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Original Article

**Does Adjuvant Chemotherapy for Locally Advanced Resectable Rectal Cancer treated with Neoadjuvant Chemoradiotherapy have an impact on survival? A Single Moroccan Institute Retrospective Study**

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Medical Oncology Department, University Hospital Mohammed VI, Oujda, Morocco

**Abstract**

**Background:** In the locally advanced stage, the prognosis of rectal cancer was improved by preoperative chemoradiotherapy and radical surgery including complete total mesorectal excision. At present, the place of adjuvant chemotherapy remains controversial. We aimed to assess the impact of this chemotherapy on our patient survival.

**Methods and Materials:** This is a retrospective study including patients with locally advanced resectable cancer in the middle and low rectum, treated by neoadjuvant chemoradiotherapy and radical surgery including complete total mesorectal excision at the Medical Oncology Department of the University Hospital Mohammed VI–Oujda, Morocco over a period of six years from January 2007 to December 2012. Patients were divided into two groups: with chemotherapy (Group A) and without it (Group B). In group A, adjuvant chemotherapy was started 4–8 weeks after surgery, constituted of CAPOX (Capecitabine and oxaliplatin) or Capecitabine alone for 8 cycles.

We assessed the median overall survival (OS), the median disease-free survival (DFS), the 3-year OS and the 3-year DFS in both groups.

**Results:** Forty patients were included in this study. Nineteen patients in group A: CAPOX (n= 14), Capecitabine alone (n=5). Twenty-one patients in group B. After a median follow-up of 57 months (range 7–129). Median OS was 94 months in the group A and 119 months in group B [HR = 1.773, 95% CI: 0.759–1.773; P =0.186]. Median DFS was 30 months in group A and 17 months in group B [HR= 1.898, 95% CI: 0.634–5.683; P =0.252]. 3-year OS was 86.4% in group A and 92.5% in group B [HR= 1.549, 95% CI: 0.548–4.383; p = 0.409]. 3-year DFS was 66.7% in group A and 57.2% in group B [HR= 2.166, 95% CI: 0.712–6.591; p = 0.173].

**Conclusion:** Although there are some limitations in our study, namely its retrospective design and small size of the cohort, adjuvant chemotherapy for locally advanced resectable rectal cancer treated with neoadjuvant chemoradiotherapy did not improve OS nor DFS.

**Keywords:** Locally advanced resectable cancer, rectal cancer, adjuvant chemotherapy, overall survival, disease free survival.

**Introduction**

In Morocco, rectal cancer is the second most common digestive cancer after that of the stomach. Neoadjuvant chemoradiotherapy (NACR) followed by radical surgery including complete total mesorectal excision (TME) is the gold standard treatment for locally advanced resectable rectal cancer (LARRC). The benefit of adjuvant chemotherapy (ACT) in patients who have received NACR followed by surgery remains unclear. We aimed to assess the efficacy of ACT on our patient survival.

**Methods and Materials**

This is a retrospective study including patients with LARRC treated at the Medical Oncology Department of the University Hospital Mohammed VI–Oujda, Morocco over a period of six years from January 2007 to December 2012.
Does Adjuvant Chemotherapy for LARRC have an impact on survival? Y. Seddik, et al.

2012. Inclusion criteria were: Histological confirmation of adenocarcinoma of the middle and low rectum, clinical stage T3–T4 N0 N+ (UICC criteria), performance Status: 0–2, age: from 18 to 85 years. We excluded patients with upper rectum cancer, with distant metastases in body CT scan, who didn’t have NACR, those who had not been operated and those who had a surgery without complete TME.

All patients received conventional schedule of NACR: 45–50 Gy in 25 fractions (1.8–2 Gy/fraction) with Capecitabine based chemotherapy at dose of: 825 mg/m² Per Os twice daily five days per week, on days of radiotherapy. Surgery was planned 4–8 weeks after chemoradiotherapy.

Histopathological response of the surgical specimens was evaluated according to Dworak’s classification.

Patients were divided into two groups: with ACT (Group A) and without it (Group B). ACT was started 4–8 weeks after surgery, constituted of CAPOX (Oxaliplatin 130 mg/m² and Capecitabine 2000 mg/m² Per Os twice daily for 14 days followed by 7 days of rest. Cycles were repeated every 21 days), or Capecitabine alone at the dose of 2500 mg/m² Per Os twice daily for 14 days followed by 7 days of rest. Cycles were repeated every 21 days. A complete laboratory examination was done before each treatment cycle.

The severity of adverse events was graded in accordance with the National Cancer Institute Common Terminology Criteria version 4.0.

Patients were followed up until death or until last data assessment done in 31 December 2017.

The statistical analysis was performed using SPSS version 21.0. We assessed the median overall survival (OS), the median disease–free survival (DFS), the 3–year OS, and the 3–year DFS in group A and B. Relative risks and their 95% Confidence interval (CI) were estimated from Cox models. Survival curves from the Kaplan Meier model. A value p ≤ 0.05 was considered to be statistically significant.

**Results**

Forty patients were included in this study. Nineteen patients in group A. Twenty–one patients in group B. The average age of patients in group A was 52.68 years (22–84); in group B: 50.33 (25–75). The female sex was predominant: 52.63% in group A, and 66.66% in group B. Epidemiological, clinico–pathological features are shown in Table 1.

<table>
<thead>
<tr>
<th>Group A (with ACT) N=19</th>
<th>Group B (without ACT) N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.68 (22–84)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
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<td>T4</td>
<td>12</td>
</tr>
<tr>
<td>Clinical N Stage</td>
<td></td>
</tr>
<tr>
<td>N+</td>
<td>15</td>
</tr>
<tr>
<td>N0</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1. Epidemiological, clinico–pathological characteristics

Histopathological response of the surgical specimens based on Dworak classification revealed: in Group A: 0 cases of pathological complete response (pCR), 3 cases of stage II (ypT3–4N0), 16 cases of stage III (ypTany N1–2). In group B: 4 cases of pCR, 17 cases of stage II, 0 case of stage III. (Table 2)

<table>
<thead>
<tr>
<th>yp Stage</th>
<th>Group A (with ACT) N=19</th>
<th>Group B (without ACT) N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II (ypT3–4N0)</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Stage III (ypTanyN1–2)</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>pCR (ypT0 N0)</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2. Post–operative histopathological response (Dworak classification)

There were two schedules of ACT: CAPOX realized in 14 patients, and Capecitabine alone for 5 patients. All of them had ACT for 6 months. The most observed toxicities were in descending order: vomiting, neurotoxicity, haematological toxicity, diarrhea, mucositis, and hand–foot syndrome. These toxicities were classified as Grade 1–2 in 14 patients, while 5 patients had Grade 3 (3 cases of neurotoxicity, 1 case of diarrhea, and 1 case of hand–foot syndrome). Grade 4 toxicity was not observed in any patient. All adverse events are detailed in Table 3.
After a median follow-up of 57 months (range 7–129). Median OS was 94 months in group A and 119 months in group B [HR = 1.773, 95% CI: 0.759–1.773; P =0.186] (Figure 1). Median DFS was 30 months in group A and 17 months in group B [HR= 1.898, 95% CI: 0.634–5.683; P =0.252] (Figure 2). 3-year OS was 86.4% in group A and 92.5% in group B [HR: 1.549, 95% CI: 0.548–4.383; p= 0.409]. 3-year DFS was 66.7% in group A and 57.2% in group B [HR: 2.166, 95% CI: 0.712–6.591; p= 0.173].

### Table 3. Adverse events of adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1–2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Hematological toxicity</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Mucositis</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**Discussion**

The role of adjuvant chemotherapy in rectal cancer is still unclear. The QUASAR trial (4) showed a small improvement in survival of 3.6%, but rectal cancer represented only 29% of the cohort, 21% of them received preoperative radiotherapy. ACT was based on intravenous 5–fluorouracil (5FU) without oxaliplatin.

In the Italian phase III randomized trial, I–CNR–RT (5), 655 patients with LARRC treated with NACR and surgery, were randomized between observation or ACT based on 5FU and folinic acid. There was no difference in 10–year OS between the two groups (63.4% with ACT and 63.0% without). Quarter of patients were unable to start any ACT and 55% received only three to six cycles. Same results were observed in the French study EORTC 2292 (6). 10–year OS was 51.8% for the ACT group and 48.4% for the surveillance group (p=0.32). 10–year DFS was 47.0% for the ACT group and 43.7% for the surveillance group (p=0.29). In this study, there was no interaction between the tumour down staging effect induced by the neoadjuvant treatment (radiotherapy or radio chemotherapy).

The phase III randomized trial PROCTOR–SCRIPT (7), which included rectal cancer patients treated with neoadjuvant (chemo)radiotherapy and surgery, showed no impact of ACT on 5–year OS nor DFS. ACT consisted of 5–FU–folinic acid (PROCTOR) or Capecitabine (SCRIPT). Subgroup analysis found a 5–year OS advantage of ACT only for tumors located above 10 cm from the anal verge (p=0.028). However planned accrual was not completed in this trial.

The CHRONICLE (8) study randomly assigned patients receiving NACR for LARRC, to 6 months of ACT based six cycles of CAPOX versus observation. The 3–year DFS rate was 78% with CAPOX and 71% with observation (P = 0.56). The 3–year OS for CAPOX and observation were 89% and 88% respectively (P = 0.75). These results are difficult to interpret because of the small numbers of patients and poor accrual.

All of these data were included in a meta–analysis (9) published in the lancet oncology in 2015. There was no significant impact of ACT on OS, nor DFS. However, subgroup analyses showed a significant improvement in DFS (HR= 0.59; p=0.005), for patients with a tumour 10–15 cm from the anal verge when treated with ACT.

On the extrapolation of findings from patients with colon cancer, Yong Sang Hong et al. evaluated in the phase II randomized trial ADORE (10) the addition of Oxaliplatin to 5FU in adjuvant setting for patients with LARRC pre–treated by NACR and surgery. This trial was positive in terms of its primary endpoint: 3–year DFS was
71.6% in the FOLFOX group and 62.9% in the 5 FU group (p=0.047). Although there were some limitations related to phase II design, ADORE is the first study to show the benefits of adjuvant FOLFOX in this category of patients.

Like I--CN--RT, PROCTOR--SCRIPT, CHRONICLE trials, our study showed no significant impact of ACT on survival. Epidemiological, clinico--pathological features were well balanced between the 2 groups. We excluded all patients who didn’t receive optimal treatment in neoadjuvant setting or those who didn’t have complete surgery, so that these factors didn’t have an impact on the data analysis. Stage III (ypT3--4N0) was predominant ingroup A (with ACT), and stage II (ypTanyN0) in group B (with ACT), because our therapeutic decision was made based on European Society of Medical Oncology which recommend ACT for ypT3--4N0 and ypTanyN0. There were 2 schedules of ACT (CAPOX and Capecitabine alone) because Oxaliplatin was not allowed for 5 patients given their age > 70 years old or PS = 2.

The major drawbacks of our study are the retrospective design which is not as convincing as a randomized trial, the small size of the sample, and the short median follow--up (only 4.75 years), so we have no idea about the evolution of long--term results.

Conclusion

Our study didn’t show any significant impact of ACT on survival for patients with LARRC treated with NACR and surgery. Large studies are needed to clarify the role of ACT for this category of patients. Any therapeutic decisions in this setting must be made in a multidisciplinary meeting.

Ethics, consent, and permissions

This study was approved by the ethics committee of the university hospital Mohammed VI--Oujda. All patients included in this study have given their consent to participate.

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