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Original Article

The INTERACT Trial: Long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)–cT3 rectal cancer

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ABSTRACT

Background and purpose: Capecitabine-based radiochemotherapy (cbRCT) is standard for preoperative long-course radiochemotherapy of locally advanced rectal cancer. This prospective, parallel-group, randomised controlled trial investigated two intensification regimens. cT4 lesions were excluded. Primary objective: pathological outcome (TRG 1-2) among arms.

Materials and methods: Low-located cT2N0–2M0, cT3N0–2M0 (up to 12 cm from anal verge) presentations were treated with cbRCT randomly intensified by either radiotherapy boost (Xelac arm) or multidrug concomitant chemotherapy (Xelox arm). Xelac: concomitant boost to bulky site (45 Gy/1.8 Gy/die, 5 sessions/week to the pelvis, +10 Gy at 1 Gy twice/week to the bulky) plus concurrent capecitabine (1650 mg/mq/die). Xelox: 45 Gy to the pelvis + 5.4 Gy/1.8 Gy/die, 5 sessions/week to the bulky site + concurrent capecitabine (1300 mg/mq/die) and oxaliplatin (130 mg/mq on days 1,19,38). Surgery was planned 7–9 weeks after radiochemotherapy.

Results: From June 2005 to September 2013, 534 patients were analysed: 280 in Xelac, 254 in Xelox arm. Xelox arm presented higher G $\geq$ 3 haematologic ($p = 0.01$) and neurologic toxicity ($p < 0.001$). Overall, 98.5% patients received curative surgery. The tumour regression grade distribution did not differ between arms ($p = 0.102$). TRG 1+2 rate significantly differed: Xelac arm 61.7% vs. Xelox 52.3% ($p = 0.039$). Pathological complete response (ypT0N0) rates were 24.4 and 23.8%, respectively (p non-significant). Median follow-up:5.62 years. Five-year disease-free survival rate were 74.7% (Xelac) and 73.8% (Xelox),

Abbreviations: APR, abdominoperineal resection; BED, biological equivalent dose; cbRCT, capecitabine-based radiochemotherapy; CI, confidence intervals; CT, computed tomography; DFS, disease-free survival; FUFA, capecitabine or 5-fluoruracile plus folinic acid; GTV, gross tumour volume; LAR, low anterior resection; LE, local excision; LC, local control; MRI, magnetic resonance imaging; LCRCT, long-course radiochemotherapy; OS, overall survival; pCR, pathological complete response; RCTs, randomised controlled trials; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SCRT, short-course radiotherapy; TME, total mesorectal excision; TRG, tumour regression grade.

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respectively ($p = 0.444$). Five-year overall survival rate were 80.4% (Xelac) and 85.5% (Xelox), respectively ($p = 0.155$).
Conclusion: Xelac arm significantly obtained higher TRG1-2 rates. No differences were found about clinical outcome. Because of efficacy on TRG, inferior toxicity and good compliance, Xelac schedules or similar radiotherapy dose intensification schemes could be considered as reference treatments for cT3 lesions.

Introduction

Randomised controlled trials (RCTs) established, for locally advanced (i.e. cT3–4N0–2M0) resectable rectal cancers, preoperative radiotherapy (RT) plus total mesorectal excision (TME) either alone (short-course radiotherapy, SCRT) [1] or combined with concurrent chemotherapy (long-course radiochemotherapy, LCRCT) [2], as standard option [3,4]. The clinical benefit is strongly evident when obtaining a pathological complete response (pCR): predicts survival outcome [5], and allows personalisation of subsequent therapies [6].

The optimal preoperative RT schedule remains unclear. Oxaliplatin is a drug concomitantly applied as a chemosensitiser in LCRCT schedules; it improved clinical outcome and pCR rates in some series [7] although other did not reveal clinical benefit [8,9]. Some reports confirmed a correlation between increased delivered RT dose, and improved pCR rates, and clinical outcome [10–14]. Preoperative imaging staging by magnetic resonance imaging (MRI) is crucial for baseline and response-to-treatment evaluation [15–17].

We report on the long-term analysis of the INTERACT trial: a multicentric randomised controlled trial investigating two different intensification regimens of preoperative capecitabine-based radiochemotherapy (cbRCT), for patients with locally advanced rectal cancer, focused on cT2-low-lying/T3, N0–2 (excluding cT4) lesions. Primary objective: major pathological response rate.

Methods

Study design

The INTERACT trial was a prospective, parallel-group, randomised controlled trial on cT2-low lying/T3-up to 12 cm from anal verge, lesions investigating capecitabine-based LCRCT providing treatment intensification by either concomitant boost or multidrug intensification. The trial was performed in accordance with the ethical principles of the Declaration of Helsinki (1996), Good Clinical Practice, and applicable regulatory requirements. Ethical Committee's approval was obtained at Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore (Rome-Italy). The INTERACT trial was performed at hospitals and university hospital among 13 Italian Institutions.

Patients

Eligibility criteria were as follows: histologically confirmed primary adenocarcinoma of the rectum; clinical staging groups (according to UICC classification): cT2 N0–2M0 low-located tumours (candidate to abdominoperineal resection, APR) and cT3 N0–2M0 tumours within 12 cm from the anal verge confirmed by proctoscopic examination, or within 10 cm from the anorectal ring confirmed by MRI evaluation; resectable tumour at diagnosis; age $\geq$18 years; Karnofsky's Performance Status $\geq$ 60; WBC $\geq$ 4,000 cells/ml; platelets $\geq$ 100,000 cells/ml. The exclusion criteria were: cT4 or metastatic *(M1)* disease; previous chemotherapy, immunotherapy, or RT to the pelvis; multiple primary cancers involving both the colon and rectum; other major surgery; active inflammatory bowel disease; other co-existing malignancies or malignancies diagnosed within the last five years (with the exception of basal cell carcinoma or cervical cancer in situ); cardiovascular disease with a New York Heart Association Functional Status > 2; pregnancy or breastfeeding (women of child-bearing potential); any evidence of severe or uncontrolled systemic disease (e.g. unstable or uncompensated respiratory, cardiac, hepatic, or renal disease).

The Principal Investigator at each centre ensured that patients were given full and adequate oral and written information on the nature, purpose, and possible risks and benefits of the trial. Signed and dated informed consent was obtained for each patient before conducting any procedure specifically pertaining to the trial.

Randomisation and masking

We performed a multicentre prospective randomised trial by parallel groups design, following the accrual method in patient recruiting. Patient assignment to the Xelac or Xelox arm was randomly conducted, using an electronically based table of random numbers, centrally managed by the biostatistic centre.

In each centre, patients were stratified by gender and age. For the latter, the patient categorisation was based on a difference of ±5 years. Randomization results were provided to the investigators by the telephone call to the trial office. When a particular individual of a certain gender and age was assigned to one arm, the randomisation process allowed a previously unselected individual with the same characteristics to be recruited in the other arm. The Xelac arm was designed as the control arm. As this study could not be double-blinded, the statistician was blinded to the treatment received by each patient.

Procedures

Clinical and instrumental evaluation

Before randomisation, patients underwent digital rectal examination, total colonoscopy, pelvic MRI with contrast medium to define T and N staging, and total body computerised tomography (CT) with a contrast medium for M staging. Endoscopic ultrasound and/or CT were also used for T and N staging in some patients. T and N restaging was performed 6–7 weeks after the end of LCRCT using the same imaging procedures.

Treatment

Patients received preoperative cbRCT randomly intensified by either a concomitant RT boost to the bulky tumour (Xelac arm) or by oxaliplatin (Xelox arm).

Radiotherapy

Pelvic dose and volume (both arms). The delivered dose was 45 Gy at 1.8 Gy daily, 5 times per week. The clinical target volume (CTV) was the same in both arms: the entire mesorectum, the presacral, internal iliac, and obturator nodes [18].

Boost dose and volume. Xelac arm (concomitant boost) [19]: A boost of 10 Gy was delivered to the primary tumour (i.e. the gross

tumour volume, GTV) at 1 Gy per fraction, in 10 fractions over 5 weeks, twice a week, to a total dose of 55 Gy. The boost planning target volume was defined as the mesorectum corresponding to the primary tumour and mesorectal nodes plus 1-cm margin, in all directions. The daily boost dose was delivered immediately after the daily dose administered to the pelvis. In the Xelac arm, RT dose was calculated to globally account for a biological equivalent dose (BED) of 67.7 Gy.

Xelox arm (sequential boost): A boost of 5.4 Gy was added to the GTV with the corresponding mesorectum, at 1.8 Gy daily and in three fractions, to a total dose of 50.4 Gy. The boost was sequentially delivered after the end of the pelvic volume irradiation (BED: 59.4 Gy).

Concomitant chemotherapy

During radiotherapy, in the Xelac arm capecitabine was orally administered at a dose of 1650 mg/mq in a chronomodulated schema: three times a day (25% of the daily dose at 8 a.m., 25% at 6p.m., and 50% at 11p.m.), seven days a week. In the Xelox arm, capecitabine was delivered at a dose of 1300 mg/mq using the same chrono-modulation as for the Xelac arm; the oxaliplatin was administered as a 2-h infusion on days 1, 19, and 38 at a dose of 130 mg/mq per day [20]. Dose adjustment was performed in the case of toxicity, graded according to the Radiation Therapy Oncology Group (RTOG) toxicity scale.

Surgery and pathology. Surgery was performed 7–9 weeks after radiation course completion. The accepted procedures were APR, low anterior resection (LAR), or local excision (LE). LE was only permitted for major clinical responses (yT0–T1) presenting at least a tumour regression at a full-thickness specimen with negative lateral and deep margins.

The surgical approach and whether or not a temporary colostomy was performed after LAR were at the surgeon's discretion. TME was always performed in both anterior resection and abdominoperineal resection. The tumour regression grade (TRG) was quantified according to the TRG Scheme [21].

Postoperative chemotherapy. Adjuvant chemotherapy was recommended for all patients with histological evidence of tumours in the lymph nodes (pN+) or with TRG4-5. The recommended drugs were capecitabine or 5-fluoruracile plus folinic acid (FUFA)-based, according to the centre preference, with each centre also deciding on the administration schedule.

Outcomes

Objectives and end points

Primary objective. Evaluation of major pathological T downstaging.

Primary endpoint. T pathological major downstaging was considered as the overall rate of any patients with TRG1 or 2 scores according to Mandard's score [21].

Secondary objectives. Treatment toxicity rates and compliance to treatment schedule; tumour downstaging; sphincter-saving outcome; clinical outcome evaluation.

Secondary endpoints. Acute toxicity graded using RTOG toxicity scales; sphincter-saving surgical procedure rates; time to local recurrence (i.e. time from therapy initiation to any pelvic or rectal/colonic disease recurrence); Disease-free survival (DFS; i.e. time from therapy initiation to any pelvic or distant disease recurrence); overall survival (OS; i.e. time from therapy initiation to death).

Statistical analysis

With regard to sample size, pT0 (i.e. TRG1) prevalence rates of 20% and 30% for the control arm (Xelac) and experimental arm (Xelox) were considered, respectively. Considering a drop-out of 5%, the sample size was fixed to 308 patients for each arm. Type I error = 5%; Type II error = 20%.

The scientific coordination of the study chose to power the study on TRG1 rate to increase the sample size with respect to TRG 1+2, main endpoint of the study, to guarantee an higher number of patients, enhancing the potential value in defining the outcome of the secondary endpoints.

Survival rates were determined using the Kaplan–Meier method and the prognostic significance of potential parameters was assessed via univariate analysis (log-rank test and Breslow's test). We calculated the Hazard Ratio (Cox regression) or Odds Ratio (logistic regression) and 95% confidence intervals (CI) for each variable included in the model. The stepwise (backward elimination) procedure was used. Statistical analysis was performed using SPSS software for Windows™.

Annually, representatives from each centre attended a central meeting to discuss the patient accrual. For quality assurance, a central revision of the first group of enroled clinical cases, as well of the respective anatomopathological blocks (after surgery), was performed.

Follow-up

Follow-up was applied as described in Table 3 (Supplementary Material).

Results

INTERACT trial accrued, between June 2005 and September 2013, 589 consecutive patients. Hence, 560 patients with resectable, locally advanced, rectal cancer were randomised through 13 Italian institutions. Overall, 26 patients were excluded from the trial after giving consent because of refusal or multidisciplinary reassessment of the primary lesion as T4 at QA central meetings. Thus, definitive analysis was conducted on 534 patients (280 in the Xelac arm and 254 in the Xelox arm). The planned global accrual of 616 patients was reduced to 560 after an interim analysis considering the slow accrual, after 360 patients had already been enroled. The accrual of 200 additional patients was defined.

Fig. 1 is the trial profile. The pre-treatment patient baseline characteristics were balanced among the two groups, without significant differences (Table 1). The predominant clinical stage in the entire population was cT3N1M0, low or medium, located in 47.3% of patients; cT2N0M0 (1.3%), cT2N1M0 (8%), and cT2N2M0 (1.3%) very low located tumours were also included. Table 2 lists the main outcomes for the analysed data.

The RT dose was delivered as prescribed, to 263/278 patients (95%) in the Xelac arm and 243/252 patients (96.4%) in the Xelox arm ($p = 0.367$), not counting for 5 patient missing data. The concomitantly administered drug doses were reduced because of toxicity as follows: capecitabine was reduced in 23 (8.2%) and 35 (13.7%) patients in the Xelac and Xelox arms, respectively ($p = 0.039$); the oxaliplatin was reduced in 46 (18.1%) patients.

Significantly higher toxicity rates for some haematologic and non-haematologic parameters were reported for Xelox arm; in particular, haemoglobin (any grade: Xelox 24.1% vs. Xelac 15%; Grade $\geq$ 3: Xelox 1.3% vs. Xelac 0%; $p = 0.04$); platelets (any grade: Xelox 18.2% vs. Xelac 8.7%; Grade $\geq$ 3: Xelox 1.7% vs. Xelac 0%; $p = 0.011$); neurological (any grade: Xelox 21.7% vs. Xelac 1.7%; Grade $\geq$3: Xelox 0.5% vs Xelac 0%; $p < 0.001$); Upper Gastrointestinal (any grade: Xelox 16.9% vs. Xelac 10.2%; Grade $\geq$3: Xelox 0.9% vs

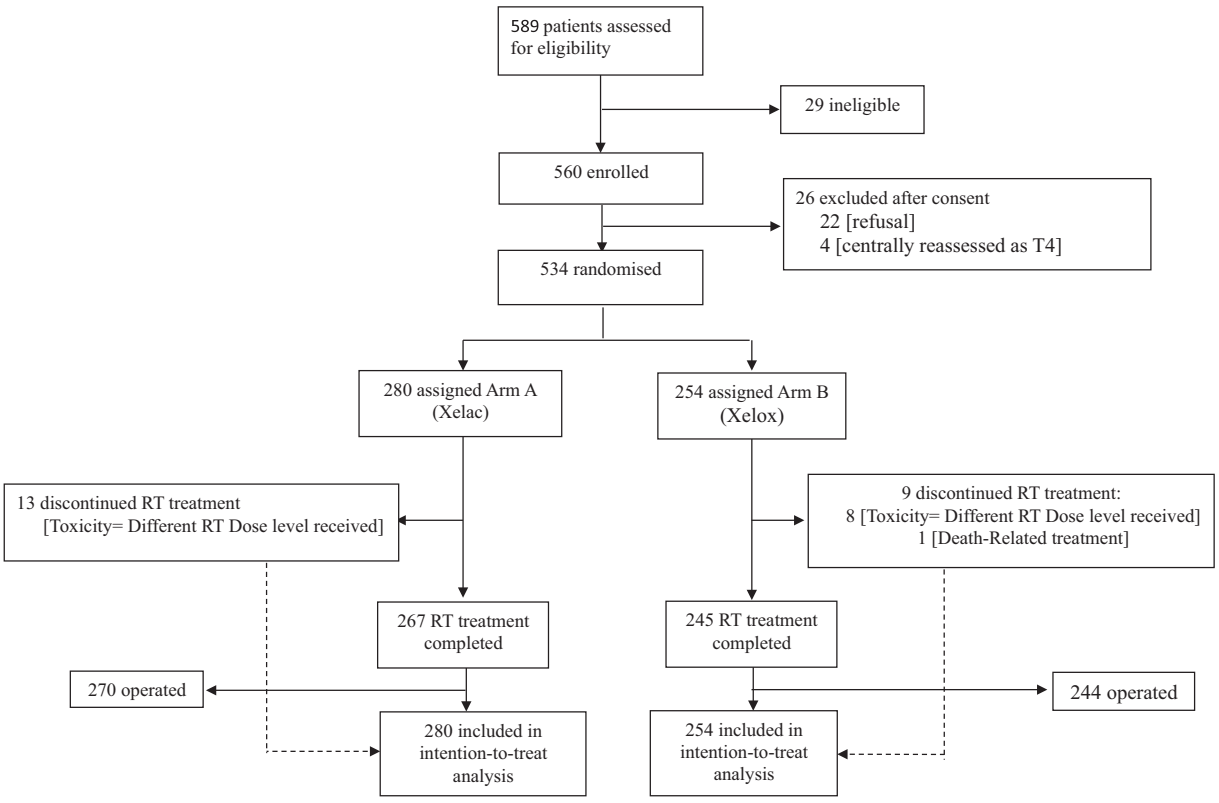


Fig. 1. Trial profile.

Table 1
Baseline characteristics of study population.

	Xelac arm 280/534 pts (52.5%)	Xelox arm 254/534 pts (47.5%)
Age	Median 60 (32–83) $p > 0.05$	Median 58 (32–79)
Gender	M = 188 (67.1%) F = 92 (32.9%) $p > 0.05$	M = 174 (68.4%) F = 80 (31.6%)
Tumour distance from internal anal margin (mm)	0–50 = 181 (67.3%) 51–100 = (31.6%) ≥101 = (1.1%) $p > 0.05$	0–50 = 162 (65.6%) 51–100 = 82 (33.2%) ≥101 = 3 (1.2%)
Tumour length (mm) N° rectal quarters involved	Mean = 45.3 1/4 = 37 (13.6%) 2/4 = 126 (46.5%) 3/4 = 45 (16.6%) 4/4 = 63 (23.3%) (Missing = 9) $p > 0.05$	Mean = 45.7 1/4 = 30 (12.2%) 2/4 = 107 (43.5%) 3/4 = 54 (22%) 4/4 = 55 (22.3%) (Missing = 8)
cTNM stage	cT2N0M0 = 3 (1.1%) cT2N1M0 = 21 (7.6%) cT2N2M0 = 4 (1.3%) cT3N0M0 = 55 (19.8) cT3N1M0 = 139 (50%) cT3N2M0 = 56 (20.2%) (Missing = 2) $p > 0.05$	cT2N0M0 = 3 (1.2%) cT2N1M0 = 22 (8.7%) cT2N2M0 = 3 (1.2%) cT3N0M0 = 61 (24.1%) cT3N1M0 = 112 (44.3%) cT3N2M0 = 52 (20.5%) (Missing = 1)

Xelac 0.4%; $p = 0{,}054$). The other parameters did not significantly differ between the two arms (see Table 4 – Supplementary Material).

After an overall median time to surgery of 61 days (63 and 60 for the Xelac and Xelox arms, respectively; $p = 0.072$), 99% and 98% received curative surgery in the Xelac and Xelox arms, respectively ($p = 0.175$). Some patients did not receive surgery: one in the Xelac arm, because of disease progression, and five in the Xelox arm, because of toxicity and occurring comorbidities (including one toxic death). The incidence of definitive colostomy (as rate at last follow-up) was similar in the two groups: sphincter-saving surgery was possible in 70.8 % and 72.4% of the Xelac- and Xelox-arm patients, respectively.

Table 2
Outcome summary.

	Xelac arm 280/534 pts (52.5%)	Xelox arm 254/534 pts (47.5%)
Compliance to RT	>55 Gy: 2 (0.7%) =55 Gy: 263 (95%) <55 Gy: 12 (4.3%) (Missing: 3)	>50.4 Gy: 1 (0.4%) =50.4 Gy: 243 (96.4%) <50.4 Gy: 8 (3.2%) (Missing: 2)
Surgery	SSS = 198 (72.6%) DS = 41 (15%) LE = 31 (11.3%) Not Resected = 3 (1.1%) (Missing: 7)	SSS = 184 (73.3%) DS = 38 (15.1%) LE = 22 (8.8%) Not Resected = 7 (2.8%) (Missing: 3)
TRG	1 = 80 (32.3%) 2 = 73 (29.4%) 3 = 69 (27.8%) 4 = 24 (9.7%) 5 = 2 (0.8%) (Missing = 32) $p = 0.102$	1 = 73 (32.9%) 2 = 43 (19.3%) 3 = 85 (38.3%) 4 = 20 (9%) 5 = 1 (0.5%) (Missing = 32)
TRG1 [calculated among evaluable pts for PE, excluding missing data]	80 (32.3%) $p = 0.885$	73 (32.9%)
TRG 1+2 [calculated among evaluable pts for PE, excluding missing data]	153 (61.7%) $p = 0.039$	116 (52.3%)

Legend: pt: patients; Gy: gray; SSS: sphincter-saving surgery; DS: definitive stoma; LE: local excision; NResec: not resected; TRG: tumour regression grade; PE: primary endpoint.

The primary study endpoint was cumulative major response rates (i.e. TRG 1-2): when analysed by evaluable patient (not accounting for missing data: 64/534 patients, 11.9%), the TRG 1-2 rate was significantly higher in the Xelac arm than in the Xelox arm: 61.7% vs.52.3% ($p = 0.039$), as detailed in Table 2. Overall, no statistical difference was reported for the global TRG grade distribution between the two arms ($p = 0.102$). TRG 1 rates did not significantly differ among arms: 32.3% vs.32.9% for Xelac and Xelox arms, respectively ($p = 0.885$).

About the global margin status: 121 patients are described for MRF baseline status (7.5% – 9/121 – MRF-positive, and 92.5% – 112/121 – MRF-negative, respectively).

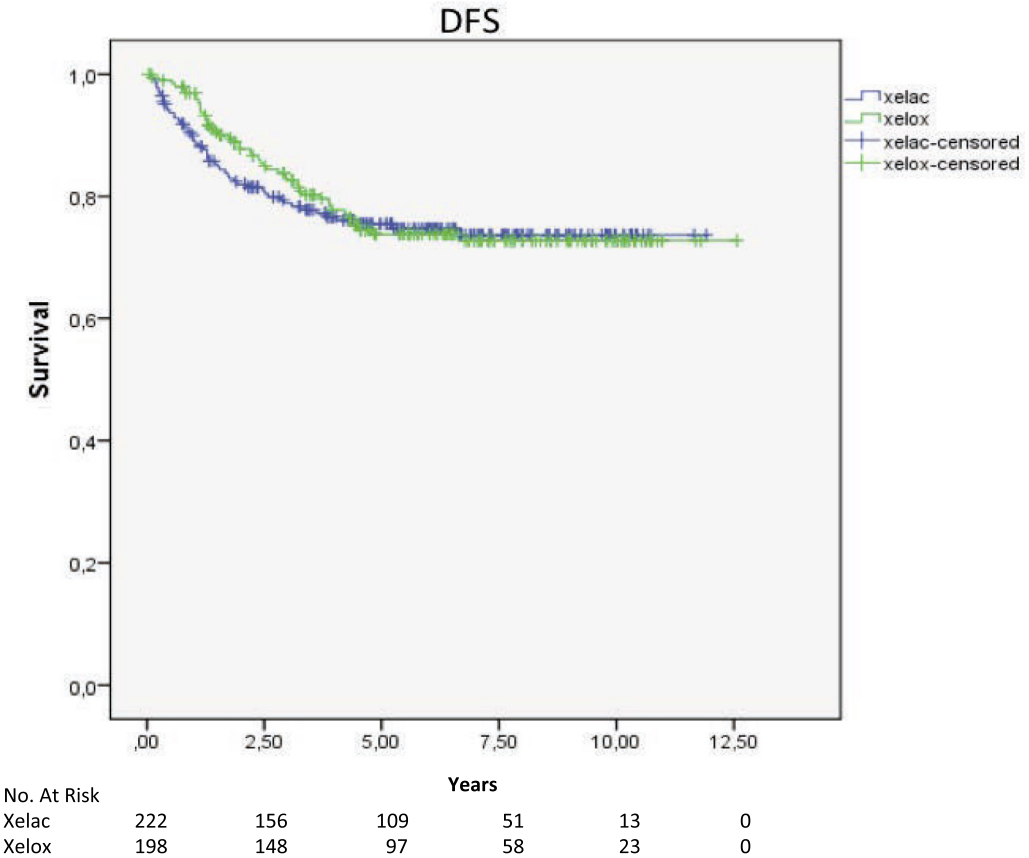


Fig. 2. Disease-free survival.

Overall 316 patients are described for CRM status (2.2% – 7/316 – CRM-positive, 97.8% – 309/316 – CRM-negative).

Adjuvant chemotherapy was similarly administered among the two arms: 40.4% and 35.4% of patients received six months of chemotherapy in the Xelac and Xelox arms, respectively ($p = 0.28$).

The median follow-up was 5.62 years (0.1–12.6). The main endpoint analysis results for clinical outcome (DFS and OS) were not statistically different between groups. Globally, 127 patients experienced a recurrence: patients free from recurrence globally accounted for 76.2% and 76.4% of the Xelac and Xelox arms, respectively ($p = 0.772$). The DFS is depicted in Fig. 2.

The three-year DFS rates were 78.3 and 82.6% ($p = 0.444$) in the Xelac and Xelox arms, respectively; the five-year DFS rates were 74.7 and 73.8% ($p = 0.444$) in the Xelac and Xelox arms, respectively.

Globally, 101 patients died in the two arms: globally alive patients accounted for 79.6% and 82.7% of the Xelac and Xelox arms, respectively ($p = 0.155$). The OS is depicted in Fig. 3.

The three-year OS did not significantly differ among the two groups: 88.3% and 92.4% in the Xelac and Xelox arms, respectively ($p = 0.155$). The five-year OS was also similar for the two groups: 80.4% and 85.5% in the Xelac and Xelox arms, respectively ($p = 0.155$). Local recurrence was overall confirmed for 37 patients (Xelac 7.5%, Xelox 6.3%; $p = 0.585$). The Local Control (LC) rate at 5 years was: Xelac 92.6%, Xelox 93.2% ($p = 0.519$), respectively (Fig. 4). The achievement of a TRG 1-2 response vs. any other grade (i.e. TRG 3-5) was confirmed to be a strong predictor of both significantly higher DFS (three, five and ten-year, for TRG 1-2 versus TRG 3-5: 86.6%, 83.5% and 79.8% versus 76.4%, 68.7% and 62.1%, respectively – $p < 0.001$) and OS (three, five and ten-year, for TRG 1-2 versus TRG 3-5: 94.3%, 86.2% and 84.4% versus 89.2%, 79.7% and 66%, respectively – $p = 0.019$) irrespective of the treatment arm allocation. Fig. 5 depicts the DFS for TRG 1-2 versus TRG 2-5.

Moreover, the achievement of a TRG 1 response vs. any other grade (i.e. TRG 2-5) was a strong predictor of both significantly higher DFS and OS irrespective of the treatment arm allocation ($p < 0.001$). Fig. 6 (Supplementary Material) depicts the DFS for TRG 1 versus TRG 2-5.

Discussion

The INTERACT trial considered two approaches for LCRCT intensification in a cbRCT treatment finding equivalence in the pathological responses for the two approaches. In Xelac arm, a concomitant boost of RT dose up to 55 Gy was added, whereas a second drug (oxaliplatin) was also administered in the Xelox arm, concurrent to a lower RT dose (50 Gy). Previous RCTs investigating oxaliplatin and LCRCT, both analysed cT3 and cT4 lesions. The study focused on the accrual of only cT2 (low-lying)/T3 N0-2M0 clinical presentations. No statistically significant difference in the overall pathological response was found. Both schedules gained a pCR rate at the highest boundaries of the literature, likely related to the earlier stage of the selected population. The Xelac arm met the primary endpoint of the study, significantly improving the major pathological response rates (i.e.: TRG 1-2): 61.7% vs.52.3% ($p = 0.039$). Moreover, although the overall acute toxicity

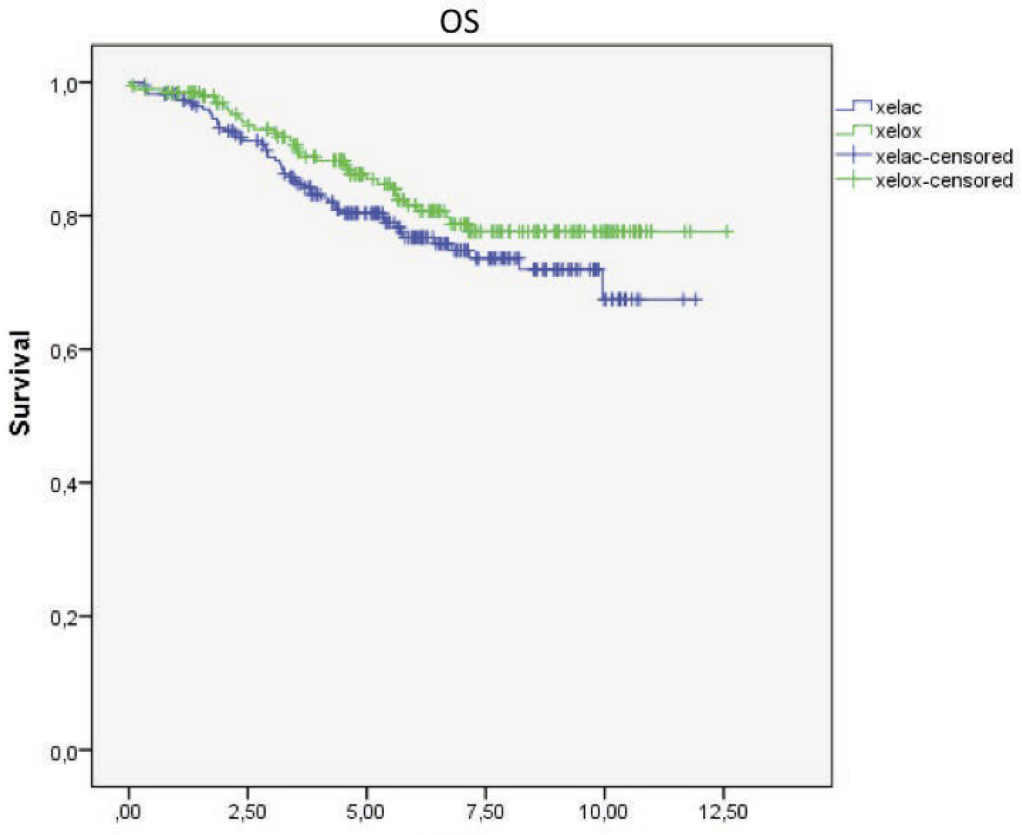
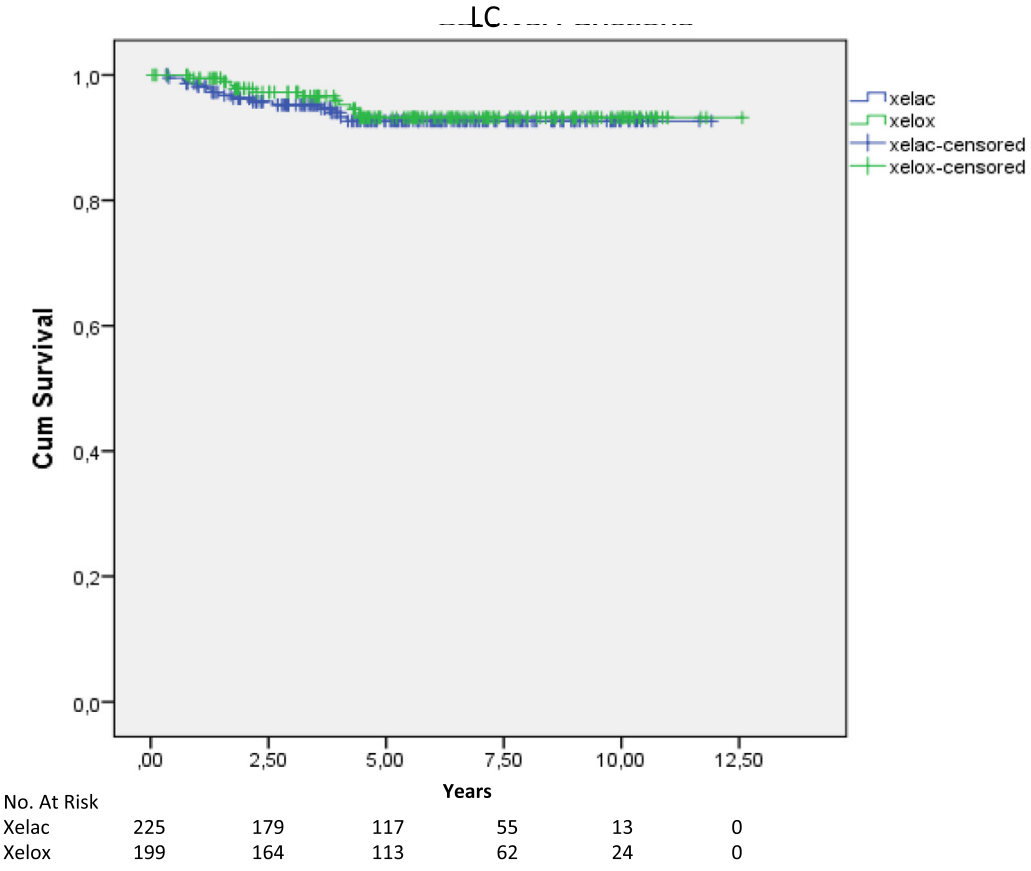
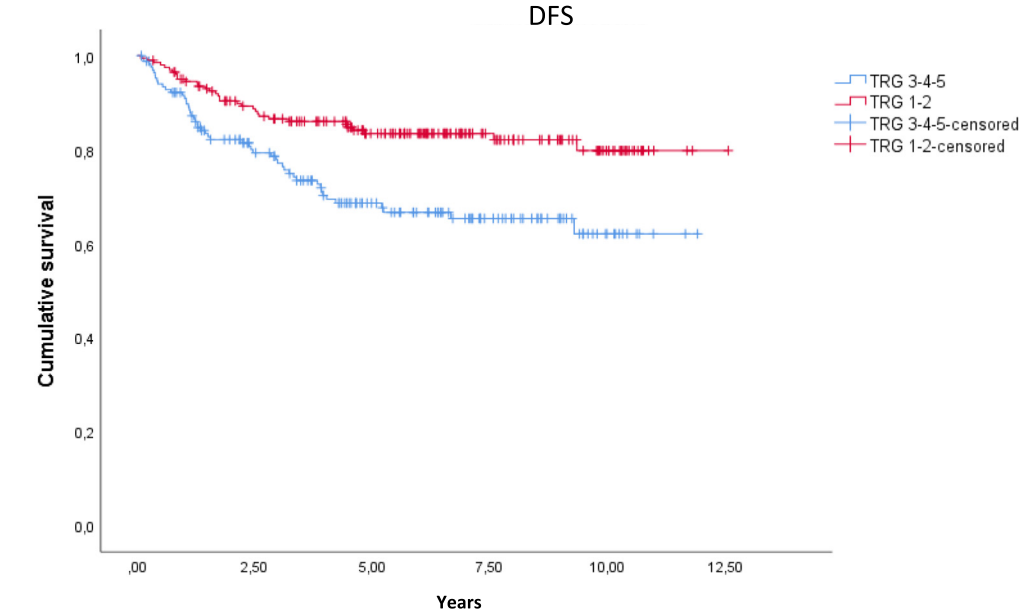


Fig. 3. Overall survival.



No. At Risk						
Xelac	225	179	117	55	13	0
Xelox	199	164	113	62	24	0

Fig. 4. Local control.



No. At Risk						
TRG 1-2	201	163	119	61	25	0
TRG 3-5	168	112	75	39	10	0

Fig. 5. Disease-free survival among TRG 1-2 vs. TRG 3-5.

profile was acceptable, Xelac arm obtained lower rates of acute toxic adverse events compared to the Xelox arm. In summary, the arm in which the RT dose was escalated by adding a concomitant boost to the standard cbRCT (Xelac), presented higher efficacy for the primary endpoint and a safe profile compared to both the randomised counterpart schedule of intensification (Xelox) and

to the standard reference data from the literature. The ACCORD 12/0405-Prodige 2 trial [9] considered two cbRCT regimens (“Cap 45” and “Capox50” with different drug and RT doses administered) only gained a non-significant difference in the primary endpoint (pCR: 13.9 vs.19.2%; $p = 0.09$) favouring the higher dose schedule. Moreover, inferior compliance to the schedule and a significantly higher overall rate of grade 3–4 toxicity was reported for “Capox 50” (10 vs.25.4%; $p = 0.001$). Nevertheless, the positive circumferential rectal margin (0–2 mm) rates were 19.3% and 9.9% with “Cap 45” and “Capox 50”, respectively ($p = 0 \cdot 02$). Tepper et al. [22] suggested an insufficient patient number, drug dose, inappropriate drug and RT timing, or end points insufficient for effect detection as alternative explanations to the ineffectiveness of oxaliplatin as radiation sensitiser. Obtaining superior responses by increasing RT dose has been investigated. In 222 patients, Appelt and coworkers demonstrated a significant dose–response relationship for the pathological outcome by tumour dose level in the range of 50.4–70 Gy, higher than that usually administered [10]. Recently, Burbach et al. confirmed high doses associated with a high pCR rate and acceptable early toxicity (pooled rate: 20.4–95% CI 16.8–24.5%) in a meta-analysis on 18 trials of preoperative RT delivery doses $\geq$60 Gy for locally advanced rectal cancers [11]. Therefore, in recent years, research interest has turned to administration of a concomitant boost to increase the dose to the tumour. In the available Phase I and II reports, the boost was administered in different ways with regard to timing, technique, and dose [12,23]. Moreover, three-dimensional conformal [12] or intensity modulated (IMRT) techniques for simultaneous dose escalation to the target (i.e. simultaneous integrated boost, SIB) [24] have been tested. The delivered dose ranged between different series, from 52.5 to 57.5 Gy. Alternatively, the treatment was combined to multidrug intensification gaining pCR rates in the range of 24–30.6%, mostly with acceptable toxicity [25].

Finally, it should be noted that, a concomitant boosting schedule could also have an important impact on the cost-effectiveness of oncological treatments. A recent microcosting study on direct costs of RT in rectal cancers for the two more adopted schedules (i.e. SCRT and LCRCT) confirmed that traditional RT is relatively inexpensive in itself and, thus, competitive with multiple (or single expensive) drug concurrent administration [26].

Because of the equivalence of the two treatment arms for the primary endpoint, the Authors wished to focus on the long-term clinical outcome represented by secondary endpoints to potentially allow identification of the more efficient approach. The findings of the report confirm that the achievement of a pCR is associated with a significantly improved DFS, independent of the administered treatment as reported in published series [5]. Although a significant correlation between pCR and survival endpoints has been detected in the literature [21], the efficacy of an incomplete response (TRG 2-5) [27] or of any pathological parameter [28] in general has been questioned. Although some pooled analyses [4] and meta-analyses [29] have confirmed the long-term survival benefit of pCR, the issue remains open to concern [30].

This trial has two main weaknesses. First, there was no third arm in which a non-intensified RT treatment delivering 45 Gy was administered (deliberately excluded because of the estimated difficulties in recruiting a very large number of patients, over 1000). Second, the accrual was prolonged; despite this, our data were consistent over time.

To the best of our knowledge, the trial is the first randomised clinical trial comparing a schedule of capecitabine-based LCRCT providing treatment intensification by concomitant boost versus multidrug intensification (capecitabine-based LCRCT plus oxaliplatin at 50.4 Gy), focused on cT2-low-lying/T3 lesions, demonstrating superior efficacy of dose versus multidrug intensification on major pathological outcome (i.e.: TRG 1-2), with a more favourable acute toxicity profile. Future trials should consider radiotherapy dose intensification as effective and tolerable.

Individual author contributions

VV, MAG, CA, CC, BB, SP, ADP: Performed the concept of the protocol.

FC: edited the draft of the paper.

GLT: Addressed the statistical Analysis.

BB: Defined the protocol and reviewed details for Imaging.

CC, SA, DDU, RP, AC, CB, GBD, SP: Defined the protocol and reviewed details for Surgery.

VV, MAG, FC, CA, FD, ML, GM, FN, CB, LC, MCB, EM, DG, AGM, ADP: Defined the protocol and reviewed details for Radiotherapy.

AB, SL: Defined the protocol and reviewed details for Medical Oncology.

FMV: Defined the protocol and reviewed details for Pathology.

All Authors: did review the final text.

Conflict of interest

Authors have no conflict of interest.

Trial registration

ClinicalTrials.gov Identifier NCT01653301.

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Appendix A. Supplementary data

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