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Comparison of neoadjuvant oral chemotherapy with UFT plus Folinic acid or Capecitabine concomitant with radiotherapy on locally advanced rectal cancer

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ABSTRACT

Aim: To evaluate the differences in treatment response and the impact on survival with both oral agents (UFT and Capecitabine) as neoadjuvant chemotherapy administered concomitantly with radiotherapy.

Background: There are still no studies comparing the use of neoadjuvant oral chemotherapy either with UFT plus Folinic acid or Capecitabine concomitant with radiotherapy in locally advanced rectal cancer (LARC).

Materials and methods: A set of 112 patients with LARC were treated preoperatively. GROUP 1 – 61 patients underwent concomitant oral chemotherapy with Capecitabine (825 mg/m^2 twice daily). GROUP 2 – 51 patients submitted to concomitant oral chemotherapy with UFT (300 mg/m^2/d) + Folinic acid (90 mg/d) and radiotherapy. 57.1% of patients were submitted to adjuvant chemotherapy.

Results: GROUP 1: acute toxicity – 80.3%; pathological complete response (pCR) – 10.5%; tumor downstaging (TD) – 49.1%; nodal downstaging (ND) – 76.5%; loco-regional response (LRR) – 71.9%; toxicity to adjuvant chemotherapy – 75%. GROUP 2: acute toxicity – 80.4%; pCR – 28%; TD – 62%; ND – 75.6%; LRR – 78%; toxicity to adjuvant chemotherapy – 56%. There was no difference in survival nor loco-regional control between the groups.

Conclusions: Patients treated with neoadjuvant oral UFT + Folinic acid had a higher rate of pathologic complete response than patients treated with Capecitabine concomitant with radiotherapy. There were no differences in downstaging, LRR, toxicity, survival or loco-regional control between both groups. There was a trend to a higher rate of toxicity to adjuvant chemotherapy in the Capecitabine group.

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1. Background

The neoadjuvant use of CT and RT in locally advanced rectal cancer (LARC) allows a higher rate of resectability associated to a tumor and nodal downstaging.[1] Concomitant neoadjuvant 5-FU CT + RT provides a pathological complete response (pCR) in 8–27% of patients and is associated to an increased local control.[1–13] Theoretically, oral fluoropyrimidines are suitable to replace 5-FU protracted infusion and avoid catheter-related complications, such as infection, sepsis, pneumothorax, thrombosis and blockage.[14,15] In general, patients tend to prefer oral treatments, provided that efficacy is not compromised.[16]

UFT is an oral combination of uracil and tegafur in a fixed 1:4 molar ratio.[17] Tegafur is a prodrug converted to 5-FU by the hepatic microsomal system following intestinal absorption. Uracil competitively inhibits dihydropyrimidine dehydrogenase, the chief catabolic enzyme of 5-FU, which results in elevated and maintained concentrations of 5-FU for a prolonged period and thus simulates a continuous infusion of 5-FU to improve the absorption and bioavailability of tegafur.[18–20]

In preclinical experiments, leucovorin (LV) has been combined with UFT in an attempt to enhance antitumor activity.[21] In patients with advanced colorectal cancer, the combination of UFT and oral LV produced objective response rates ranging from 25% to 42%.[22] Preliminary results from two large randomized studies in patients with metastatic colorectal cancer suggested that patients treated with UFT/LV and those receiving bolus intravenous 5-FU/LV may have an equivalent response and survival rate.[22,23] In the adjuvant setting, Japanese investigators compared postoperative UFT to surgery alone; UFT led to a significantly improved 4-year disease-free survival, particularly in patients with rectal cancer.[24] Like infusional 5-FU, UFT is generally well tolerated, with diarrhea, nausea, and anorexia being the most frequent adverse effects. In reported trials, grade 3 or 4 diarrhea occurred in 4% to 21% of patients.[18,22,23] UFT is not associated with significant myelosuppression, mucositis, hand–foot syndrome, or alopecia.

Pharmacokinetic studies have shown that 5-FU plasma levels in patients receiving protracted infusions of 5-FU are similar to those found in patients receiving oral UFT, although peak levels of 5-FU are higher with UFT.[18] Although a large number of patients have received UFT plus oral LV as adjuvant chemotherapy or to treat metastatic disease, there is little data on the use of UFT/LV with radiation therapy in patients with rectal cancer.

Capecitabine is a fluoropyrimidine carbamate prodrug of 5-FU designed to generate 5-flurouracil (5-FU) preferentially in tumor cells[25] as concentration of the key enzyme thymidine phosphorylase is higher in tumor cells compared with normal tissue. In preclinical studies, irradiation with thymidine phosphorylase was found to be upregulated in tumor tissue resulting in a selective synergistic effect of Capecitabine on radiotherapy.[26–28] Capecitabine is administered daily to mimic a continuous infusion of 5-FU.[29] This continuous regimen is likely to have a more constant cytotoxic action, thereby limiting tumor regrowth. The side-effect profile of Capecitabine is similar to that observed when 5-FU is given as a protracted infusion and consists mainly in diarrhea. The dose-limiting toxicity is the hand–foot syndrome, occurring as the Capecitabine dose reaches 1000 mg/m^2 b.i.d. Other toxicities were generally mild to moderate.[30,31]

A phase I study on rectal cancer (Dunst) defined the recommended dose of Capecitabine to be 825 mg/m^2 b.i.d., administered 7 d/week during a conventional RT period of about 6 weeks for preoperative therapy in LARC.[32]

2. Aim

As the standard schedule of preoperative CT + RT for rectal cancer remains to be established and given the convenience of oral prodrugs *vs.* 5-FU and the lack of studies comparing different kinds of oral chemotherapy, we wanted to compare the therapeutic response to oral chemotherapy either with UFT/Folinic acid (FA) or Capecitabine combined with preoperative RT in patients with stages II–III rectal cancer. Toxicity and survival were also analyzed for those groups of patients, as well as the relationship between pathological response, tumor and nodal downstaging, loco-regional response and survival.

3. Materials and methods

3.1. *Patients*

We prospectively analyzed 112 patients with LARC treated with neoadjuvant oral chemotherapy and radiation from January 2003 to September 2009. Patients were divided into 2 groups. GROUP 1: consisting of 61 patients who were treated with RT and concomitant oral CT with Capecitabine. GROUP 2: consisting of 51 patients, submitted to RT and concomitant oral CT with UFT plus FA. Patients' characteristics corresponding to the different groups are described in Table 1.

3.2. *Neoadjuvant chemotherapy*

GROUP 1 was treated with RT concomitant to oral CT with Capecitabine 825 mg/m^2 twice daily for the duration of RT, 7 d/week (61 patients). GROUP 2 was treated with RT concomitant to oral CT with UFT at 300 mg/m^2/d together with Folinic acid 90 mg/d (51 patients), in 3 fractions/d, 5 d/week (Monday through Friday, with the weekend as a rest period).

3.3. *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 above 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.[33,34]

The planning target volume (PTV) was defined as CTV + 1 cm margin. The treatment was delivered through

Table 1 – Comparison of patients' characteristics and surgical status between patients treated with Capecitabine and UFT + Folinic acid.

Patients' characteristics	Capecitabine ($n = 61$)	UFT + LV ($n = 51$)	p value
Age (years)			
Min–Max	38–82	35–82	
Median	64	64	
Sex			
Male	37 (60.7%)	38 (74.5%)	0.158
Female	24 (39.3%)	13 (25.5%)	
Karnofsky			
100%	35 (57.4%)	38 (74.5%)	
90%	24 (39.3%)	11 (21.6%)	0.129
80%	2 (3.3%)	2 (3.9%)	
Distance to anal margin			
0–5 cm	36 (59%)	28 (54.9%)	0.704
6–11 cm	25 (41%)	23 (45.1%)	
Imaging staging (CT/MRI scan)	18%/82%	5.9%/92.2%	0.090
Clinical staging			
cT2	9 (14.8%)	2 (3.9%)	
cT3	48 (78.3%)	44 (86.3%)	0.144
cT4	4 (6.6%)	5 (9.8%)	
cN0	6 (9.8%)	5 (9.8%)	1.0
cN+	55 (90.2%)	46 (90.2%)	
Timing to surgery (median)	7 weeks	7 weeks	
Surgical resection			
R0	51 (83.7%)	47 (92.1%)	
R1	6 (9.8%)	3 (5.9%)	0.664
Unresectable	3 (4.9%)	1 (2%)	
Non operated	1 (1.6%)	–	

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, 5 d/week. The prescribed dose was specified at the International Commission on Radiation Units and Measurements point and isodose distribution to the PTV (95–107%).

3.4. *Surgery*

Surgery was performed by specialized surgeons of the Surgical Department of our Institution. 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 and a rectal anterior resection was done whenever possible.

3.5. *Toxicity assessment*

Toxicity was evaluated weekly in each patient using Common Terminology Criteria for Adverse Events *vs.* 3.0 (CTCAE).[35] 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.[36] 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 pathological 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 (64 patients). Adjuvant chemotherapy was selected according to the previous neoadjuvant CT scheme administered concurrently with RT. Patients previously treated with UFT in the neoadjuvant setting, were treated with UFT in the adjuvant setting as well. The same applied to patients treated with Capecitabine in the neoadjuvant setting who also were treated with Capecitabine in the adjuvant setting. In those cases, where there was a tumor or nodal upstaging, as long as tolerated by the patient, an Oxaliplatin-based chemotherapy was administered. The protocols of adjuvant CT used were UFT (42.2%), Capecitabine (37.5%), CAPOX (10.9%), FOLFOX (3.1%), or others (4.7%). The majority of patients from GROUP 1 were treated with Capecitabine and the majority from GROUP 2 with UFT.

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 the 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 toxicities are shown in Table 2. In GROUP 1, 80.3% of patients presented acute toxicity, while only

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

Acute toxicity (%)	GROUP 1		GROUP 2	
	Grades 1–2	Grades 3–4	Grades 1–2	Grades 3–4
Diarrhea	26.2	8.2	29.4	2
Vomiting	4.9		2	
Radiodermatitis	50.8	4.9	58.8	3.9
Hand–foot syndrome	11.5			
Hematologic	13.1		13.7	3.9
Others	13.1		11.8	

Table 3 – Incidence of postoperative complications.

Postoperative complications	GROUP 1 ($n = 57$)	GROUP 2 ($n = 50$)
Suture dehiscence	4 (7%)	7 (14%)
Sub-occlusion/occlusion	4 (7%)	2 (4%)
Fistula	4 (7%)	1 (2%)
Infection	11(19.3%)	14 (28%)

7 (11.5%) had grades 3–4 toxicity. GROUP 2 showed an acute toxicity in 80.4% of patients, 4 of which (7.8%) were grades 3–4. There was no significant difference related to acute toxicity ($p = 1.0$) or grades 3–4 acute toxicity ($p = 0.751$) 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. One patient was not operated due to intercurrent illness (Table 1). There was no statistical difference in postoperative complications between the two groups (42.1% *vs.* 42%; $p = 1.0$). The main postoperative complications are described in Table 3. One patient died postoperatively due to pulmonary thromboembolism.

4.1.3. *Postoperative treatment*

Of the 107 patients submitted to radical surgery and who were candidates for adjuvant CT, only 59.8% received the proposed treatment (36 patients from GROUP 1 and 28 patients from GROUP 2). The majority of patients from GROUP 1 were treated with Capecitabine (63.9%) and the majority of patients from GROUP 2 were administered UFT + FA (92.9%) as adjuvant CT.

There was a trend for higher toxicity incidence in the Capecitabine group than in UFT + FA group, although it was not statistically significant (75% *vs.*50%, $p = 0.065$). The respective toxicities are described in Table 4.

The main reason why the 43 patients did not receive adjuvant CT was postoperative complications (53.5%), 16.3% of patients did not undergo adjuvant CT because of pCR and pT2N0M0, 9.3% due to disease progression and 4.6% were not referred to a medical oncology consult.

4.2. *Treatment response*

We found a statistically significant higher pCR in the group of patients treated with oral UFT/FA + RT when compared to patients who were treated with oral Capecitabine + RT (28% *vs.* 10.5%, $p = 0.026$). Tumor downstaging was also higher in GROUP 2 although this difference was not statistically significant (62% *vs.* 49.1%, $p = 0.243$). There was no difference between both groups either in nodal downstaging ($p = 1.0$) or in loco-regional response ($p = 0.510$) (Table 5).

With a median follow-up time of 30 months (5–91 months), the global 5-year PFS was 71.5%, global 5-year OS was 80.5% and LRC was of 94.7%. Of those, 5 patients who had loco-regional recurrence, 2 of them had been submitted to an R1 resection, 2 had distant recurrence, 1 had interrupted RT due to sub-occlusive disease.

Considering our patients as a whole, we noted that patients with pCR had a 5-year OS of 100% while in those without pCR OS was of 76.6% with a p value of 0.063.

Comparing GROUP 1 and GROUP 2, we realized that there was no difference in 5-year OS (81.8% *vs.* 80.7%, $p = 0.613$) or in LRC (94.5% *vs.* 95.4%, $p = 0.908$), respectively. PFS was superior

Table 4 – Adjuvant CT acute toxicities incidence.

Adjuvant CT toxicities CTCAE (v. 3.0)	GROUP 1		GROUP 2	
	Grades 1–2	Grades 3–4	Grades 1–2	Grades 3–4
Diarrhea	–	2 (7.4%)	1 (7.1%)	3 (21.4%)
Vomiting	1 (3.7%)	–	1 (7.1%)	1 (7.1%)
Nausea	1 (3.7%)	–	1 (7.1%)	1 (7.1%)
Anemia	16 (59.3%)	–	5 (35.7%)	1 (7.1%)
Neutropenia	8 (29.6%)	1 (3.7%)	6 (42.9%)	–
Thrombocytopenia	6 (22.2%)	–	2 (14.3%)	–
Paresthesia	5 (18.5%)	–	–	–
Hand–foot syndrome	2 (7.4%)	6 (22.2%)	–	–
Weight loss	1 (3.7%)	–	–	–
Bilirrubin	–	1 (3.7%)	–	–
Transaminases	–	–	3 (21.4%)	–
Renal	–	–	1 (7.1%)	2 (14.3%)
Asthenia	1 (3.7%)	–	1 (7.1%)	–
Anorexia	–	–	1 (7.1%)	–

Table 5 – Therapeutic response to neoadjuvant treatment.

	GROUP 1 ($n=57$)	GROUP 2 ($n=50$)	p value
Pathologic complete response	10.5%	28%	0.026
Tumor downstaging	49.1%	62%	0.243
Nodal downstaging	76.5%	75.6%	1.00
Loco-regional response	71.9%	78%	0.510

in GROUP 1 although without statistical significance (75.2% *vs.* 68.2%, $p=0.258$).

When we analyzed the impact of each treatment on OS, PFS or LRC, we found that the type of combined neoadjuvant treatment prescribed was not determinant for survival in any of the patients' subgroups, whether they had pathological complete response, tumor downstaging, nodal downstaging or loco-regional response (Table 6).

5. Discussion and conclusions

Neoadjuvant pelvic RT combined with CT should be regarded as the standard treatment for stages II and III rectal cancer, leading to a higher loco-regional tumor control, tumor downstaging and improved resectability not altering treatment compliance.[3,12,37–39] Preoperative RT with continuous i.v. 5-FU infusion has the biologic advantage of prolonging tumor cells exposure to 5-FU and improving antitumor activity, however, its disadvantages include the requirement of a central venous access with potential complications, such as bleeding, thrombosis, infection and pneumothorax.[40] Oral CT mimics the pharmacokinetics of continuous 5-FU infusion and avoids technical barriers of i.v. infusion with the advantage of convenience. Oral fluoropyrimidines, such as UFT and Capecitabine, constitute an attractive alternative.

Although there are some studies comparing infusional preoperative chemoradiotherapy with oral neoadjuvant chemoradiotherapy either with Capecitabine or UFT,[7,10] there is not yet a single randomized study comparing the results of both of these modalities of oral neoadjuvant chemotherapy along with radiotherapy. Hence, we thought it worthwhile to perform this single-institution prospective study, even though it is not a randomized trial.

The majority of studies usually report pCR, tumor downstaging and nodal downstaging as early endpoints of neoadjuvant chemoradiotherapy. The pCR appears to be associated in some non-randomized studies with improvement on PFS.[8,41,42] It has been shown in one randomized trial that the time interval between RT and surgery influences the degree of downstaging, with 10% of patients operated within 2 weeks of RT experiencing pathological downstaging compared to 26% of patients operated 6–8 weeks after RT ($p=0.005$).[43] Many studies have shown that neoadjuvant CT+RT significantly increases the rate of pCR, as well as nodal and tumor downstaging,[2–13] however, none of them have compared these results between different modalities of oral chemotherapy.

Analyzing our set of patients we verified a significantly better pCR rate ($p=0.026$) in the group of patients treated with neoadjuvant oral UFT/FA with concomitant RT (28%) comparing with patients treated with oral Capecitabine + RT (10.5%) and tumor downstaging, although not significant ($p=0.243$), was also higher in GROUP 2. There were no differences in nodal downstaging ($p=1.00$) and loco-regional response rates ($p=0.510$) between both groups of patients. The overall response rates were similar to those reported in several other studies,[2,4–7,10,13,44,45] with the exception of pCR rate in patients treated with neoadjuvant UFT/LV CT + RT that were higher than those reported in former studies (Table 7). The patient's characteristics, neoadjuvant therapy acute toxicity and postoperative complications were identical in both groups.

The most recently published article by the Korean Radiation Oncology Group (KROG 09-01) collected clinical data for 333 LARC patients with ypT0 following preoperative CRT and curative radical resections and they observed that even after total regression of primary tumor, ypT0N0 patients had favorable long-term outcomes with a 5-year DFS and OS of 88.5% and 94.8%, respectively, whereas ypT0N+ patients had a poor prognosis (5-year DFS and OS of 45.2% and 72.8%, respectively, $p<0.001$).[46]

Maas et al. have recently[47] evaluated the long-term outcome in patients with pCR after CT + RT for rectal cancer and have concluded that patients with pCR have a better long-term outcome than those without it. They stated that pCR might be indicative of a prognostically favorable biological tumor profile with lower 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

Table 6 – Impact of treatment response on survival.

		OS		PFS		LRC	
		5-Year	p value	5-Year	p value	5-Year	p value
Pathologic complete response	GROUP 1	100%	1.0	66.7%	0.665	100%	1.0
	GROUP 2	100%		79.6%		100%	
Tumor downstaging	GROUP 1	87.1%	0.118	83.5%	0.664	100%	1.0
	GROUP 2	100%		86.4%		100%	
Nodal downstaging	GROUP 1	82.2%	0.870	75%	0.695	94.9%	0.684
	GROUP 2	90%		72.8%		96.8%	
Loco-regional response	GROUP 1	83.5%	0.972	76.3%	0.923	95.1%	0.624
	GROUP 2	91.4%		77.4%		97.2%	

Table 7 – Neoadjuvant chemoradiotherapy results (2, 4–7, 10, 13, 44, 45).

Authors	No.	RT	CT	Downstaging, T (%)	Downstaging, N (%)	pCR (%)
De Paoli [4]	53	50.4	C	57	78	24
Krishnan [5]	54	52.5	C	51	52	18
Kim [6]	95	50.4	C	57	69	12
Korkolis [44]	30	50.4	C	75	53	23
Kim [10]	145	50.4	5FU, L	–	–	11.3
	133		C	–	–	16.1
De la Torre [7]	77	45–50.4	5-FU	43.3	25	13.2
	78		UFT, L	59.2	23.7	13.2
Fernandez-Martos [13]	94	45	UFT	54	–	15
Feliu [2]	41	50.4	UFT, L	61	–	15
Wang [45]	65	45	UFT, L	75	–	25

C, Capecitabine; L, leucovorin.

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.[48]

Conde et al.[42] 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. also showed excellent oncologic outcomes in patients with pCR, with the pathologic N stage being the most important factor for oncologic outcomes.[49] Another study also verified that pCR or intermediate response was related to an improved PFS after CT + RT.[50] Julio Garcia-Aguilar et al. analyzed a group of 168 patients treated with CT + RT and showed a 5-year LRC of 95%, an 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.[51]

Valentini et al.[41] demonstrated that, after preoperative CT + RT, clinical response and the tumor and nodal pathologic downstaging are closely related to 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 no 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%) rate, 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.[52]

In our study we observed a trend to a higher OS in those patients who had pCR ($p = 0.063$), which converges to those results referred in literature. If we look into the impact of pCR on the outcome in each group of patients we verify that OS, PFS and LRC were similar in the two groups of patients. One of the reasons that might explain this lack of evidence is the low absolute number of patients who actually had pCR (GROUP 1: 6 patients; GROUP 2: 14 patients).

The global 5-year LRC, PFS and OS were 94.5%, 75.2% and 81.8%, respectively. There were no differences in survival between GROUP 1 and 2. Tumor downstaging was higher in patients treated with UFT/FA + RT, but this result was not statistically significant. Nodal downstaging and loco-regional response did not have any impact on survival or on LRC in any group of patients.

Comparing our results with the single randomized phase III trial[7] that compared 5-FU *vs.* oral fluoropyrimidine, we noticed that 3-year OS (74%) and LRC (91.1%) from oral CT group were similar to 3-year OS (87.6%) and LRC (94.7%) that we found, although slightly higher in our study.

Carlos 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 downstaged patients and 51% for patients who had not responded ($p < 0.00001$). OS was significantly higher ($p = 0.002$) for patients with downstaging following preoperative treatment than for patients who had not responded.[13]

Regarding the use of adjuvant chemotherapy after preoperative treatment with chemoradiation, there is still insufficient data to allow us to draw a conclusion about its use.[53,54] A recent study showed that adjuvant CT was still of borderline significance (worse for adjuvant CT).[47] 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, probably because these patients had a disease which was responsive to both preoperative and adjuvant treatment.[55] This data supports other trials as QUASAR trial that showed a significant benefit on survival of 3–6%.[56]

A recent review published by Bjuko et al. concluded that the use of adjuvant chemotherapy in patients undergoing preoperative radio(chemo)therapy is not evidence based and recommended that a meta-analyses of the most relevant studies was performed, along with new trials that explore new drug combinations *vs.* observation.[57]

We noticed that there was a trend for higher toxicity incidence in the Capecitabine group than in UFT/FA group,

although not statistically significant (75% *vs.* 50%, $p = 0.065$). This is probably due to the administered absolute dose which is higher in patients treated with Capecitabine in the adjuvant setting (2500 mg/m^2/d) than in the neoadjuvant setting (1650 mg/m^2/d). In the patients treated with UFT/FA, the administered dose was the same whether on neoadjuvant or adjuvant setting (UFT at 300 mg/m^2/d; FA at 90 mg/d).

In conclusion, we found that there is a statistically significant higher pCR rate in patients treated with neoadjuvant UFT/FA + RT than in patients treated with preoperative Capecitabine + RT (28% *vs.* 10.5%, respectively, $p = 0.026$). Patients with pCR from both groups had a trend to a higher OS but we did not observe differences in survival between the two groups.

Compliance to neoadjuvant oral chemotherapy concomitant to radiotherapy was good with no difference found in acute toxicity or post-operative complications between both groups.

Although these are very promising results, 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.

Conflict of interest

None declared.

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