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ORIGINAL ARTICLE

# Comparison of Capecitabine (Xeloda) vs. Combination of Capecitabine and Oxaliplatin (XELOX) as Neoadjuvant CRT for Locally Advanced Rectal Cancer

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## Abstract

We decided to compare pathologic complete response (pCR) and disease-free survival (DFS) in rectal adenocarcinoma patients who received neoadjuvant chemoradiotherapy (CRT) with capecitabine plus oxaliplatin (XELOX) or capecitabine (Xeloda). In this study, patients with non-metastatic locally advanced rectal cancer (tumor stages of T2, T3, or T4) with or without lymph node involvement were retrospectively included. Patients received concomitant radiation (50.4–54 Gy external beam radiation in 28 to 30 fractions) and neoadjuvant therapy as either Xeloda (capecitabine, 2500 mg/m$^2$ concomitantly with radiation therapy) (42patients) or XELOX [(oxaliplatin (50 mg/m$^2$ intravenously once a week for five weeks) and capecitabine)] (72 patients). Surgery was done eight weeks after CRT. The endpoints were pCR (defined as no evidence of viable tumoral cells) and DFS (the interval from the initial treatment to the first tumor recurrence). Rectal sphincter preservation via low-anterior resection (LAR) was achieved in 73.8% of Xeloda group which was similar to XELOX group (70.8%), $P = 0.61$. pCR was documented in 11 (26.9%) of Xeloda group and 26 patients (36.1%) of XELOX group ($P = 0.27$). Tumor recurrence was recorded in 97 patients (85.1%). Mean (±SD) DFS was 52.13 (±31.92) months (median = 48 months). Mean (95% CI) DFS was 129.42 (110.19 to 148.64) in Xeloda group vs. 122.77 (110.72 to 134.83) in XELOX group ($P = 0.74$). Addition of oxaliplatin to capecitabine as neoadjuvant CRT for locally advanced rectal cancer did not result in improved pCR or better DFS.

**Keywords** Chemotherapy · Capecitabine · Oxaliplatin · Rectal cancer

## Introduction

Neoadjuvant chemotherapy, radiation, and surgical resection has nowadays been identified as the standard care of locally advanced colorectal cancer by many experts [1]. Such multimodal therapeutic regimens have a favorable effect on the outcome via improving overall survival, tumor recurrence [2, 3], and sphincter preservation [4]. It also does not impair sphincter function before surgery [5]. One of the main indications for neoadjuvant chemotherapy is tumor stage (T3 or T4). However, regional lymph node involvement and distally located tumors are other relative indications for neoadjuvant chemoradiotherapy (CRT) [6].

Several chemotherapy regimens are used for neoadjuvant CRT of rectal cancer. Fluorouracil-based chemotherapy (5-fluorouracil/leucovorin, 5-FU/LV) is one of the established methods [7]. Capecitabine (Xeloda) is also another acceptable option. Infusional FU and daily capecitabine are currently accepted standard neoadjuvant therapy agents for T3 or T4 rectal cancer [8].

Capecitabine has several advantages over 5-FU and now a mainstay agent in neoadjuvant therapy of colorectal cancer. It is a prodrug and is converted to 5-FU through enzymatic reactions. The main advantage of capecitabine is that it is

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administered orally abates the need for venous access and infusion pumps [9]. It is used for adjuvant, neoadjuvant, and in combination with other antitumor agents for metastatic colorectal cancer.

Oxaliplatin is an alkylating agent and DNA cross-linking agent gained attention as an additive agent for neoadjuvant therapy of coloretctal cancers. However, the use of oxaliplatin in neoadjuvant therapy is not completely clear. Although there are studies about the benefits of oxaliplatin, there is no consensus currently to add this agent to previously established regimens [10]. Oxaliplatin has demonstrated additive effect to radiotherapy in gastrointestinal tract tumors. Some clinical trials have investigated the addition of oxaliplatin to capecitabine as adjuvant or neoadjuvant therapy in colorectal cancer [11–15]. There is controversy among the findings. For example, while XELOXART trial reported no beneficial effect of combination of capecitabine and oxaliplatin for pathologic complete response (pCR) observed in 12% of cases [14], another trial showed this combination regimen resulted in nearly complete response in 35% of patients [13].

One of the important prognostic characteristics in rectal cancer is pCR. In comparison to partial response or no response, pCR is associated with better overall survival and disease-free survival (DFS) [16].

As comparative studies about the addition of oxaliplatin in neoadjuvant CRT of rectal cancers are not enough and the benefit of this combination (XELOX regimen) is not completely understood, we decided to compare capecitabine vs. capecitabine and oxaliplatin in locally advanced rectal cancer.

## Materials and Methods

### Study Design and Setting

This study compared capecitabine (Xeloda) vs. combination of capecitabine and oxaliplatin (XELOX) as neoadjuvant CRT for locally advanced rectal cancer. This study was carried out from 2002 to 2016 at our university hospital radiology and oncology department.

### Eligibility Criteria

Inclusion criteria consisted of patients of either gender, > 18 years old, advanced non-metastatic rectal adenocarcinoma accompanied by histological confirmation, clinical stage T2 (T2 N1, but not T2 N0), T3, or T4 with or without lymph node (LN) involvement, no prior history of chemotherapy or CRT (chemoradiation therapy), WHO performance status 0–1, life expectancy of more than 6 months, normal hematologic, hepatic and renal function. Exclusion criteria included receiving radiotherapy or chemotherapy for the disease, those who had not fully recovered from a recent (within 4 weeks) major surgery, presence of a significant cardiac disease or a myocardial infarction within the previous 12 months, and a serious uncontrolled infection. Patients were also excluded if screening evaluations revealed significant abnormalities in neutrophils (< 1500), platelets (<100,000), serum creatinine or serum bilirubin (> 1.5 times of the upper normal limit), alanine aminotransferase (ALT), aspartames aminotransferase (AST) or alkaline phosphatase (>2.5 times of upper normal limit).

### Sample

A total number of 114 patients were studied including 42 patients in Xeloda group and 72 individuals in XELOX group.

### Intervention

In Xeloda group, capecitabine (2500 mg/m$^2$) was given concomitantly with radiation therapy (50.4 to 54 Gy five days weekly for 5–6 weeks in 28 to 30 fractions). In XELOX group, concomitant radiation therapy with same dose in Xeloda group) was used in addition to oxaliplatin (50 mg/m$^2$ intravenously once a week for five weeks during radiation therapy) and capecitabine (2500 mg/m$^2$).

### Data Collection

At first, tumor staging was determined using spiral computed tomography (CT) scan of the thorax with and without intravenous (IV) contrast media, spiral CT scan of the abdomen with and without IV and oral contrast materials, and magnetic resonance imaging (MRI) of the pelvis with and without IV contrast media, and endoultrasonography (EUS) of the rectum. Distance of the tumor to the anal verge was also registered.

Laboratory studies consisted of complete blood count (CBC diff), blood urea nitrogen, serum creatinine, ALT, AST, alkaline phosphatase, bilirubin (total and direct), and carcinoembryonic antigen (CEA).

Pelvic radiation therapy was done with three doses in a range of 4500–5400 Gy (45 Gy, 50.4 Gy, and 54 Gy) five days weekly (for four weeks). After this period, abdominal, pelvic, and thoracic CT scans were applied and in case of metastasis, the patient was not included.

Four weeks following completion of the CRT, CT scan of the abdomen, pelvis, and thorax was performed for restaging and evaluation of metastasis and in case of no evidence of metastasis, surgical intervention was performed about 8 weeks after CRT. At our center, the surgeries performed include low anterior resection (LAR) or abdomino-peritoneal resection (APR).

## Endpoints

The surgical specimens were examined by a board-certified pathologist. The primary endpoint was pCR defined as no evidence of viable tumoral cells. Stable disease was described as no change in tumor stage after surgery, and downstaging was defined as reduction of at least one T stage of the tumor. DFS was defined as the interval from the initial treatment to the first tumor recurrence.

## Statistics

The descriptive indices including frequency, percentage, mean and its standard deviation (SD) were used to express data. In order to compare nominal variables between the two groups, the Chi-square test or the Fischer's exact test was used. DFS was compared using the Kaplan-Meier analysis. Significance level was set at 0.05. All analyses were performed using SPSS software (ver. 20.0, IBM).

## Ethics

The study protocol was fully supported by the Research Council Ethics Committee of our medical university. The study objectives were explained to the patients and they were asked to provide written consent for enrolment. The study was in conformity with the Declaration of Helsinki.

# Results

A total of 114 patients were analyzed. There were 70 males (61.4%) and 44 females (38.6%). About half of the patients aged 50 to 70 years (63 cases, 55.3%). There was no statistically significant difference regarding age group and gender distribution between the two studied groups (Table 1).

Most patients had histopathologic tumor stage of T3 (88 patients, 77.2%) with positive regional lymph node involvement detected in 72% of the patients. CEA level was less than 10 ng/mL in most patients (98 subjects, 86%). Tumor distance from anal verge was less than 6 cm in 63 patients (55.3%). Table 2 presents comparison of tumor stage, regional lymph node involvement, CEA level categories, and tumor distance from anal verge. As observed, except for lymph node involvement which was marginally more common in XELOX group, other variables were comparable between the two groups.

According to the findings, there was no significant difference regarding surgical tumor resection between the two chemotherapy groups. Regarding sphincter preservation, low-anterior resection (LAR) was performed in 73.8% of Xeloda group which was similar to XELOX group (70.8%), $P = 0.61$; Table 3.

pCR was documented in 11 (26.9%) of Xeloda group and 26 patients (36.1%) of XELOX group ($P = 0.27$). Local tumor recurrence was recorded in 16 patients (14%). Six patients in Xeloda group (14.3%) and 10 cases in XELOX group (13.9%) experienced local tumor recurrence ($P = 0.95$). Mean (±SD) disease-free survival was 52.13 (±31.92) months (median = 48 months). Disease-free survival did not show significant difference between the two groups (Table 4, Fig. 1).

In comparison of the studied variables between the pathology groups (complete response vs. downstage/stable disease) no significant difference was noted regarding age groups, gender, lymph node involvement, CEA groups, tumor distance from anal verge groups, and type of surgery. Complete response was significantly higher in T2 or T3 group (26 patients, 70.3%) compared to T4 group (11 cases, 27.9%); $P = 0.009$.

## Toxicity

No chemotherapy interruption required in any group. Dose adjustments were made if necessary according to BC Cancer Agency guidelines. Side effects were comparable between the groups. Fever and neutropenia which required hospitalization was not reported in either group. Grade 3 neuropathy occurred in 5% of patents in Xeloda group and in 12% of XELOX group.

# Discussion

Neoadjuvant CRT with concurrent radiotherapy is used widely before surgical resection for locally advanced rectal cancer. Undoubtedly, improving overall survival of patients is one of

**Table 1** Comparisons of demographic variables among 114 patiemts with rectal adenocarcinoma who received capecitabine plus oxaliplatin (XELOX) or capecitabine (Xeloda)

| | | Total ($N = 114$) | Xeloda ($N = 42$) | XELOX ($N = 72$) | $P$ value |
|---|---|---|---|---|---|
| Gender | Female | 44 (38.6%) | 17 (40.5%) | 27 (37.5%) | 0.75 |
| | Male | 70 (61.4%) | 25 (59.5%) | 45 (62.5%) | |
| Age | < 40 | 13 (11.4%) | 6 (14.3%) | 7 (9.7%) | 0.28 |
| | 40 to 50 | 19 (16.7%) | 5 (11.9%) | 14 (19.4%) | |
| | 50 to 70 | 63 (55.3%) | 21 (50%) | 42 (58.3%) | |
| | > 70 | 19 (16.7%) | 10 (23.8%) | 9 (12.5%) | |

**Table 2** Comparisons of the tumor stage, lymph node involvement, CEA category in 114 patients with rectal adenocarcinoma who received capecitabine plus oxaliplatin (XELOX) or capecitabine (Xeloda)

| | | Total ($N = 114$) | Xeloda ($N = 42$) | XELOX ($N = 72$) | $P$ value |
|---|---|---|---|---|---|
| Tumor stage | T2 | 7 (6.1%) | 5 (11.9%) | 2 (2.8%) | 0.059 |
| | T3 | 88 (77.2%) | 33 (78.6%) | 55 (76.4%) | |
| | T4 | 19 (16.7%) | 4 (9.5%) | 15 (20.8%) | |
| Lymph node involvement | | 83 (72.8%) | 26 (61.9%) | 57 (79.2%) | 0.046 |
| CEA, ng/mL | < 10 | 98 (86%) | 35 (83.3%) | 63 (87.5%) | 0.63 |
| | 10 to 50 | 10 (8.8%) | 5 (11.9%) | 5 (6.9%) | |
| | 50 to 100 | 1 (0.9%) | 0 | 1 (1.4%) | |
| | > 100 | 5 (4.4%) | 2 (4.8%) | 3 (4.2%) | |
| Tumor distance from anal verge | 0 to 6 cm | 63 (55.3%) | 21 (50%) | 42 (58.3%) | 0.2 |
| | 6 to 10 cm | 38 (33.3%) | 18 (42.9%) | 20 (27.8%) | |
| | > 10 cm | 13 (11.4%) | 3 (7.1%) | 10 (13.9%) | |

the priorities in research regarding experimental studies on various chemotherapeutic agents.

Several clinical trials have studied various chemotherapy agents to enhance overall survival as well as DFS in locally advanced rectal cancer population. pCR is one of the prognostic factors which implies better prognosis in colorectal cancer. Five-year survival rate in such patients has been reported to be significantly higher (83%) in pCR compared to those without complete response [17]. Hence, this endpoint has become of high priority in many studies. Here, although pCR was higher in XELOX group (36%) than in Xeloda group (26%), the difference did not reach statistical significance. It is possible that by larger sample size, this difference becomes more obvious. In a previous study including 63 patients with rectal cancer (T3 or T4), pCR was detected in a higher number of patents received capecitabine plus oxaliplatin (34%) than those who received capecitabine alone (13%) ($P = 0.07$) [10]. These figures have been reported fewer in some other studies. In a trial involving 25 patients with locally advanced rectal cancer (T3/T4 or positive-node), pCR was detected in 12% of the patients and 20% achieved trace tumor residue [8]. The observed pCR rate is higher than previously reported rates with different XELOX protocols which range from 10% to 25% [18, 19]. In addition to pCR, tumor downstaging is another finding which pertinent results seem to be more promising [14]. In contrast, tumor downstaging was comparable in our study between the two arms.

Our results are in agreement with a previous study that adding oxaliplatin to capecitabine did not have significant effect on not only on pCR but also on sphincter preservation rate and downstaging [20, 21]. Even more toxicities occurred with combination of capecitabine and oxaliplatin (Capox) which was 25% compared to capecitabine alone (1%) [21]. In the latter study, pCR was 19% in Capox compared to 14% in capecitabine group which was not statistically different. Studies whose publication date back to the 1990s reported promising results regarding oxaliplatin in terms of improving overall survival and DFS when administered in combination with 5-FU. These ended in the recommendation of adding oxaliplatin at least as a second-line chemotherapy in colorectal cancer [22]. However, more recent studies, including the presented study, do not show beneficial effect of adding oxaliplatin to 5-FU or capecitabine. Another issue is the addition of oxaliplatin to 5-FU which seems to be more adminis-

**Table 3** Comparisons of surgery type and histopathologic examinations in 114 patients with rectal adenocarcinoma who received capecitabine plus oxaliplatin (XELOX) or capecitabine (Xeloda)

| | | Total ($N = 114$) | Xeloda ($N = 42$) | XELOX ($N = 72$) | $P$ value |
|---|---|---|---|---|---|
| Surgery | CAA | 1 (0.9%) | 0 | 1 (1.4%) | 0.61 |
| | LAR | 82 (71.9%) | 31 (73.8%) | 51 (70.8%) | |
| | APR | 31 (27.2%) | 11 (26.2%) | 20 (27.8%) | |
| Pathology | Downstage | 56 (49.1%) | 19 (45.2%) | 37 (51.4%) | 0.09 |
| | Stable disease | 21 (18.4%) | 12 (28.6%) | 9 (12.5%) | |
| | Complete response | 37 (32.5%) | 11 (26.2%) | 26 (36.1%) | |

*LAR* low-anterior resection, *APR* abdomino-peritoneal resection

**Table 4** Disease-free survival comparison in 114 patients with rectal adenocarcinoma who received capecitabine plus oxaliplatin (XELOX) or capecitabine (Xeloda) (Kaplan-Meier analysis)

| | Number of tumor recurrences | Number censored | Mean disease-free survival in months (95% CI) | *P* value[a] |
|---|---|---|---|---|
| Xeloda (*N* = 42) | 6 | 27 (81.8%) | 129.42 (110.19 to 148.64) | 0.74 |
| XELOX (*N* = 72) | 10 | 54 (84.4%) | 122.77 (110.72 to 134.83) | |

[a] Breslow (Generalized Wilcoxon)

tered at least in some centers [23] and reported to be more tolerable [24]. However, controversies continue in the literature as at least three single-arm non-comparative trials have advocated the beneficial effect of adding oxaliplatin to capecitabine [8, 15, 25]. In a previous study, adding Eloxatin (oxaliplatin) to 5-FU did not end in more pCR or more preserved sphincter surgeries in rectal adenocarcinoma [26].

In analyzing the predictors of pCR, only pre-treatment tumor stage was found to be a significant predictor. A higher proportion of patients with T3 stage (70%) achieved pCR compared to T4 stage group (27%). CEA which has been shown to be a prognostic factor for pCR [27] did not show such a relationship here. CEA level of >2.5 ng/mL along with tumor circumferential extent of >60% have been reported to be significant predictors of pCR [27]. Likewise, another study on 96 patients demonstrated that CEA level was associated with pCR [28]. However, the mentioned study used a cut-off value of 5 ng/mL and non-smokers with CEA levels of <5 ng/mL showed association with pCR. This finding has also been reported by another group who showed not only CEA < 5 ng/mL is associated with pCR, but the interval between neoadjuvant therapy and surgery (more than 7 weeks) was also another significant predictor factor for pCR [29].

Lower grade of tumor which was observed here is in agreement with a recent report. In a study using a national database of 27,532 patients with non-metastatic rectal cancer, low grade tumor was found one of the variables to predict pCR [1]. Other variables revealed to have prognostic implication were female gender, recent diagnosis, size, and lower clinical N classification.

## Conclusion

In conclusion, addition of oxaliplatin to capecitabine as neoadjuvant CRT for locally advanced rectal cancer did not result in improved pCR or longer DFS. In our opinion, adding oxaliplatin does not associate with better outcomes and is not recommended.

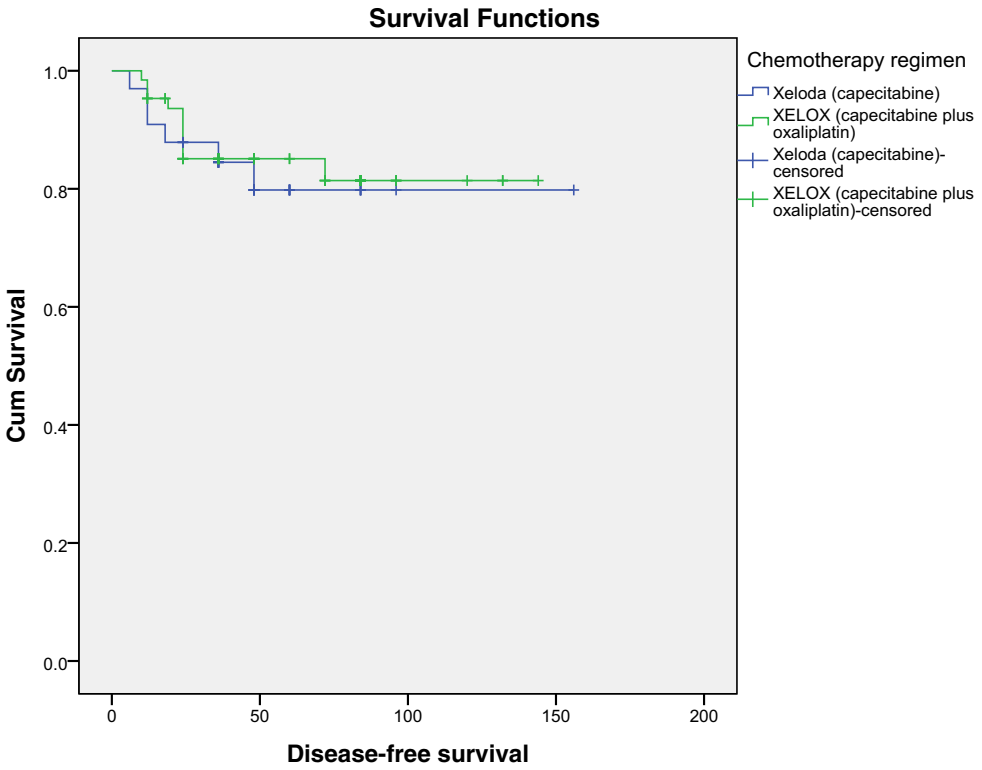


**Fig. 1** Disease-free survival curves for Xeloda and XELOX groups among patients with rectal adenocarcinoma

**Data Availability** The raw data are available in statistical software.

## Compliance with Ethical Standards

**Declarations** Ethics approval and consent to participate: Ethical approval was obtained from our medical university research deputy. Informed written consent was obtained from patients.

**Consent for Publication** The authors consent to publish the article.

**Competing Interests** There is no competing interest with contents of this article.

**Abbreviations** *APR,* abdomino-peritoneal resection; *CEA,* carcinoembryonic antigen; *CRT,* chemoradiotherapy; *DFS,* disease-free survival; *EUS,* endoultrasonography; *LAR,* low-anterior resection; *LN,* lymph node; *pCR,* pathologic complete response

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