curative surgery. The following prognostic factors were considered at univariate and multivariate analyses: age, sex, tumor location, surgery procedure, pathological stage, histology, tumor grade, surgical margins and radiotherapy technique.

**Results.** The 5-year actuarial rates for local control, disease-free survival, cancer-specific survival and overall survival were respectively 89.7%, 59.7%, 68.6% and 61.4% for the 278 patients (91%) treated with postoperative chemoradiation. Univariate analysis showed that abdominal-perineal resection impacted disease-free survival and that the T4 variable had an impact on cancer-specific survival and disease-free survival. Instead, age  $\geq 70$ , N2, IIIB (p T3 p N1) and IIIC (p T3 p N2) stage impacted cancer-specific survival, disease-free survival and rate of distant metastases. Multivariate analysis showed as significant variables age  $\geq 70$  years, pN1 and pN2 and extraperitoneal tumor location.

**Conclusions.** Our retrospective study showed a good 5-year local control. Factors such as individual pT4, pN1, pN2, age  $\geq 70$  years, abdominal-perineal resection, stages IIIB-IIIC versus II-III A and extraperitoneal tumor location negatively influenced disease-free survival, distant metastases and cancer-specific survival. Differences exist between stages II and III rectal cancer and treatment modulation and intensification are required in order to offer the most appropriate and effective adjuvant treatment and to improve survival of rectal cancer patients.

---

### Introduction

A randomized German trial showed a benefit in local control (LC), acute and late toxicity and sphincter-saving rate for preoperative chemoradiation compared with postoperative chemoradiation<sup>1,2</sup> in locally advanced rectal cancer (International Union Against Cancer UICC Stages II and III)<sup>3</sup>. Nevertheless, postoperative chemoradiation remains a valid option for locally advanced rectal cancer patients, and it still represents a treatment of choice at the moment.

Several important randomized studies have shown improved LC and demonstrated a survival benefit in terms of overall survival (OS) and disease-free survival (DFS) after postoperative 5-fluorouracil (5-FU)-based radiochemotherapy versus surgery

**Key words:** adjuvant treatment, prognostic factors, radiochemotherapy, rectal cancer.

Correspondence to: Domenico Genovesi, MD, Radiation Oncology Department, "G. d'Annunzio University", SS Annunziata Hospital, Via dei Vestini, 66100 Chieti, Italy.  
Tel 0871-358244;  
fax 0871-357473;  
e-mail d.genovesi@tin.it

Received December 18, 2008;  
accepted May 11, 2009.

alone or surgery followed by adjuvant therapy with radiotherapy or chemotherapy alone<sup>4-13</sup>. Therefore, combined chemoradiation improves LC, rate of distant metastases and OS with a satisfactory overall gastrointestinal and hematological acute toxicity<sup>14-16</sup>. The beneficial effect of adjuvant treatment was only achieved by combined chemoradiation with radiation doses >45-50 Gy/reference point in daily fractions of 1.8-2.0 Gy<sup>4,8</sup>.

In 1990, a US NIH Consensus Conference recommended postoperative 5-FU-based radiochemotherapy as standard treatment for stages II and III rectal cancer<sup>17</sup>, and some retrospective studies reviewed clinical outcome (LC, DFS and OS) referred to a mean 5-year follow-up<sup>18-21</sup>. Moreover, many factors could influence local recurrence, DFS and OS<sup>18,21-39</sup>.

Although with all the limitations of a retrospective study, the aim of the present analysis was to determine 5-year LC rates, DFS, cancer-specific survival (CSS) and OS of 278 patients with UICC stages II and III rectal cancer treated with postoperative chemoradiation. Particularly, it analyzed the impact of some factors on DFS, CSS and distant metastases at univariate and multivariate analyses.

## Methods and materials

We retrospectively reviewed 306 patients (217 male and 89 female) with UICC stages II and III rectal cancer treated between 1993 and 2003 at the Radiation Oncology Department of Chieti with postoperative radiotherapy with or without concomitant 5-FU chemotherapy schedules. Selection criteria were: postoperative 5-FU-based chemoradiation (278 patients), no exclusion according to the drugs and performed surgery between 1993-2003.

Tumor site was defined as low for tumors located within 5 cm of the anal verge, middle for tumors located between 6 and 10 cm, and high (or rectosigmoid junction tumors) for tumors between 11 and 15 cm. Tumor site was identified by endoscopy, preoperative computerized tomography (CT) and surgical clips. Local recurrence was defined as pelvic relapse after surgery, and it was histologically or radiologically proven. The following variables were considered: age (<70 and ≥70 years), sex, tumor site, surgery procedure, pathologic stage, histology, tumor grade, surgical margins and radiotherapy technique.

All patients were surgically treated with anterior rectal (ARR) or abdominal-perineal resection (APR). A total of 278 patients was treated with postoperative concomitant radiotherapy and 5-FU, and 28 patients were treated with postoperative radiotherapy alone. The UICC-TNM system was used for tumor staging<sup>3</sup>.

Radiotherapy was delivered with a total dose of 50 Gy (1.8-2.0 Gy/die for five days a week) and a mean time interval of 16 weeks from surgery. A 2D radiotherapy technique

was used from 1993 to 2000, whereas a 3D technique was used from 2001 to 2003 according to International Commission on Radiation Units and Measurements (ICRU) recommendations<sup>40-41</sup>.

All patients were treated in prone position with a 10 MV photon linear accelerator: target volume included surgical clips suggesting tumor bed, internal iliac nodes, obturator nodes, presacral and perirectal spaces; for T4 tumors, external iliac nodes were also included. After abdominal-perineal amputation (Miles' amputation), the perineal scar was also included in the target volume.

Six cycles of 5-FU-based chemotherapy were administered to 278 patients. The treatment consisted of two cycles of an endovenous bolus infusion of 5-FU (500 mg/m<sup>2</sup>/die for five consecutive days followed by an interval of four weeks) and then another two cycles of 5-FU (endovenous bolus of 500 mg/m<sup>2</sup>/die for three consecutive days) administered during the first and the last week of the radiotherapy treatment. Another two cycles of chemotherapy (endovenous bolus of 400 and 500 mg/m<sup>2</sup>/die respectively, for five consecutive days) were administered four weeks after the end of the radiochemotherapy treatment. Acute and late toxicity were assessed using the Radiation Therapy Oncology Group (RTOG) scale<sup>42</sup>.

Patients were followed every four months the first year, every six months from the second to the fifth year, and then once a year. Follow-up evaluation started after the completion of adjuvant treatment. During the follow-up, physical examination, performance status evaluation, complete blood count, serum chemistry, tumor markers (CEA and CA 19-9 levels), chest radiography and colonoscopy were performed every four months for the first year. Moreover, chest-abdominal-pelvic CT scan was performed at the fourth and twelfth month for the first year. All these studies were repeated every six months for the subsequent 5 years. After 5 years, a colonoscopy and chest-abdominal-pelvic CT scan were performed every 12 months.

## Statistical analysis

All qualitative factors were summarized as frequency and percentage and all quantitative factors as mean and standard deviation or median and range. The Kaplan-Meier method was used to analyze LC, DFS and CSS and also to estimate CSS, DFS and distant metastases rate and the standard error at 60 months of follow-up. Statistical significance between curves was evaluated using the logrank test. Multivariate analysis was performed using the Cox proportional hazards model. Covariates were: age, gender, T and N stage, margin status, grading, tumor location and radiation therapy technique. Calculating the exponential of regression coefficients from the Cox model provided an estimate of the hazard ratio and the 95% confidence interval<sup>43</sup>.

Follow-up was defined as the interval between surgery and death or as the time between surgery and the

first verified event or the last follow-up.  $P \leq 0.05$  was considered statistically significant. All statistical analyses were performed using SPSS® software 11.0 (SPSS Inc, Chicago, IL, USA).

**Results**

Median follow-up was 53 months (range, 6-194), and the median age was 62 years (range, 28-86). Characteristics of patients are shown in Table 1. At surgery, 240 patients (78.4%) were <70 years and 66 (21.6%) were ≥70 years. A total of 203 of 306 patients (66.3%) were treated with ARR and 103 of 306 patients (33.7%) with APR.

**Table 1 - Demographic, histologic and treatment characteristics of patients**

Variable	No. of patients	%
Overall no.	306	
Age at surgery (yr)		
<70	240	78.4
≥70	66	21.6
Gender		
Male	217	70.9
Female	89	29.1
Tumor location		
Low rectum	74	24.2
Middle rectum	80	26.1
High rectum-rectosigmoid	103	33.7
Junction unknown	49	16.0
Pathologic stage		
II	132	43.1
III	174	56.9
Margin status		
Negative	228	74.5
Positive	5	1.6
Unknown	73	23.9
Surgery		
ARR	203	66.3
APR	103	33.7
Radiation therapy technique		
3-field	25	8.2
4-field	71	23.2
AP/PA technique	210	68.6
Tumor grading		
1	35	11.4
2	223	72.9
3	23	7.5
Not evaluated	25	8.2
Chemotherapy		
Yes	278	90.8
No	28	9.2
Histology		
Adenocarcinoma	302	98.7
Mucinous	4	1.3
Months of follow-up, median, range	53	6-194

ARR, anterior rectal resection; APR, abdominal-perineal resection; AP/PA, anterior-posterior/posterior-anterior.

**Table 2 - Distribution of pathological staging (pTN)**

T	N0	N1	N2
1	-	1 (0.3)	-
2	-	19 (6.2)	5 (1.6)
3	125 (40.9)	80 (26.2)	59 (19.3)
4	7 (2.3)	5 (1.6)	5 (1.6)

Chemotherapy was contraindicated in 28 of 306 patients (9.2%) because of comorbidities. Distribution of pathological staging (T and N) is shown in Table 2. The 28 patients (9.2%) treated with adjuvant radiotherapy alone had no local recurrence, whereas 2 of them (7.1%) were alive with systemic disease at the last follow-up and 11 patients (39.3%) died because of metastatic disease. No local or distant recurrence was observed in 15 patients (53.6%).

For the 278 patients (91%) treated with postoperative chemoradiation, LC was 89.7%, DFS was 59.7%, CSS was 68.6%, and OS was 61.4% at 5 years, respectively. LC seemed to be constant for patients with a longer follow-up, whereas DFS and CSS seemed to be worse for patients with a longer follow-up (Figure 1). Twenty-six patients treated with postoperative chemoradiation experienced local recurrence, and 14 of them, who had distant metastases, died for disease-related causes.

The individual evaluation of pT and pN characteristics showed that the pT4 variable had a statistically significant impact on CSS and DFS ( $P < 0.01$  and  $P < 0.05$ , respectively) and that the pN2 variable had a statistically significant impact on distant metastases, CSS and DFS ( $P < 0.001$ ).

Pathologic stages IIIB (pT3pN1) and IIIC (pT3pN2) had a statistically significant impact on CSS, DFS and distant metastases ( $P < 0.05$  and  $P < 0.001$ , respectively) (Table 3).

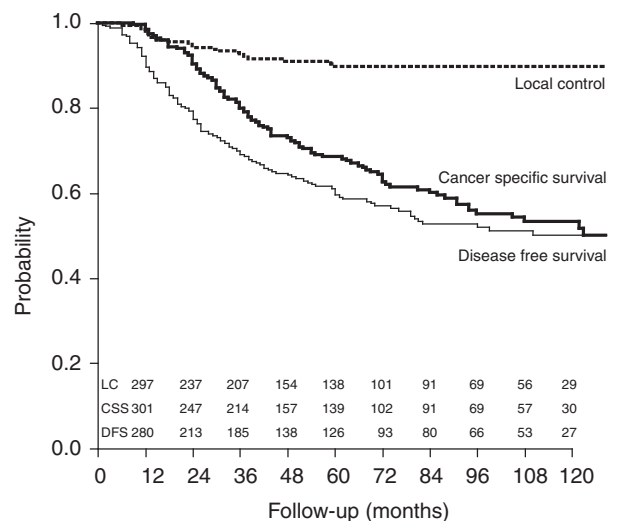


Figure 1 - Kaplan-Meier curves of local control, disease-free survival and cancer-specific survival for 278 patients treated with postoperative chemoradiation.

**Table 3 - Univariate analysis of impact of T stage, N stage and TN stage on cancer-specific survival, disease-free survival and distant metastases at 60 months of follow-up**

Variable	Cancer-specific survival		Disease-free survival		Distant metastases	
	60 mo rate ± SE*	P <sup>§</sup>	60 mo rate ± SE*	P <sup>§</sup>	60 mo rate ± SE*	P <sup>§</sup>
<b>T-stage</b>						
T1-2	76.8 ± 9.2	-	67.4 ± 9.5	-	68.8 ± 9.8	-
T3	69.4 ± 3.1	ns	60.5 ± 3.2	ns	64.7 ± 3.2	ns
T4	41.7 ± 12.7	<0.01	36.8 ± 12.3	<0.05	46.2 ± 13.5	ns
<b>N-stage</b>						
N0	78.0 ± 4.0	-	68.9 ± 4.3	-	72.8 ± 4.2	-
N1	66.1 ± 4.9	ns	60.7 ± 5.0	ns	64.5 ± 5.0	ns
N2	53.9 ± 6.5	<0.001	40.3 ± 6.5	<0.001	45.9 ± 6.9	<0.001
<b>TN stage</b>						
IIIA (pT1-2 pN1)	75.7 ± 10.8	-	69.3 ± 10.5	-	73.0 ± 10.4	-
IIIC (pT1 pN2)	80.0 ± 17.9	ns	60.0 ± 21.9	ns	40.0 ± 21.9	ns
IIA (pT3 pN0)	79.2 ± 4.0	-	74.0 ± 4.1	-	74.7 ± 4.2	-
IIIB (pT3 pN1)	65.5 ± 5.7	<0.05	60.0 ± 5.8	<0.05	63.1 ± 5.8	<0.05
IIIC (pT3 pN2)	54.0 ± 7.0	<0.001	39.8 ± 7.1	<0.001	44.8 ± 7.4	<0.001
IIB (pT4 pN0)	57.1 ± 18.7	-	42.9 ± 18.7	-	42.9 ± 18.7	-
IIIB (pT4 pN1)	40.0 ± 21.9	ns	40.0 ± 21.9	ns	50.0 ± 25.0	ns
IIIC (pT4 pN2)	30.0 ± 22.3	ns	26.7 ± 22.6	ns	53.3 ± 24.8	ns

\*Unadjusted Kaplan-Meier estimates expressed as percentage.

§Logrank test versus the first category.  
ns, not significant.

The 5-year univariate analysis showed that pathologic stages IIIB (pT3pN1) and IIIC (pT3pN2) compared with stages IIIA and II had a statistically significant impact on CSS, DFS and distant metastases. Age ≥70 years and pathologic III stage also had a statistically significant impact on CSS, DFS and distant metastases.

The APR surgical procedure and tumor location had an impact on DFS and distant metastases, respectively (Table 4).

Multivariate analysis of factors influencing CSS, DFS and distant metastases showed that age ≥70 years was a statistically significant factor for DFS ( $P < 0.05$ ) and distant metastases ( $P < 0.01$ ).

The N1 variable was a statistically significant factor only for CSS ( $P < 0.05$ ), whereas the N2 variable was a statistically significant factor for CSS ( $P < 0.001$ ), DFS ( $P < 0.001$ ) and distant metastases ( $P < 0.01$ ).

An intraperitoneal tumor location (high rectum and rectosigmoid junction) was better than other extraperitoneal locations as a prognostic factor for CSS ( $P < 0.05$ ) and DFS ( $P < 0.01$ ) (Table 5).

Grades 3 and 4 acute gastrointestinal toxicity occurred in 6% of patients and acute hematologic toxicity in 8%. Twenty-three patients experienced grades 3-4 gastrointestinal late toxicity and 12 patients experienced grade 4 late toxicity in terms of intestinal obstruction.

## Discussion

The historical combined randomized postoperative 5-FU-based chemoradiation trials demonstrated an im-

provement of LC ranging from 83% to 92%, with a mean survival rate of 60%<sup>9-12,44</sup>. Although with all limitations of a retrospective analysis, with a long period of collection and some differences in technologies, radiotherapy and surgery procedures, we confirmed the importance of some factors which explain the heterogeneity within stages II and III regarding prognosis.

In the present study, for the postoperative chemoradiation group (278 patients), the 5-year results showed that LC was 89.7%, and this seems to remain the same for patients with a longer follow-up. DFS was 59.7% and CSS was 68.6% at 5-years, with worse results for patients with a longer follow-up. OS was 61.4% at 5-years.

Wulf *et al.*<sup>18</sup>, in their retrospective surveillance study of 198 patients with stages II-III rectal cancer, observed a 5-year LC of 75%, a DFS of 53% and a CSS of 53%. Bagatzounis *et al.*<sup>19</sup> retrospectively analyzed 112 stage II-III patients treated with radiotherapy (44 patients) and adjuvant 5-FU-based radiochemotherapy (68 patients) and reported a 5-year LC rate of 67% (radiotherapy group) and 69% (chemoradiation group), DFS of 50%-52% for the two groups, and OS of 53% (radiotherapy group) and 63% (chemoradiation group).

In our study, univariate analysis showed that the most important factors significantly influencing DFS, distant metastases and CSS were age ≥70, the APR surgical procedure, individual factors pT4 and pN2, IIIB and IIIC stage. Multivariate analysis confirmed the impact of age ≥70, N1-2 factors and extraperitoneal site on survival. The most important historical studies showed that prognostic factors influencing local recurrences and survival in stages II-III/TNM (UICC) rectal cancer were primary tumor extension and positive nodes<sup>9-11,18,20-39</sup>.

**Table 4 - Univariate analysis of impact of clinical characteristics on cancer-specific survival, disease-free survival and distant metastases at 60 months of follow-up**

Variable	Cancer-specific survival		Disease-free survival		Distant metastases	
	60 mo rate $\pm$ SE*	P <sup>§</sup>	60 mo rate $\pm$ SE*	P <sup>§</sup>	60 mo rate $\pm$ SE*	P <sup>§</sup>
Gender						
Male	65.0 $\pm$ 3.5	-	56.5 $\pm$ 3.6	-	60.8 $\pm$ 3.6	-
Female	77.4 $\pm$ 4.7	ns	69.7 $\pm$ 5.1	ns	72.5 $\pm$ 5.1	ns
Age at surgery (yr)						
<70	70.4 $\pm$ 3.1	-	66.1 $\pm$ 3.2	-	67.5 $\pm$ 3.3	-
$\geq$ 70	60.8 $\pm$ 6.9	<0.05	46.1 $\pm$ 6.9	<0.05	51.0 $\pm$ 7.0	<0.05
Tumor location						
Low rectum	66.2 $\pm$ 6.0	-	56.6 $\pm$ 6.1	-	60.3 $\pm$ 6.1	-
Medium rectum	72.6 $\pm$ 5.3	ns	65.7 $\pm$ 5.5	ns	71.6 $\pm$ 5.3	<0.05
High rectum-rectosigmoid junction	70.8 $\pm$ 4.9	ns	68.5 $\pm$ 4.8	ns	72.4 $\pm$ 4.7	ns
Pathologic staging						
II	78.0 $\pm$ 4.0	-	68.9 $\pm$ 4.3	-	72.8 $\pm$ 4.2	-
III	61.3 $\pm$ 4.0	<0.001	52.9 $\pm$ 4.0	<0.01	57.5 $\pm$ 4.1	<0.01
Margin status						
Negative	69.1 $\pm$ 3.4	-	60.0 $\pm$ 3.5	-	66.1 $\pm$ 3.4	-
Positive	80.0 $\pm$ 17.9	ns	80.0 $\pm$ 17.9	ns	100.0	ns
Surgery						
ARR	71.2 $\pm$ 3.5	-	63.3 $\pm$ 3.7	-	67.5 $\pm$ 3.6	-
APR	63.2 $\pm$ 5.0	ns	53.8 $\pm$ 5.1	<0.05	57.5 $\pm$ 5.2	ns
Technique						
3-4 field	72.4 $\pm$ 5.6	-	55.1 $\pm$ 7.6	-	56.7 $\pm$ 7.6	-
AP/PA	67.1 $\pm$ 3.3	ns	60.2 $\pm$ 3.4	ns	65.9 $\pm$ 3.4	ns
Tumor grading						
G1 or G2	68.6 $\pm$ 3.1	-	61.5 $\pm$ 3.2	-	66.5 $\pm$ 3.2	-
G3	66.0 $\pm$ 10.6	ns	54.5 $\pm$ 10.9	ns	57.6 $\pm$ 10.9	ns

\*Unadjusted Kaplan-Meier estimates expressed as percentage.

<sup>§</sup>Logrank test versus the first category.

ARR, anterior rectal resection; APR, abdominal-perineal resection; AP/PA, anterior-posterior/posterior-anterior; ns, not significant.

**Table 5 - Multivariate analysis of factors influencing cancer-specific survival, disease-free survival and distant metastases**

Variable	Cancer-specific survival		Disease-free survival		Distant metastases	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age at surgery (yr)						
<70	1	-	1	-	1	-
$\geq$ 70	1.57 (0.97-2.76)	ns	1.61 (1.08-2.52)	<0.05	2.07 (1.26-3.39)	<0.01
N-stage						
N0	1	-	1	-	1	-
N1	1.70 (1.08-3.13)	<0.05	1.57 (0.98-2.54)	ns	1.54 (0.90-2.63)	ns
N2	3.42 (2.10-6.29)	<0.001	3.01 (1.90-4.95)	<0.001	2.40 (1.35-4.27)	<0.01
Tumor location						
Low rectum	1	-	1	-	1	-
Middle rectum	0.68 (0.41-1.16)	ns	0.65 (0.41-1.11)	ns	0.64 (0.34-1.21)	ns
High rectum-rectosigmoid junction	0.57 (0.34-0.95)	<0.05	0.53 (0.33-0.85)	<0.01	0.62 (0.32-1.17)	ns
Technique						
3-4 field	1	-	1	-	1	-
AP/PA	1.64 (0.96-2.88)	ns	1.09 (0.69-1.72)	ns	0.89 (0.41-1.92)	ns

HR, hazard ratio estimated by Cox proportional hazards model adjusted for T-stage, gender, margin status, surgery and grading.

AP/PA, anterior-posterior/posterior-anterior; ns, not significant.

As regards tumor stage, Gunderson *et al.*<sup>28</sup>, in their pooled analysis of 2551 patients, analyzed the influence of individual factors T and N and pathological stage on LC, DFS and OS. They demonstrated a negative influence of T and N factors because a locally advanced tumor (T3-T4, N plus) had a worse prognostic evolution than others

with a single factor alone (T3N0 or T1-2 N1). Therefore, stages II (T3-4 N0) and IIIA (T1-2 N1) had a better prognosis than stages IIIB (T3N1) and IIIC (T3-4 N2).

Greene *et al.*<sup>29</sup> analyzed data entered in a National Cancer Data Base for 5,987 stage III patients with rectal cancer between 1991 and 1993. Stage IIIA patients had

an observed 60% 5-year survival, IIIB patients 41%, and IIIC patients 29%, with significant differences in all stages.

Our data confirmed these evaluations: univariate analysis confirmed that factors such as pT4, pN2, IIIB and IIIC stage influenced DFS, distant metastases and CSS, whereas multivariate analysis identified N1 and N2 as factors that influenced DFS, distant metastases and CSS.

In the retrospective study of Bagatzounis *et al.*<sup>19</sup>, they revealed that positive lymph node stage and high tumor differentiation were independently statistically significant for DFS and OS. Other studies evidenced the importance of number of removed nodes ( $\geq 12$ ) and the negative prognostic impact on clinical outcome of node-positive number  $\geq 3$ <sup>18,21,45-46</sup>. Mean number of removed nodes was 14 (range, 5-43) in our study, and we showed the importance of N1 and N2 factors at multivariate analysis.

Factors such as tumor grade have been shown to influence survival, LC and metastasis rate<sup>18-19,24</sup>. However, in our analysis such a factor was not statistically significant.

Jatzko *et al.*<sup>34</sup> found that age was not a significant factor at univariate analysis, but it became significant at multivariate analysis because age  $\geq 65$  years influenced DFS. Other studies have demonstrated the influence of age on survival<sup>47-48</sup>, but Myerson *et al.*<sup>24</sup> did not find an influence of age on LC and DFS. Our study showed an impact of age ( $\geq 70$  years) on DFS both at univariate and multivariate analysis and also an influence on CSS and metastasis rate at multivariate analysis.

Other variables have also been considered as factors that influence LC, metastasis rate, DFS and OS, such as negative surgical margins<sup>18</sup>, lymphatic vascular invasion<sup>19</sup>, tumor fixation at surgery, gender<sup>49</sup> and intraperitoneal versus extraperitoneal rectal cancer location<sup>50</sup>. In our analysis, surgical margins and tumor grade were not statistically significant variables, probably due to the few number of patients with positive or unknown margins and to the few number of G3 cases or with an unknown tumor grade.

As regards tumor location, Benzoni *et al.*<sup>50</sup> examined clinical outcome in patients enrolled in a neoadjuvant chemoradiation followed by surgery protocol for rectal cancer, distinguishing between intraperitoneal and extraperitoneal cancer. The DFS and OS were worse for extraperitoneal than for intraperitoneal rectal cancer. Our data confirmed these evaluations in the multivariate analysis, with a negative influence of extraperitoneal tumor location on DFS and CSS. This could be explained by either an incomplete lymphatic resection or inappropriate application of chemoradiation protocols. It could be that extraperitoneal tumors are more aggressive than intraperitoneal tumors, spreading precociously or less responsive to adjuvant chemoradiation because of their localization, rather than differences in biological characteristics.

## Conclusions

Even though the standard of therapy for locally advanced rectal cancer (stages II and III) is preoperative chemoradiation, the postoperative chemoradiation regimen represents a valid treatment option and is still a treatment choice for locally advanced rectal cancer in Italy at the moment. Although there are important differences between stages II and III in terms of biological aspects and prognosis, patients with stages II or III rectal cancer are often treated with similar adjuvant chemoradiation schedules in terms of radiation doses and drugs. Although with all limitations of a retrospective study, our results confirmed those of larger retrospective analyses. We pointed out the importance of prognostic factors in treatment modulation and intensification based on clinicopathologic characteristics, especially with regard to T and N substages<sup>51,52</sup>.

## References

1. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R; German Rectal Cancer Study Group: Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*, 351: 1731-1740, 2004.
2. Valentini V, Beets-Tan R, Borras JM, Krivokapi Z, Leer JW, Pahlman L, Rödel C, Schmoll HJ, Scott N, Velde CV, Verfaille C: Evidence and research in rectal cancer. *Radiother Oncol*, 87: 449-474, 2008.
3. International Union Against Cancer (UICC): Colon e retto. In: TNM Classificazione dei tumori maligni, Sobin LH, Wittekind Ch (Eds.), 6th edn, pp 72-76, Raffaello Cortina Editore, Milano, 2002.
4. Caffero F, Gipponi M, Lionetto R, PAR Cooperative Study Group: Randomised clinical trial of adjuvant postoperative RT vs. sequential postoperative RT plus 5-FU and levamisole in patients with stage II-III resectable rectal cancer: a final report. *J Surg Oncol*, 83: 140-146, 2003.
5. Arnott SJ: Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. Medical Research Council Rectal Cancer Working Party. *Lancet*, 348: 1610-1614, 1996.
6. Valencia J, Escó R, Polo S, Bascón N, Escudero P, Alonso V: Postoperative radiochemotherapy in rectal cancer comparison of two combination schemes: alternating versus concomitant. *Tumori*, 90: 216-224, 2004.
7. Folprecht G, Köhne CH: Principles of postoperative therapy in rectal carcinoma. *Chirurg* 75: 32-37, 2004.
8. Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerham DL, Fisher ER, Caplan R, Jones J, Lerner H, Gordon P, Feldman M, Cruz A, Legault-Poisson S, Wexler M, Lawrence W, Robidoux A and other NSABP investigators: Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst*, 80: 21-29, 1988.
9. Gastrointestinal Tumor Study Group (GITSG): Prolongation of disease-free interval in surgically treated rectal carcinoma. *N Engl J Med*, 312: 1465-1472, 1985.
10. Gastrointestinal Tumor Study Group (GITSG): Radiation therapy and fluorouracil with or without semustine for the treatment of patients with surgical adjuvant adenocarcinoma of the rectum. *J Clin Oncol*, 10: 549-557, 1992.

11. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, Kubista TP, Poon MA, Meyers WC, Mailliard JA: Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med*, 324: 709-715, 1991.
12. O'Connell MJ, Martenson JA, Wieand HS, Krook JE, Macdonald JS, Haller DG, Mayer RJ, Gunderson LL, Rich TA: Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med*, 331: 502-507, 1994.
13. Tveit KM, Guldvog I, Hagen S, Trondsen E, Harbitz T, Nygaard K, Nilsen JB, Wist E, Hannisdal E: Randomized controlled trial of postoperative radiotherapy and short-term time-scheduled 5-fluorouracil against surgery alone in the treatment of Dukes' B and C rectal cancer. Norwegian Adjuvant Rectal Cancer Project Group. *Br J Surg*, 84: 1130-1135, 1997.
14. Douglass HO, Stablein D: Ten-year follow-up of first generation surgical adjuvant studies of the gastrointestinal tumor study group. In: Adjuvant therapy of cancer VI. Proceedings of the Sixth International Conference on the Adjuvant Therapy of Cancer, Salmon SE (Ed), pp 405-415, W.B. Saunders, Philadelphia, 1990.
15. Ensminger WD, Gyves JW: Regional cancer chemotherapy. *Cancer Treat Rep*, 68: 101-115, 1984.
16. Hafström L, Domellöf L, Rudenstam CM, Norryd C, Bergman L, Nilsson T, Hansson K, Wählby L, Asklöf G, Kugelberg C: Adjuvant chemotherapy with 5-fluorouracil, vincristine and CCNU for patients with Dukes' C colorectal cancer. The Swedish Gastrointestinal Tumor Adjuvant Therapy Group. *Br J Surg*, 77: 1345-1348, 1990.
17. NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA*, 264: 1444-1450, 1990.
18. Wulf J, Krämer K, van Aaken C, Dietzel F, Lucas D, Pfänder K, Schimpke T, Schulze W, Thiel HJ, Ziegler K, Flentje M: Outcome of postoperative treatment for rectal cancer UICC Stage II and III in day-to-day clinical practice. Results from a retrospective quality control analysis in six institutions in North Bavaria (Germany). *Strahlenther Onkol*, 1: 5-14, 2004.
19. Bagatzounis A, Willner J, Oppitz U, Flentje M: The postoperative adjuvant radiation therapy and radiochemotherapy for UICC stage II and III rectal cancer. A retrospective analysis. *Strahlenther Onkol*, 176: 112-117, 2000.
20. Lupattelli M, Maranzano E, Bellavita R, Tarducci R, Latini R, Castagnoli P, Bufalari A, Corgna E, Pinaglia D, Rossetti R, Ribacchi R, Latini P: Adjuvant radiochemotherapy in high-risk rectal cancer results of a prospective non-randomized study. *Tumori*, 87: 239-247, 2001.
21. Scandolaro L, Cazzaniga LF, Bianchi E, Cagna E, Prina M, Valli MC, Barsacchi L, Frigerio M: Postoperative adjuvant radio(chemo)therapy for rectal cancer: an appraisal. *Tumori*, 90: 208-215, 2004.
22. Hermanek P, Wiebelt H, Staimmer D, Riedl S: Prognostic factors of rectal carcinoma – experience of the German Multicentre Study SGCRC. German Study Group Colo-Rectal Carcinoma. *Tumori*, 81: 60-64, 1995.
23. Pahlman L: Local recurrence rate in a randomised multicentre trial of preoperative radiotherapy compared with operation alone in respectable rectal carcinoma. *Swedish Rectal Cancer Trial*. *Eur J Surg*, 162: 397-402, 1996.
24. Myerson RJ, Michalski JM, King ML, Birnbaum E, Fleshman J, Fry R, Kodner I, Lacey D, Lockett MA: Adjuvant radiation therapy for rectal carcinoma: predictors of outcome. *Int J Radiat Oncol Biol Phys*, 32: 41-50, 1995.
25. Hermanek P, Hermanek PJ: Role of the surgeon as a variable in the treatment of rectal cancer. *Semin Surg Oncol*, 19: 329-335, 2000.
26. Hall NR, Finan PJ, al-Jaberi T, Tsang CS, Brown SR, Dixon MF, Quirke P: Circumferential margin involvement after mesorectal excision of rectal cancer with curative intent. Predictor of survival but not local recurrence? *Dis Colon Rectum*, 41: 979-983, 1998.
27. Miholic J, Loimer L, Wrba F, Markis E, Wollenek G, Dieckmann-Miholic A, Moeschl P, Wolner E: Risk factors for local recurrence of rectal carcinoma. *Wien Klin Wochenschr*, 103: 169-175, 1991.
28. Gunderson LL, Sargent DJ, Tepper JE, O'Connell MJ, Allmer C, Smalley SR, Martenson JA, Haller DG, Mayer RJ, Rich TA, Ajani JA, Macdonald JS, Goldberg RM: Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer: a pooled analysis. *Int J Radiat Oncol Biol Phys*, 54: 386-396, 2002.
29. Greene FL, Stewart AK, Norton HJ: New tumor-node-metastasis staging strategy for node-positive (stage III) rectal cancer: an analysis. *J Clin Oncol*, 22: 1778-1784, 2004.
30. Merkel S, Mansmann U, Papadopoulos T, Wittekind C, Hohenberger W, Hermanek P: The prognostic inhomogeneity of colorectal carcinomas stage III: a proposal for subdivision of stage III. *Cancer*, 92: 2754-2759, 2001.
31. Willet CG, Badizadegan K, Ancukiewicz M, Shellito PC: Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? *Dis Colon Rectum*, 42: 167-173, 1999.
32. Tepper JE, O'Connell MJ, Niedzwiecki D, Hollis D, Compton C, Benson AB 3rd, Cummings B, Gunderson L, Macdonald JS, Mayer RJ: Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol*, 19: 157-163, 2001.
33. Link KH, Staib L, Schatz M, Suhr P, Röttinger E, Beger HG: Adjuvant radiochemotherapy – what is the patients benefit? *Langenbecks Arch Surg*, 383: 416-426, 1998.
34. Jatzko GR, Jagoditsch M, Lisborg PH, Denk H, Klimpfinger M, Stettner HM: Long-term results of radical surgery for rectal cancer: multivariate analysis of prognostic factors influencing survival and local recurrence. *Eur J Surg Oncol*, 25: 284-291, 1999.
35. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, Hammond ME, Henson DE, Hutter RV, Nagle RB, Nielsen ML, Sargent DJ, Taylor CR, Welton M, Willett C: Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med*, 124: 979-994, 2000.
36. Bamias A, Basdanis G, Xanthakis I, Pavlidis N, Fountzilas G: Prognostic factors in patients with colorectal cancer receiving adjuvant chemotherapy or chemoradiotherapy. A pooled analysis of two randomized studies. *Int J Gastrointest Cancer*, 36: 29-38, 2005.
37. Gill S, Loprinzi CL, Sargent DJ, Thomè SD, Alberts SR, Haller DG, Benedetti J, Francini G, Shepherd LE, Francois SJ, Labianca R, Chen W, Cha SS, Heldebrant MP, Goldberg RM: Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? *J Clin Oncol*, 22: 1797-1806, 2004.
38. Shen M-Y, Lin J-K, Lin T-C: Prognostic significance of lymph node metastasis in resected colorectal cancer. *J Soc Colon Rectal Surgeon (Taiwan)*, 14: 7-14, 2003.
39. Valentini V, Glimelius B, Minsky BD, Van Cutsem E, Bartelink H, Beets-Tan Regine GH, Gerard JP, Kosmidis P, Pahlman L, Picciocchi A, Quirke P, Tepper J, Tonato M, Van de Velde CJ, Cellini N, Latini P: The multidisciplinary rectal cancer treatment: main convergences, controversial aspects and investigational areas which support the need for a European consensus. *Radiother Oncol*, 76: 241-250, 2005.
40. International Commission on Radiation Units and Measurements: Prescribing, Recording and Reporting Photon Beam Therapy. ICRU Report 50, ICRU, Bethesda, MD, 1993.
41. International Commission on Radiation Units and Measurements: Prescribing, Recording and Reporting Photon

- Beam Therapy (Supplement to ICRU Report 50). ICRU Report 62, ICRU, Bethesda, MD, 1999.
42. Cox JD, Stetz J, Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*, 31: 1341-1346, 1995.
  43. Marubini E, Valsecchi MG: *Analysing Survival Data From Clinical Trials and Observational Studies*. John Wiley & Sons, New York, 1995.
  44. Smalley SR, Benedetti JK, Williamson SK, Robertson JM, Estes NC, Maher T, Fisher B, Rich TA, Martenson JA, Kugler JW, Benson AB 3rd, Haller DG, Mayer RJ, Atkins JN, Cripps C, Pedersen J, Periman PO, Tanaka MS Jr, Leichman CG, Macdonald JS: Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. *J Clin Oncol*, 24: 3542-3547, 2006.
  45. Cionini L, Marzano S, Boffi L, Cardona G, Ficari F, Fucini C, Tonelli F: Adjuvant postoperative radiotherapy in rectal cancer: 148 cases treated at Florence University with 8 years median follow-up. *Radiother Oncol*, 40: 127-135, 1996.
  46. Martenson JA Jr, Willett CG, Sargent DJ, Mailliard JA, Donohue JH, Gunderson LL, Thomas CR Jr, Fisher B, Benson AB 3rd, Myerson R, Goldberg RM: Phase III study of adjuvant chemotherapy and radiation therapy compared with chemotherapy alone in the surgical adjuvant treatment of colon cancer: results of Intergroup Protocol 0130. *J Clin Oncol*, 22: 3277-3283, 2004.
  47. Bentzen SM, Balslev I, Pedersen M, Teglbaerg PS, Hanberg-Soerensen E, Bone J, Jacobsen NO, Overgaard J, Sell A, Bertelsen K, et al: A regression analysis of prognostic factors after resection of Dukes' B and C carcinoma of the rectum and rectosigmoid. Does post-operative radiotherapy change the prognosis? *Br J Cancer*, 58: 195-201, 1988.
  48. Fietkau R, Zettl H, Klöcking S, Kundt G: Incidence, therapy and prognosis of colorectal cancer in different age groups. A population-based cohort study of the Rostock Cancer Registry. *Strahlenther Onkol*, 180: 478-487, 2004.
  49. Martijn H, de Neve W, Lybeert ML, Crommelin MA, Ribot JG: Adjuvant postoperative radiotherapy for adenocarcinoma of the rectum and rectosigmoid. A retrospective analysis of locoregional control, survival, and prognostic factors on 178 patients. *Am J Clin Oncol*, 18: 277-281, 1995.
  50. Benzoni E, Terrosu G, Bresadola V, Cerato F, Cojutti A, Milan E, Dado G, Bresadola F: Analysis of clinical outcomes and prognostic factors of neoadjuvant chemoradiotherapy combined with surgery: intraperitoneal versus extraperitoneal rectal cancer. *Eur J Cancer Care*, 15: 286-292, 2006.
  51. Rodel C, Sauer R: Integration of novel agents into combined modality treatment for rectal cancer patients. *Strahlenther Onkol*, 183: 227-235, 2007.
  52. Kalofonos HP, Bamias A, Koutras A, Papakostas P, Basdanis G, Samantas E, Karina M, Misailidou D, Pisanidis N, Pentheroudakis G, Economopoulos T, Papadimitriou C, Skarlos DV, Pectasides D, Stavropoulos M, Bafaloukos D, Kardamakis D, Karanikiotis C, Vourli G, Fountzilas G, Hellenic Cooperative Oncology Group Study: A randomised phase III trial of adjuvant radio-chemotherapy comparing irinotecan, 5FU and leucovorin to 5FU and leucovorin in patients with rectal cancer: a Hellenic Cooperative Oncology Group Study. *Eur J Cancer*, 44: 1693-1700, 2008.