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Neoadjuvant oral *vs.* infusional chemoradiotherapy on locally advanced rectal cancer: Prognostic factors

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ABSTRACT

Aim: To evaluate the prognostic factors and impact on survival of neoadjuvant oral and infusional chemoradiotherapy in patients with locally advanced rectal cancer.
Background: There is still no definitive consensus about the prognostic factors and the impact of neoadjuvant chemoradiotherapy on survival. Some studies have pointed to an improvement in overall survival (OS) and progression-free survival (PFS) in patients with tumor downstaging (TD) and nodal downstaging (ND).
Materials and methods: A set of 159 patients with LARC were treated preoperatively. Group A – 112 patients underwent concomitant oral chemoradiotherapy: capecitabine or UFT + folinic acid. Group B – 47 patients submitted to concomitant chemoradiation with 5-FU in continuous infusion. 63.6% of patients were submitted to adjuvant chemotherapy.
Results: Group A: pathologic complete response (pCR) – 18.7%; TD – 55.1%; ND – 76%; loco-regional response – 74.8%. Group B: pCR – 11.4%; TD – 50%; ND – 55.8%; LRR – 54.5%. The loco-regional control was 95.6%. There was no difference in survival between both groups. Those with loco-regional response had better PFS.
Conclusions: Tumor and nodal downstaging, loco-regional response and a normal CEA level turned out to be important prognostic factors in locally advanced rectal cancer. Nodal downstaging and loco-regional response were higher in Group A. Those with tumor downstaging and loco-regional response from Group A had better OS. Adjuvant chemotherapy had no impact on survival except in those patients with loco-regional response who achieved a higher PFS.

1. Background

Rectal adenocarcinoma is associated with a very high rate of local relapse after surgery alone. Some studies have demonstrated that adjuvant chemotherapy (CT) and radiotherapy (RT) reduce the rate of local relapse and prolong survival in patients whose tumors extend into the perirectal fat (T3) or who have mesorectal or pelvic lymph nodes involvement (N1–3).[1]

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Preoperative chemoradiotherapy (CT + RT) offers some theoretical advantages over adjuvant therapy for patients with a tumor of the middle to lower rectum[2]: (i) micrometastases are treated early in the course of the disease; (ii) the risk of tumor seeding during surgery is reduced; (iii) RT toxicity is also reduced; (iv) the efficacy of CT and RT is higher in a tumor with an intact vasculature; (v) if the tumor shrinks, a sphincter preserving procedure can be performed. Nevertheless, this treatment also has some drawbacks: (i) definitive therapy is delayed, which may allow the growth and dissemination of the tumor; (ii) as preoperative staging is not very precise, patients on early stages (T1–2N0) of the disease, who do not need this therapy because of their very low risk of relapse, would be overtreated.

After the randomized trial CAO/ARO/AIO,[3] neoadjuvant CT + RT became the standard of care, since the 5-year local recurrence rate is reduced, adherence is better and it has fewer acute and long-term toxic effects than postoperative CT + RT. Neoadjuvant use of CT and RT allows a higher rate of resectability associated to a tumor and nodal downstaging.[4]

Concomitant neoadjuvant 5-FU CT + RT provides a pathologic complete response (pCR) in 8–27% of cases and is associated with an increased local control.[2–14] The single randomized trial that compared preoperative *vs.* postoperative CT + RT concluded that there was a lower 5-year local relapse (6% *vs.* 13%, $p = 0.006$) and a decrease in acute and late toxicity with preoperative CT + RT, although there was no difference in overall survival.[3] Theoretically, oral fluoropyrimidines are suitable to replace protracted infusion of 5-FU and avoid more invasive procedures.

Elevated preoperative serum carcinoembryonic antigen (CEA) levels, the most widely used tumor marker for the management of colorectal cancer, has been reported to be associated with a pathologic complete response, tumor downstaging and with an increased risk of relapse and poor patient outcome.[15–17]

The impact of neoadjuvant CT + RT on survival has been controversial. Some studies have pointed to an improvement in overall survival (OS) and progression-free survival (PFS) in patients with pathological response after neoadjuvant therapy.[9,18,19]

2. Aim

Since the standard schedule of preoperative CT + RT for rectal cancer remains to be established, and due to the convenience of oral drugs, we evaluate the therapeutic response to 5-FU and oral chemotherapy either with UFT and folinic acid or capecitabine combined with preoperative RT in patients with stages II–III rectal cancer in order to establish the best regimen for neoadjuvant treatment. Toxicity and survival were also analyzed for both groups, as well as the relationship between pathologic response, tumor downstaging, nodal downstaging and loco-regional response and survival. We analyze the impact of adjuvant chemotherapy in these patients, as this has also been a controversial issue.[20,21]

3. Materials and methods

3.1. *Patients*

We analyzed prospectively 159 patients with locally advanced rectal cancer (LARC) treated with neoadjuvant chemoradiotherapy from December 2002 to September 2009. We included all patients with endoscopic and/or radiologic tumors staged as II–III rectal cancer from our Institution, without associated co-morbidities that preclude the proposed therapy and group selection was done according to the ability to adhere to oral therapy. Patients were divided into 2 groups. Group A: consisting of 112 patients who were treated with RT and concomitant oral CT. Group B: consisting of 47 patients, submitted to RT and concomitant CT with continuous infusion of 5-FU. Patients' characteristics corresponding to the different groups are described in Table 1.

3.2. *Neoadjuvant radiotherapy*

The patient's prone position was recommended, and a belly board immobilization device was used. A pelvic CT scan in the treatment position was performed in all patients, from L5-S1 to 2 cm distal to the anus. All patients underwent three-dimensional treatment planning. CT scan was used to define gross tumor volume (GTV). Clinical target volume (CTV) included the GTV + 2 cm in all directions, perirectal, internal iliac and presacral nodes up to the promontory; for T4 (seminal vesicles, prostate, vagina or uterus involvement) external iliac nodes were also included; the inguinal areas were irradiated in those patients who had invasion of the anal canal.[22,23]

The planning target volume (PTV) was defined as CTV + 1 cm margin. The treatment was delivered through three to four fields *via* the isocenter technique, shaped with multileaf collimator, and high-energy photons of 18 MV. The total dose administered was 50.4 Gy with conventional fractionation of 1.8 Gy/d, five days per week. The prescribed dose was specified at the International Commission on Radiation Units and Measurements point and isodose distribution to the PTV (95% to 107%).

3.3. *Neoadjuvant chemotherapy*

Group A was treated with oral CT concomitant to RT, including capecitabine or UFT. The capecitabine subgroup (61 patients) received an oral 825 mg/m^2 dose twice daily for the duration of RT (Monday–Sunday, including technical breaks). the UFT subgroup received a dose of 300 mg/m^2/d of UFT together with folinic acid 90 mg/d (51 patients), in three fractions/d, 5 days/week (Monday–Friday, with the weekend as a rest period). Group B was treated with RT concomitant to infusional CT and 5-FU was administered at a dose of 225 mg/m^2/d in a continuous infusion, 7 days/week.

3.4. *Surgery*

Patients were scheduled for surgery between the sixth and eighth week following the conclusion of the neoadjuvant therapy and were treated with a total mesorectum excision.

Table 1 – Patients' characteristics and surgical status.

Patients' characteristics		Group A ($n = 112$) RT + oral CT	Group B ($n = 47$) RT + infusional CT	p Value
Age (years)	Min–max	35–82	20–81	
	Median	64	61	
Sex	Male	75 (67%)	26 (55.3%)	0.206
	Female	37 (33%)	21 (44.7%)	
Karnofsky	100%	73 (65.2%)	30 (63.8%)	0.973
	90%	35 (31.2%)	15 (31.9%)	
	80%	4 (3.6%)	2 (4.3%)	
Distance to anal margin	0–5 cm	64 (57.1%)	22 (46.8%)	0.296
	6–11 cm	48 (42.9%)	25 (53.2%)	
Imaging staging (CT/MRI scan)	12.5/86.6%	0/100%	0.031	
Clinical staging	cT2	11 (9.8%)	5 (10.6%)	0.001
	cT3	92 (82.1%)	30 (63.8%)	
	cT4	9 (8.0%)	12 (25.5%)	
	cN0	11 (9.8%)	1 (2.1%)	0.112
	cN+	101 (90.2%)	46 (97.9%)	
CEA	<5.4	73 (67.6%)	30 (63.8%)	0.112
	≥5.4	35 (32.4%)	17 (36.2%)	
CA 19.9	<37	93 (84.5%)	40 (85.1%)	1.0
	≥37	17 (15.5%)	7 (14.9%)	
Timing to surgery (median)		7 weeks	7 weeks	
Surgery	RAR	62 (55.4%)	26 (56.5%)	0.550
	APR	45 (40.2%)	19 (41.3%)	
Unresectable		4 (3.6%)	1 (2.2%)	
Non operated		1 (0.9%)	1 (2.2%)	
Surgical resection	R0	98 (87.5%)	42 (91.3%)	
	R1	9 (8.0%)	2 (4.3%)	

ARR: rectal anterior resection; APR: abdomino-perineal resection.

3.5. *Toxicity assessment*

Toxicity was evaluated weekly in each patient using common terminology criteria for adverse events *vs.* 3.0 (CTCAE).[24] A complete blood count and biochemical tests were obtained weekly.

3.6. *Definition of response*

Evaluation of response to preoperative treatment was defined pathologically. Resected tumors were classified pathologically according to the TNM staging system, version 6.[25] Tumor downstaging was defined as postoperative ypT stage lower than preradiotherapy clinical cT stage. Nodal downstaging was defined as postoperative ypN stage lower than preradiotherapy clinical cN stage. Loco-regional response was defined as a downstaging from cTN to pTN. A pathologic complete response (pCR) was considered when there were no residual malignant cells.

3.7. *Adjuvant treatment*

After surgery, adjuvant CT was given to patients who were considered by the treating physician to potentially benefit from postoperative therapy (96 patients). The protocols of adjuvant CT used were FOLFOX (21.9%), CAPOX (10.4%), De Gramont (bolus 5-FU, infusional 5-FU and folinic acid) in 11.4% patients, capecitabine (25%), UFT (28.1%) or others (3.1%).

3.8. *Follow-up*

Following the conclusion of treatment, patients had outpatient clinic appointments every 3 months for the first 2 years, and then every 6 months.

3.9. *Patterns-of-failure analysis and survival*

Loco-regional failure was defined as a relapse in the pelvis (tumor bed, pelvic nodes, anastomosis, or perineal scar). Failure at distance was defined as relapse in any other site. OS, PFS, and loco-regional control (LRC) were calculated from the date of beginning of treatment.

3.10. *Statistical considerations*

Statistical analyses were performed using the SPSS 16.0 statistical package. The p-value was calculated by the chi-square test to compare variables. OS, PFS and LRC probabilities were calculated by the Kaplan–Meier method, and differences were evaluated by the log–rank test. A two-sided p-value of <0.05 was considered statistically significant.

4. Results

4.1. *Toxicity and treatment adherence*

4.1.1. *Preoperative treatment*

Overall, preoperative therapies were well tolerated and the most commonly reported events are shown in Table 2. Group A

Table 2 – Neoadjuvant chemoradiotherapy acute toxicities incidence. CTCAE (v. 3.0).

Acute toxicity (%)	Group A			Group B	
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3
Diarrhea	27.7	4.5	0.9	23.9	6.5
Vomiting	3.6			4.3	2.2
Radiodermitis	54.5	4.5		54.3	
Hand–foot synd.	6.3			4.3	
Haematologic	13.4	1.8		4.3	2.2
Others	12.5				2.2

presented acute toxicity in 80.4% of patients, but only 11 (9.8%) were grades 3–4. GROUP B showed an acute toxicity in 65.2% of patients, of whom 5 (10.9%) were grades 3–4. One patient has not completed treatment due to allergic reaction to 5-FU and was excluded from this analysis.

There was a trend to a higher acute toxicity profile on Group A ($p = 0.064$), however, if we only compare grades 3–4 acute toxicity, there was no significant difference ($p = 0.781$) among the two groups.

4.1.2. *AT surgery*

The median time interval between the end of RT and surgery was 7 weeks. A complete resection was done in the majority of patients undergoing CT + RT. Four patients from GROUP A and one patient from Group B were considered unresectable. One patient was not operated due to disease progression and another by intercurrent illness (Table 1).

There was no statistical difference in postoperative complications between the two groups (42.1% *vs.* 31.8%; $p = 0.274$). The main postoperative complications in Groups A and B were, respectively, surgical wound infections (23.4% *vs.* 6.8%), fistula (4.7% *vs.* 9.1%), suture dehiscence (10.3% *vs.* 4.5%) and sub-occlusive disease (5.6% *vs.* 2.3%). Two patients died postoperatively due to pulmonary thromboembolism.

4.1.3. *Postoperative treatment*

Of the 151 patients submitted to radical surgery and who were candidates for adjuvant CT, only 63.6% received the proposed treatment (64 patients from Group A and 32 patients from Group B). Acute toxicity was reported in 65.6% of patients undergoing adjuvant CT. The respective toxicities are described in Table 3.

The main reason why the majority of the 55 patients did not receive adjuvant CT was postoperative complications (60%), 16.4% of patients did not undergo adjuvant CT because of pCR and pT2N0M0, 7.2% due to disease progression, 3.6% were not referred to the oncologist and 1.8% because of poor PS (ECOG 3).

4.2. *Treatment response*

Nodal downstaging ($p = 0.027$) and loco-regional response ($p = 0.020$) were higher in patients treated with oral CT + RT. Although there was no statistical significance, pCR and tumor downstaging to ypT0-2 rates were higher in patients treated with preoperative oral CT + RT ($p = 0.340$ and $p = 0.344$, respectively). Tumor downstaging was equal in both groups (Table 4).

When we analyzed the impact of the initial tumoral markers' level on treatment response, we verified that patients with higher levels of CEA (≥5.4 ng/ml) and CA 19.9 (≥37 ng/ml) had worse rates of tumor downstaging to ypT0-2 ($p = 0.045$ and $p = 0.013$, respectively). Pretreatment CEA and CA 19.9 levels did not have any impact on nodal downstaging ($p = 0.557$ and $p = 0.122$, respectively), pCR ($p = 0.144$ and $p = 0.201$, respectively) nor on loco-regional response ($p = 0.347$ and $p = 0.121$, respectively).

The median follow-up time was 34 months (4–91 months). The LRC was 95.6%. Of those 6 patients who had locoregional recurrence, 2 were submitted to an R1 resection, 3 had distant recurrence, 1 had interrupted RT due to sub-occlusive disease and 4 had initial tumoral markers elevated. The global 5-year PFS was 70.3%. The global 5-year OS was 74.2%.

When we analyzed the impact of response to neoadjuvant therapy and initial tumoral markers' status on survival (Table 5), we found that patients with tumor downstaging, nodal downstaging, loco-regional response or normal initial CEA level (<5.4 ng/ml) had better OS and PFS. Those with tumor

Table 3 – Adjuvant CT acute toxicities incidence.

CTCAE (v. 3.0)	Adjuvant CT toxicities	
	Grades 1–2	Grades 3–4
Diarrhea	1 (1%)	6 (6.2%)
Vomiting	3 (3.1%)	2 (2.1%)
Nausea	5 (5.2%)	1 (1%)
Anemia	36 (37.5%)	1 (1%)
Neutropenia	22 (22.9%)	3 (3.1%)
Thrombocytopenia	21 (21.9%)	–
Paresthesia	19 (19.8%)	1 (1%)
Hand–foot synd.	2 (2.1%)	6 (6.2%)
Weight loss	1 (1%)	–
Bilirrubin	–	1 (1%)
Transaminases	3 (3.1%)	–
Renal	1 (1%)	2 (2.1%)
Asthenia	4 (4.2%)	–
Anorexia	1 (1%)	–

Table 4 – Therapeutic response to neoadjuvant treatment.

	Group A $n = 107$	Group B $n = 44$	p Value
Tumor downstaging	55.1%	50%	0.594
Tumor downstaging to ypT0-2, considering only cT3-4 patients	51%	41%	0.344
Nodal downstaging	76%	55.8%	0.027
Loco-regional response	74.8%	54.5%	0.020
Pathologic complete response	18.7%	11.4%	0.340

Table 5 – Impact of prognostic factors on survival.

	OS		PFS		LRC	
	5-year	*p* Value	5-year	*p* Value	5-year	*p* Value
Tumor downstaging	82.4%	0.035	81.0%	0.041	100%	0.007
No tumor downstaging	65.7%		59.3%		90.5%	
Tumor downstaging to ypT0-2, considering only cT3-4 patients	82.5%	0.016	84.0%	0.005	100%	0.014
No tumor downstaging to ypT0-2, considering only cT3-4 patients	64.0%		53.8%		90.3%	
Nodal downstaging	75.0%	0.050	75.4%	0.009	95.7%	0.852
No nodal downstaging	60.8%		45.7%		93.9%	
Loco-regional response	77.1%	0.095	77.3%	0.024	96%	0.897
No loco-regional response	67.2%		55.3%		94.7%	
Pathologic complete response	90.0%	0.068	90.7%	0.120	100%	0.272
No pathologic complete response	71.2%		66.2%		94.8%	
Elevated initial CEA	61.6%	0.007	54.4%	0.027	93.4%	0.284
Normal initial CEA	78%		75.6%		96.7%	
Elevated initial CA 19.9	75.5%	0.738	67.5%	0.604	84.4%	0.005
Normal initial CA 19.9	73.9%		70.3%		97.4%	

downstaging or normal initial CA 19.9 tumoral marker levels (<37 ng/ml) had a higher LRC.

Comparing Group A and Group B, we realized that there was no difference in 5-year OS (80.5% *vs.* 62.2%, $p = 0.186$), PFS (71.5% *vs.* 65.6%, $p = 0.861$) nor in LRC (94.7% *vs.* 97.6%, $p = 0.448$, respectively). If we only consider those patients who had loco-regional response, those who were submitted to oral CT + RT had better 5-year OS than those who had undergone infusional CT + RT (84.8% *vs.* 58.3%, respectively, $p = 0.05$). When we analyzed those patients with tumor downstaging we also verified a higher 5-year OS in patients from Group A (92% *vs.* 69.5%, respectively, $p = 0.039$). It was verified a trend to a higher OS in patients who had nodal downstaging and undergone oral CT + RT (82.9% *vs.* 58.3%, $p = 0.090$). The type of combined treatment prescribed did not have any impact on survival in those patients who had a pathologic complete response.

The addition of adjuvant CT did not add a benefit on 5-year LRC (96.5% *vs.* 94%, $p = 0.433$), on 5-year PFS (70.1% *vs.* 65.9%, $p = 0.188$) nor on 5-year OS (71.4% *vs.* 75.5%, $p = 0.749$). If we only take into account those patients who had loco-regional response, there was a benefit on 5-year PFS in those who received adjuvant CT (81.7% *vs.* 67.6%, $p = 0.05$).

For those patients cT3-4 who had pathologic downstaging to ypT0-2 the OS, PFS and LRC were similar to those who were submitted or not to adjuvant CT ($p = 0.404$, $p = 0.554$ and $p = 1.0$, respectively). In those patients who had no pathologic downstaging (ypT3-4) and were or were not treated with adjuvant CT, there was also no evidence of benefit on OS, PFS nor on LRC ($p = 0.502$, $p = 0.208$ and $p = 0.515$, respectively).

5. Discussion and conclusions

The factors which predict the response to neoadjuvant chemoradiotherapy in rectal cancer have not been well characterized. Their knowledge might be useful to clinicians and patients for predicting treatment outcomes and, hence, for making treatment decisions. A better understanding of predictive factors may eventually lead to the development of risk-adapted treatment strategies, such as more aggressive preoperative regimens, in patients who are less likely to respond to standard preoperative therapy. Hence, we performed this single-institution prospective study, the first of this kind in our country.

Neoadjuvant pelvic RT combined with CT should be regarded as a standard treatment for stage II and III rectal cancer and, although there is an increase in acute toxicity, it does not alter the treatment compliance.[26]

Preoperative CT + RT can lead to tumor downstaging and improves resectability in LARC.[27,28] Continuous i.v. 5-FU infusion is superior to 5-FU bolus in terms of tumor response, and it is associated to a slight increase in OS and LRC in advanced colorectal cancer.[29,30] Although continuous i.v. infusion has the biologic advantage of prolonging the exposure of cells to 5-FU and improving antitumor activity, its disadvantages include the requirement of a central venous access with potential complications, such as bleeding, thrombosis and pneumothorax.[31] Oral CT mimics the pharmacokinetics of continuous 5-FU infusion, with elevated and maintained concentrations of 5-FU for a prolonged period and higher peak levels of 5-FU. It also avoids technical barriers of i.v. infusion with the advantage of convenience. Therefore, oral fluoropyrimidines, UFT and capecitabine, constitute an attractive alternative.

The most commonly reported early endpoint is the rate of pCR. It appears to be associated in some non randomized studies with improvement in PFS.[9,32] It has been shown in one randomized trial that time interval between RT and surgery influences the degree of downstaging, with 10% of patients operated within 2 weeks of RT experiencing

Table 6 – Neoadjuvant chemoradiotherapy results (2–14).

Authors	No.	RT	CT	Downstaging T (%)	Downstaging N (%)	pCR (%)
De Paoli et al.[5]	53	50.4	C	57	78	24
Krishnan et al.[6]	54	52.5	C	51	52	18
Kim et al.[7]	95	50.4	C	57	69	12
De la Torre et al.[8]	77	45–50.4	5-FU	43.3	25	13.2
	78		UFT,L	59.2	23.7	13.2
Feliu et al.[2]	41	50.4	UFT,L	61	–	15
Janjan et al.[9]	117	45	5FU	62	–	27
NSABP R-03[10]	58	50.4	5FU,L	–	–	8
Sauer et al.[3]	421	50.4	5FU	–	–	8
Kim et al.[11]	145	50.4	5FU,L	–	–	11.3
	133		C	–	–	16.1
Crane et al.[12]	207	45	5FU	62	–	23
	196		–	42	–	5
Gerard et al.[13]	375	45	5FU,L	–	–	11.4
FFCD 9203	367		–	–	–	3.6
Bosset et al.[4]	473	45	5FU,L	–	–	13.7
EORTC 22921	476		–	–	–	5.3
Fernandez-Martos et al.[14]	94	45	UFT	54	–	15

C: capecitabine; L: leucovorin.

pathological downstaging compared to 26% of patients operated 6–8 weeks after RT ($p = 0.005$).[33] Many studies have shown that neoadjuvant CT + RT significantly increases the rate of pCR, as well as nodal and tumor downstaging (Table 6). However, there are few studies analyzing the impact of response to neoadjuvant CT + RT on survival.

In our study, nodal downstaging ($p = 0.027$) and loco-regional response ($p = 0.020$) were significantly better in Group A. The pCR was higher in Group A (18.7%) than in Group B (11.4%), although it was not statistically significant ($p = 0.340$). The tumor downstaging was similar in both groups (55.1% and 50%, respectively). All these results are comparable to those described in several studies.[2–14]

The role of tumor markers, CEA and CA19.9, in rectal cancer is still in debate. In 2006, Park et al. showed that elevated pretreatment CEA levels (>5ng/ml) were associated with poor tumor response to preoperative chemoradiation.[17] Das et al.[34] concluded that CEA level (>2.5 ng/ml) resulted in significantly lower pCR rates ($p = 0.015$).

We verified that those patients with higher pretreatment levels of CEA and CA 19.9 showed lower rates of tumor downstaging to ypT0-2 ($p = 0.045$ and $p = 0.013$, respectively). Nevertheless, the relationship between pretreatment CEA and CA 19.9 levels and pCR was not statistically significant.

When we analyzed the impact of response to neoadjuvant therapy and initial tumoral markers' status on survival we noticed that patients with tumor downstaging, nodal downstaging, loco-regional response or normal initial CEA level had better OS and PFS. Those with tumor downstaging or normal initial CA 19.9 tumoral marker levels had a higher LRC. The majority of these results are consistent with the literature. In our study, pCR did not have any impact on survival. The low number of patients who actually had pCR might explain this lack of evidence, described in numerous studies.

The most recent published article[35] evaluating the long-term outcome in patients with a pCR after CT + RT for rectal cancer concluded that patients with pCR have better long-term outcome than those without it. They stated that pCR might be indicative of a prognostically favorable biological tumor profile with less propensity for local or distant recurrence and improved survival.

The Gastro-Intestinal Working Group of the Italian Association of Radiation Oncology analyzed retrospectively 566 patients with LARC achieving pCR after neoadjuvant therapy and they verified that this favorable group of patients had a very low rate of local recurrence (1.2%) and a favorable clinical outcome independent of the neoadjuvant CT schedule used, achieving a 5-year PFS of 84.7% and 5-year OS of 91.6%. In such a group of patients, the use of postoperative CT could be very debatable. Conversely, the subset of patients older than 60 years, with cStage III and treated with a radiation dose of 45 Gy or less experienced a relatively worse prognosis, even after achieving ypCR. The prognosis of the high-risk group of patients compares with the outcome of a non-selected population.[20]

Conde et al.[36] also found a better PFS in those patients who had pCR (100% *vs.* 62%, $p = 0.023$). When considering only those patients cT3-4 who had downstaging to ypT0-2, they found a significantly better LRC (100% *vs.* 89, $p = 0.027$), PFS (88% *vs.* 43%, $p = 0.003$) and OS (89% *vs.* 77%, $p = 0.048$).

Kim et al.[37] also showed excellent oncologic outcomes in patients with pCR, with the pathologic N stage being the most important factor for oncologic outcomes. Another study[18] has also verified that pCR or intermediate response was related to an improved PFS after CT + RT. García-Aguilar et al. analyzed a group of 168 patients treated with CT + RT and showed a 5-year LRC of 95%, OS of 68% and a PFS of 95.2% in patients who had pCR and 55.4% in patients without pCR. Their study suggested that a pCR to CT + RT is a favorable prognostic factor in patients with LARC.[19]

Valentini et al.[32] demonstrated that, after preoperative CT + RT, clinical response and tumor and nodal pathologic downstaging have a close correlation with improved outcome. Indeed, patients with tumor downstaging had a 5-year local

control of 87.8%, a PFS of 73.1% and an OS of 82.9%, while those who had not tumor downstaging had a local control of 70.5%, a PFS of 47.2% and an OS of 60.9%. Those patients with nodal downstaging also had better 5-year local control (84.3%), PFS (67.1%) and OS (74.3%) than those who did not have nodal downstaging (72%, 42.2% and 56.1%, respectively).

On the other hand, Pucciarelli et al. did not find statistically significant differences for PFS and OS on comparing the actuarial survival curves of patients with different tumor responses to preoperative treatment, whether evaluated as tumor regression grade or as pTNM stage.[38]

Sauer et al. conducted a randomized trial comparing preoperative *vs.* postoperative CT + RT, and in the preoperative group 5-year OS was 76% and LRC 94%.[3] These results are similar to those found in our study, where the LRC was 95.6%, the global 5-year PFS was 70.3% and OS was 74.2%.

Comparing our results with the single randomized phase III trial[8] that compared 5-FU *vs.* oral fluoropyrimidine, we noticed that 3-year OS (87% *vs.* 74%) and LRC (92.5% *vs.* 91.1%) were similar to those of Groups B and A in our study (83.5% *vs.* 87.6% and 97.6% *vs.* 94.7%, respectively), although slightly higher in our study.

Fernandez-Martos et al. studied preoperative CT + RT with UFT and the actuarial rate of 3-year PFS was 72% and OS was 75%. PFS was 92% for downstaging patients and 51% for patients who did not respond ($p < 0.00001$). OS was significantly higher ($p = 0.002$) for patients with downstaging following preoperative treatment than for patients who did not respond.[14]

In our study, we also analyzed the impact of the type of neoadjuvant therapy on survival in those patients who had some kind of treatment response and verified that those with loco-regional response ($p = 0.05$) and tumor downstaging ($p = 0.039$) treated with oral CT + RT had a significantly better OS, and there was also a trend to higher OS on those patients with nodal downstaging ($p = 0.090$).

There are still insufficient data on adjuvant postoperative chemotherapy after preoperative treatment with chemoradiation to allow us to draw a conclusion about its use.[39,40] A recent study showed that adjuvant CT was still of borderline significance (worse for adjuvant CT).[20] In the EORTC 22921 trial postoperative chemotherapy had a non-significant influence on local relapse and relapse free and overall survival. Exploratory subgroup analyses suggest that only good-prognosis patients with downstaging of cT3-4 to ypT0-2 benefit from adjuvant CT, with better PFS and OS.[21] They concluded it was not because tumor downstaging was achieved that those patients also benefited from further CT, but rather that the same patients who achieved downstaging had a disease which was responsive for both preoperative and adjuvant treatment. Those data support those found in other trials as the QUASAR trial that showed a significant benefit on survival of 3–6%.[41]

In our study, the addition of adjuvant CT to the patients scheduled for neoadjuvant CT + RT did not bring a benefit on 5-year LRC (96.5% *vs.* 94%, $p = 0.433$), on 5-year PFS (70.1% *vs.* 65.9%, $p = 0.188$) nor on 5-year OS (71.4% *vs.* 75.5%, $p = 0.749$). However, if we take into account only those patients who had loco-regional response, there was a benefit on 5-year PFS in those whom received adjuvant CT (81.7% *vs.* 67.6%, $p = 0.05$).

In subgroup analyses, only considering those patients who had pathologic downstaging to ypT0-2, our results disagree from those observed in the EORTC trial, once the 5-year OS, PFS and LRC were identical for those who were submitted or not to adjuvant CT ($p = 0.404$, $p = 0.554$ and $p = 1.0$, respectively). For those patients who had no pathologic downstaging (ypT3-4), the administration of adjuvant CT also did not have any benefit on 5-year OS, PFS nor on LRC ($p = 0.502$, $p = 0.208$ and $p = 0.515$, respectively).

In conclusion, although the results of our study are very promising, we need to take into account that this study is not a randomized trial and it might have some bias in the patients' treatment modality distribution that might influence some of the results. Nevertheless, we verified a good treatment compliance without increased acute toxicity or post-operative complications in the oral CT + RT group, as well as a higher nodal downstaging and loco-regional response in this group. Tumor downstaging, nodal downstaging, loco-regional response and a normal pretreatment CEA level turned out to be important prognostic factors in survival of LARC. Tumor downstaging and a normal pretreatment CA 19.9 level had an impact on LRC as well. In subgroup analyses, we also noticed that patients with tumor downstaging and loco-regional response treated with oral CT + RT had a significantly better OS. Adjuvant CT had no impact on survival nor on LRC except in those patients with loco-regional response who had higher PFS.

Such differences between these groups of patients, although both are treated with 5-FU either i.v. or in the oral form, might be due to the pharmacokinetics of both capecitabine and UFT oral prodrugs that permits to have a more elevated and maintained concentrations of 5-FU for a prolonged period with constant cytotoxic action, thereby limiting tumor regrowth.

Conflict of interest

There are no financial relationships that might lead to a conflict of interest.

Financial disclosure

None declared.

REFERENCES

1. National Institutes of Health Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;**264**:1444–50.
2. Feliu J, Calvillo J, Escribano A, et al. Neoadjuvant therapy of rectal carcinoma with UFT-leucovorin plus radiotherapy. *Ann Oncol* 2002;**13**:730–6.
3. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;**351**:1731–40.
4. Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: Preliminary results of EORTC 22921. *J Clin Oncol* 2005;**23**:5620–7.

5. De Paoli A, Chiara S, Luppi G, et al. Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: a multicentric phase II study. *Ann Oncol* 2006;**17**:246–51.
6. Krishnan S, Janjan NA, Skibber JM. Phase II study on capecitabine (xeloda®) and concomitant boost radiotherapy in patients with locally advanced rectal cancer. *Int J Radiat Oncol Phys* 2006;**66**:762–71.
7. Kim JC, Kim TW, Kim JH, et al. Preoperative concurrent radiotherapy with capecitabine before total mesorectal excision in locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2005;**63**:346–53.
8. De la Torre A, Garcia-Berrocal MI, Arias F, et al. Preoperative chemoradiatiotherapy fr rectal cancer: randomized trial comparing oral uracil and tegafur and oral leucovorin vs. intravenous 5-fluorouracil and leucovorin. *Int J Radiat Oncol Phys* 2008;**70**:102–10.
9. Janjan NA, Crane C, Feig BW, et al. Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. *Am J Clin Oncol* 2001;**24**:107–12.
10. Roh MS, Petrelli N, Wieand L, et al. Phase III randomized trial of preoperative versus postoperative multimodality therapy in patients with carcinoma of the rectum (NSABP R-03). *Proc Am Soc Clin Oncol* 2001;**20**:123 [Abstract 490].
11. Kim DY, Jung KH, Kim TH, et al. Comparison of 5-fluorouracil/leucovorin and capecitabine in preoperative chemoradiotherapy for locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2007;**67**:378–84.
12. Crane CH, Skibber JM, Birnbaum EH, et al. The addition of continuous infusion 5-FU to preoperative radiation therapy increases tumor response, leading to increased sphincter preservation in locally advanced rectal cancer. *Int J Radiat Oncol Phys* 2003;**57**:84–9.
13. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006;**24**:4620–5.
14. Fernandez-Martos C, Aparicio J, Bosch C, et al. Preoperative uracil, tegafur, and concomitant radiotherapy in operable rectal cancer: a phase II multicenter study with 3 years' follow-up. *J Clin Oncol* 2004;**22**:3016–22.
15. Compton CC, Fielding LP, Bugart LJ, et al. Prognostic factors in colorectal cancer. College of American pathologists consensus statement 1999. *Arch Pathol Lab Med* 2000;**124**:979–94.
16. Carriquiry LA, Pineyro A. Should carcinoembryonic antigen be used in the management of patients with colorectal cancer? *Dis Colon Rectum* 1999;**42**:921–9.
17. Park Y, Sohn S, Seong J, et al. Serrum CEA as a predictor for the response to preoperative chemoradiation in rectal cancer. *J Surg Oncol* 2006;**93**:145–50.
18. Rodel C, Martus P, Papadoupolos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 2005;**23**:8688–96.
19. García-Aguilar J, de Anda EH, Sirivongs P, et al. A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. *Dis Colon Rectum* 2003:298–304.
20. Capirci C, Valentini V, Cionini L, et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. *Int J Radiat Oncol Biol Phys* 2008;**72**(1):99–107.
21. Collette L, Bosset JF, Den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organization for Research and Treatment of Cancer Radiation Oncology Group. *J Clin Oncol* 2007;**25**:4379–86.
22. Myerson RJ, Garofalo MC, Naqa IE, et al. Elective Clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. *Int J Radiat Oncol Biol Phys* 2009;**74**:824–30.
23. Roels S, Duthoy W, Haustermans K, et al. Definition and delineation of the clinical target volume for rectal cancer. *Int J Radiat Oncol Biol Phys* 2006;**65**:1129–42.
24. Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, Version 3.0, DCTD, NCI, NIH, DHHS; 2006.
25. AJCC. *Cancer staging handbook*. 6th ed. Springer; 2001.
26. Bosset JF, Calais G, Daban A, et al. Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance: Report of the 22921 radomised trial conducted by the EORTC Radiotherapy Group. *Eur J Cancer* 2004;**40**:219–24.
27. Janjan NA, Khoo VS, Abbruzzese J, et al. Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: the M.D. Anderson Cancer Center experience. *Int J Radiat Oncol Biol Phys* 1999;**44**:1027–38.
28. Minsky BD, Cohen AM, Enker WE, et al. Preoperative 5-FU, low-dose leucovorin, and radiation therapy for locally advanced and unresectable rectal cancer. *Int J Radiat Oncol Biol Phys* 1997;**37**:289–95.
29. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994;**331**:502–7.
30. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998;**16**:301–8.
31. Grem JL. Systemic treatment options in advanced colorectal cancer: perspectives on combination 5-fluorouracil plus leucovorin. *Semin Oncol* 1997;**24**(Suppl. 18):8–18.
32. Valentini V, Coco C, Picciocchi A, et al. Does downstaging 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* 2002;**53**:664–74.
33. Francois Y, Nemoz C, Baulieux J, et al. Influence of the interval between radiation therapy and surgery on downstaging and rate of sphincter sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol* 1999;**17**:2396–402.
34. Das P, Skibber JM, Rodriguez-Bigas MA, et al. Predictors of tumor response and downstaging in patients who receive preoperative chemoradiation for rectal cancer. *Cancer* 2007;**109**:1750–5.
35. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010;**11**(September (9)):835–44.
36. Conde S, Borrego M, Teixeira T, et al. Impact of neoadjuvant chemoradiation on pathologic response and survival of patients with locally advanced rectal cancer. *Rep Pract Oncol Radiother* 2010;**15**:51–9.
37. Kim NK, Baik SH, Seong JS, et al. Oncologic outcomes after neoadjuvant chemoradiation followed by curative resection with tumor-specific mesorectal excision for fixed locally advanced rectal cancer: Impact of postirradiated pathologic

downstaging on local recurrence and survival. *Ann Surg* 2006;**244**(December (6)):1024–30.
38. Pucciarelli S, Toppan P, Friso ML, et al. 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* 2004;**47**:1798–807.
39. Valentini V, Beets-Tan R, Borras JM, et al. Evidence and research in rectal câncer. *Radiother Oncol* 2008;**87**:449–74.
40. Valentini V, Aristei C, Glimelius B, et al. Multidisciplinary rectal cancer management: 2nd Europena Rectal Cancer Consensus Conference (EURECA-CC2). *Radiother Oncol* 2009;**92**:148–63.
41. QUASAR Collaborative Group. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomized study. *Lancet* 2007;**370**:2020–9.