Improved incidence of pT0 downstaged surgical specimens in locally advanced rectal cancer (LARC) treated with induction oxaliplatin plus 5-fluorouracil and preoperative chemoradiation


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Purpose: To compare efficacy in terms of pathologic response in LARC patients treated with preoperative chemoradiation, with or without a short-intense course of induction oxaliplatin.

Patients and Methods: From 05/98 to 10/02, 114 patients were treated with preoperative chemoradiation (4500–5040 cGy + oral Tegafur 1200 mg/day) for cT 3-4N+TxM0 rectal cancer. Starting 05/01, 52 consecutive patients additionally received induction FOLFOX-4, oxaliplatin (85 mg/m² iv d1), 5-FU (400 mg/m² iv bolus d1) and 600 mg/m² iv continuous infusion in 22 h with leucovorin (200 mg iv) d1 and d2, every 15 days (2 cycles), followed by the previously described Tegafur chemoradiation regime. Surgery was performed in 5–6 weeks. Pathological assessment investigated post-treatment T and N status in the rectal wall and peri-rectal tissues.

Results: Patients, tumor and treatment characteristics were comparable between groups. Incidence of pT0 specimens was significantly increased by induction FOLFOX-4 (P = 0.006). Total T and N downstaging were 58% versus 75% and 42% versus 40%, respectively (P = ns). T downstaging of ≥2 categories was significantly superior in FOLFOX-4 group (P = 0.029).

Conclusions: Short-intense induction FOLFOX-4 significantly improves pathologic complete response in LARC patients treated with tegafur-sensitized preoperative chemoradiation. The 44% rate of pT0-1 specimens observed in the oxaliplatin group should impulse innovative surgical approaches to promote ano-rectal sphincter conserving protocols.

Key words: neoadjuvant oxaliplatin, chemoradiation, tegafur, rectal cancer, downstaging

introduction

Neoadjuvant treatment for locally advanced rectal cancer has been suggested as a potential indication for sphincter preservation and favorable survival outcome [1–3]. The studies in literature have reported the incidence of complete pathological response (pT0) surgical specimens not >30% after chemoradiation with fluoropirimidine-based chemotherapy [4–7]. Oxaliplatin is one of the two most active single agents in the treatment of colorectal cancer with a 20% response rate with monotherapy in advanced disease [8, 9]. In association with 5-FU and folinic acid (FOLFOX-4 regime), it improves disease-free-survival and objective response rates (in the range of 50%) in metastatic colorectal cancer patients [10] and significantly impacts the disease-free-survival and cancer-related events at 3 years (P = 0.002) when administered as adjuvant treatment to stage II–III colon cancer patients (compared to 5-FU/folinic acid alone scheme) [11].

Neoadjuvant FOLFOX-4 (short course, two cycles), as the only treatment component in chemotherapy naïve locally advanced rectal cancer induces downsizing effects, with monitored endorectal ultrasound observations of T stage (uT) or N stage (uN), including 20% of uT downstaging, 37% uN downstaging, 42% uT1 migration morphology from deep to superficial rectal wall involvement [12].

Preoperative chemoradiation with fluoropirimidines has been reported to promote sphincter preservation compared with postoperative chemoradiation in a small subset analysis [13], but this feature remains controversial in recent prospective trials evaluation with similar methodology [14]; on the other hand, pelvic disease control and tumor sterilization is significantly improved by preoperative chemoradiation compared with
radiotherapy alone [15]. Downstaging effects are equivalent among chemoradiation schemes using protracted venous infusion of 5-FU or high daily dose of oral tegafur (53% versus 46% in T category), with an improved incidence of pathologically proven microscopic versus macroscopic tumor residue in the rectal wall (pTmic versus pTmac) observed in the tegafur treated group: 58% versus 23% (P = 0.002) [16].

Oxaliplatin administered preoperatively in full systemic neoadjuvant doses may exploit the direct damage to oxaliplatin-sensitive cells in the primary lesion and regional metastatic nodes. Oxaliplatin plus capecitabine (12 weeks delivery scheme) has reported to induce an 80% radiological and 86% symptomatic response rate; radiological evidence of response was increased to 97% if chemoradiation with concurrent capecitabine was added to induction chemotherapy [17]. Alternatively, oxaliplatin plus fluoropirimidines can be administered concomitantly to pelvic radiotherapy in an effort to exploit predominantly the radiation modulation properties of both agents [18, 19].

In order to analyze the potential differences in tumor response induced by neoadjuvant oxaliplatin + 5-FU and tegafur modulated preoperative chemoradiation versus tegafur chemoradiation alone in treatment naïve locally advanced rectal cancer patients, the pathological findings in post-resected surgical specimens have been categorized and compared. Relevant clinical data (tolerance to the neoadjuvant treatment segment) related to the treatment programs tested, has also been included in the analysis for completeness of scientific information.

It is hypothesized that a relevant proportion of oxaliplatin sensitive cells are present in the primary rectal cancer lesion. Two cell damage mechanisms (oxaliplatin plus tegafur sensitized chemoradiation) can be combined in the neoadjuvant treatment segment and their potential interactive effects can be objectively categorized by meticulous pathological specimen examination, with particular emphasis in the incidence of rectal wall complete response (pT0) histological changes [20].

patients and methods

patient selection

Patients with histologically confirmed rectal cancer, located 0–15 cm from the anal margin, T3–4, or N2, or both, plus non-metastatic clinical stage according to the AJCC’s fifth classification, ECOG performance status of 0–2, and no previous pelvic radiotherapy and systemic therapy were enrolled. Other eligibility criteria included adequate baseline organ function, defined as leucocyte count greater than 3 x 10^9/l (absolute granulocyte count, 1.5x10^9/l); platelet count greater than 100 x 10^9/l, hemoglobin >10g/ml, liver profile levels not greater than three times the ULN, and serum creatinine level less than 1.6 mg/dl. Patients with history of further malignancy, other than basal cell carcinoma of the skin or carcinoma in situ of the cervix, in the last 5 years were not eligible. There were no other restrictions due to age or co-morbid conditions if surgery was not contraindicated.

The protocol was designed following the recommendations of the Helsinki Declaration. The Institutional Ethics Committee approved the protocol, and signed informed consent was obtained from all patients.

staging and follow-up

Clinical staging included history and physical examination, complete blood count (CBC), biochemical profile, carcinoembryonic antigen (CEA), chest X-ray, and abdominopelvic computed tomography (CT). All patients except two were staged with endorectal ultrasound (EUS). Colonoscopy and biopsy were mandatory for definitive diagnosis. Patients were monitored during the preoperative chemoradiation treatment with weekly clinical consultation, CBC and biochemical profile. Surgery was performed 6 weeks after chemoradiation. Presurgical restaging included EUS and CT scan. Patients were reviewed 4 weeks after surgery, and followed up every 6 months for the first 5 years, and then annually.

treatment

chemoradiation. Preoperative radiotherapy consisted in the delivery of 45–50.4 Gy in 5–6 weeks with conventional daily fractions (1.8 Gy). High-energy photon beams generated by a linear accelerator were used: 15 MV in most cases and at least 6 MV in patients with a small pelvis and acceptable dosimetry. Conventional simulation using endoluminal contrast material was performed in all patients for target volume design and shielding verification. The anal verge was visualized using a radio-opaque metallic marker. Individualized anatomic adapted plastic devices were used to immobilize the pelvis. Multiple converging fields, conformal beam techniques using customized sheetings, and the prone position were employed. Treatment fields were designed to generate a volume that would include the primary disease, regional lymphatic drainage areas, the mesorectal, presacral and perineal regions, as well as the anal sphincter in tumors with a lower limit less than 5 cm from the anal verge. Sensitizing chemotherapy consisted of tegafur 400 mg given orally three times a day (approximately every 8 h) from day 1–28 of radiotherapy, including weekends.

From May 2001 to October 2002, 52 consecutive patients received two courses of induction FOLFOX-4, as follows: Oxaliplatin 85 mg/m² intravenous day 1; 5-FU 400 mg/m² intravenous bolus and 600 mg/m² intravenous continuous infusion in 22 h on day 1 and 2; folinic acid 200 mg/day intravenous on day 1 and 2. The cycle was repeated after 2 weeks and tegafur chemoradiation started immediately after the completion of the second FOLFOX-4 course. Figure 1 describes the treatment programs. The programmed interval between initiation of neoadjuvant treatment and surgery was 70 days in the tegafur chemoradiation alone group and 100 days in the Oxaliplatin induced group.

surgery. Radical surgery was scheduled for 4–6 weeks after completion of preoperative chemoradiation. A total of 19 senior surgeons participated in the procedures. There were no strict criteria for selecting the type of surgical procedure, appropriateness of safety distal margin distance or total mesorectal excision surgical performance.

intraoperative radiotherapy. All patients received a boost of 10–15 Gy with IOERT to the presacral space. Details of the institutional IOERT program have been published elsewhere [21].

postoperative chemotherapy. Adjuvant chemotherapy was allowed according to clinician judgment, and consisted of four to six courses of bolus 5-FU 425 mg/m² and leucovorin 20 mg/m² on days 1–5, repeated every 28 days.

toxicity

Acute toxicity was according to the Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer (RTOG/ EORTC) scales [22]. If uncontrollable grade 3 toxicity was detected with supportive treatment, administration of tegafur was suspended and radiotherapy interrupted until adverse effects could be reversed to grade 2. Once the severe toxicity had been resolved, treatment with tegafur was given at the corrected dose reduced by 33%. If grade 3 toxicity persisted for more than 2 weeks despite interruption of treatment and the application of suitable support therapy, the preoperative chemotherapy and radiotherapy was suspended and surgery scheduled. If severe adverse effects recurred after
resolving Grade 3 toxicity and reinstating treatment, the protocol required that consideration be given to suspending the preoperative segment of the program and scheduling surgery.

Pathological examination
Pathological examination of the surgical specimen prospectively included the following information: macroscopic appearance of the abnormal neoplastic lesion, bidimensional size, location within the rectal wall and degree of circumferential involvement, together with a macroscopic description of the peri-rectal tissue status and distance to the superior and inferior rectal surgical margins; microscopically, detailed information was obtained regarding tumor characteristics, cellular grade, surrounding normal tissue reactions, and depth of tumor rectal wall infiltration. Number, size, and nodal status were available, together with the microscopic finding in radial and proximal-distal surgical margins.

For histological examination, the whole intestinal segment bearing the residual lesion was serially sectioned in transversal slices and embedded in paraffin. A complete overview of the general structure of the intestinal wall was evaluated, determining the presence of fibrosis, vascular lesions, mucosal regeneration and evidence of tumor involution (mucin lakes, granulomas or calcification).

Microscopic residual disease (pTmic category) was considered for surgical specimens with minimal residual cancer, consisting in microscopically isolated nests of neoplastic cells surrounded by regenerated fibrotic repair tissue, independently of depth involvement in the rectal wall [23, 24]. The presence or absence of metastatic malignant disease exclusively categorized nodes. Downstaging effect was defined as any evidence of decrease in pathological stage (including both T and/or N categories) in relation to the initially established clinical stage. Pathological Tmic category corresponds to minimal residual disease present in the specimen, consisting of microscopic and isolated nests of tumoral cells into a matrix of repair tissue, within the different rectal wall layers (estimated as <20% of initial tumor size). Complete pathological response (pT0) consists in absence of tumor residue after extensive, meticulous and expert histo-pathological examination of the surgical specimen (minimum of 12 slides per patient evaluated in this category).

Statistical considerations
The study was based on a prospective clinical treatment program with controlled periodic follow-up, and retrospective updating of variables and results. All patients receiving the complete therapeutic program (chemoradiotherapy followed by radical surgery and IOERT) were assessable for toxicity and response. All patients entering in the treatment program were assessable for toxicity. Statistical analysis included comparison of variables using the Chi-square method or the Fisher’s Exact test for qualitative variables, and the Student’s t-test for quantitative ones.

Results

Patients, tumor and treatment characteristics
Table 1 describes demographics, tumor and treatment characteristics of cohorts of patients treated with preoperative chemoradiation alone or with previous induction chemotherapy (FOLFOX-4). These are two consecutively treated groups of patients and there are no statistically significant differences in any of the relevant clinico-therapeutic parameters analyzed. Dominant clinical T stage was cT2 and nearly half of the patients had radiological evidences of enlarged pelvic nodes (cN+ category). Radiation therapy doses and type of surgical procedures were consistent and similar among groups.

Toxicity
Along the neoadjuvant treatment component grade 3 toxicity was observed in the FOLFOX induction segment exclusively in three patients (6%), showing grade 3 gastrointestinal toxicity. No grade 3 neurotoxicity was reported in this period of treatment. Grade 3–4 RTOG/EORTC events were registered in both groups during the chemoradiotherapy, with a total incidence of 42% in tegafur chemoradiation alone and 33% in oxaliplatin induced group. Tegafur alone patients developed more gastro-intestinal toxicity (29% versus 17%) and mucocutaneous grade 3 changes (21% versus 19%). Differences were not statistically significant. One patient in tegafur exclusive group developed a grade 3 leukopenia (while no hematological toxicity at this level was observed in the oxaliplatin group) and one patient had transient grade 3 genitourinary toxicity in the oxaliplatin group. Symptomatic uncontrolled toxicity was cause of chemoradiation discontinuation or cancellation in 11 patients (18%) in the tegafur exclusive group. Similarly, the oxaliplatin induced group showed a 16% of chemoradiation discontinuation or cancellation (eight patients).

Postoperative complications had an equivalent incidence in both groups (36% versus 31%) the pelvic or wound infection being the dominant surgically related event observed. Table 2 describes toxicity and complications in relationship with treatment groups.

Downstaging effects
T downstaging after tegafur chemoradiation was 75% and 58% with or without induction FOLFOX-4, respectively (difference not significant). N downstaging was 40% versus 42% in a similar analysis. Table 3 describes pathological T and N stages in treated groups. Table 4 shows the pathological response categories showing remarkable cancer remission effects (pT0, pT0\(\Rightarrow\)1 or residue limited to the mucosal and T downstaging in two or more levels). Except for pTmic responding specimens, other categories considered as major responders due to
treatment effect in the primary rectal cancer lesion are significantly superior in the group treated with induction Oxaliplatin + 5-FU. Table 5 correlates downstaging by clinical and pathological T and N categories.

discussion

Locally advanced rectal cancer is a valid clinical model to monitor local effects of neoadjuvant treatment [25–27]. Tumor downsizing and downstaging are measurable and objective parameters to estimate degree of response to local therapy [28]. Tumor downsizing has not been reported following hypofractionated irradiation (5 × 5 Gy/day) and immediate programmed surgery (within 48 h after due completion of irradiation) [29]. Tumor downsizing was marginal (mean tumor diameter in the radiotherapy group was 4 cm while the value in the surgery alone group was 4.5 cm, \( P < 0.001 \)). This feature was explained in part on the basis of the observation of less inflammatory reaction around the tumor extension, 22% versus 10% [30]. The speculative impact of protracted pelvic irradiation in improved sphincter preserving surgical management is controversial, but this potential feature has been interpreted as a positive result related to downsizing effects [27, 28, 31]. Preoperative radiotherapy alone, regardless of the type of fractionation scheme employed, does not induce pT0 specimen rates over 10% [32–34]. Additionally, complete clinical response and sphincter preservation with preoperative radiotherapy is dose-dependent: if an endo-anal boost is randomized for patients receiving 39 Gy in 17 days the corresponding figures are 24% versus 2% and 76% versus 44% (\( P = 0.004 \)), respectively [35].

Preoperative chemoradiation primarily improves disease control in the pelvic area, but the dominant pattern of rectal cancer recurrence in modern trials is distant failure, with...
Table 3. Pathological stages observed after neoadjuvant treatment

<table>
<thead>
<tr>
<th>Pathological Stage</th>
<th>CRT  n %</th>
<th>FOLFOX-4 + CRT  n %</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT0</td>
<td>5/8</td>
<td>15/29</td>
</tr>
<tr>
<td>pT1</td>
<td>9/15</td>
<td>8/15</td>
</tr>
<tr>
<td>pT2</td>
<td>19/30</td>
<td>16/31</td>
</tr>
<tr>
<td>pT3</td>
<td>25/40</td>
<td>13/25</td>
</tr>
<tr>
<td>pT4</td>
<td>4/7</td>
<td>2/7</td>
</tr>
<tr>
<td>pN0</td>
<td>51/82</td>
<td>30/34</td>
</tr>
<tr>
<td>pN1</td>
<td>10/16</td>
<td>11/21</td>
</tr>
<tr>
<td>pN2</td>
<td>1/2</td>
<td>11/21</td>
</tr>
</tbody>
</table>

CT-RT, chemoradiation.

Table 4. Comparative analysis of downstaging effects among neoadjuvant treatment programs

<table>
<thead>
<tr>
<th>Downstaging effect</th>
<th>CRT  n %</th>
<th>FOLFOX-4 + CRT  n % (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T (total)</td>
<td>36/58%</td>
<td>39/75% (0.75)</td>
</tr>
<tr>
<td>N (total)</td>
<td>26/42%</td>
<td>21/40% (ns)</td>
</tr>
<tr>
<td>T ≥ 2 categories</td>
<td>15/24%</td>
<td>23/44% (0.029)</td>
</tr>
<tr>
<td>pT0 excl</td>
<td>29/51%</td>
<td>19/51% (ns)</td>
</tr>
<tr>
<td>pT1 excl</td>
<td>14/23%</td>
<td>23/44% (0.017)</td>
</tr>
<tr>
<td>pT0</td>
<td>5/8%</td>
<td>15/29% (0.006)</td>
</tr>
</tbody>
</table>

ns, not significant.

CRT, chemoradiation.

Table 5. T and N downstaging correlation of clinical and pathological categories by treatment groups

<table>
<thead>
<tr>
<th>Stage</th>
<th>cT2</th>
<th>cT3</th>
<th>cT4</th>
<th>cT5</th>
<th>cN0</th>
<th>cN1</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT0</td>
<td>1/1</td>
<td>4/13</td>
<td>0/0</td>
<td>0/1</td>
<td>20/11</td>
<td>21/14</td>
</tr>
<tr>
<td>pT1</td>
<td>1/2</td>
<td>8/6</td>
<td>0/0</td>
<td>0/0</td>
<td>4/3</td>
<td>5/7</td>
</tr>
<tr>
<td>pT2</td>
<td>0/1</td>
<td>17/13</td>
<td>2/2</td>
<td>0/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT3</td>
<td>0/0</td>
<td>22/9</td>
<td>3/2</td>
<td>0/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT4</td>
<td>0/0</td>
<td>2/0</td>
<td>2/0</td>
<td>0/0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CRT/FOLFOX-4+CRT.

estimated total rates over 30% [13]. A component of systemic chemotherapy given in full-doses neoadjuvantly is an attractive strategy to improve long-term disease control. Chan et al. [17] report acceptable tolerance for neoadjuvant oxaliplatin plus capecitabine (12 weeks regime) followed by synchronous capecitabine modulated chemoradiation. With a median follow-up of 23 months, the patterns of recurrences in 77 patients treated were two local and eight distant relapses (four liver involvement; failure-free survival at 1 year of 87%). This treatment strategy is open and builds upon the imperative need of systemic disease control in locally advanced rectal cancer.

Preoperative chemoradiation with 5-fluorouracil or oral fluoropirimidines increases the incidence of pT0 specimens marginally in the range of 15% to 31% [36–40]. It is important to mention that trials evaluating the effects of fluoropirimidine sensitized preoperative radiotherapy in locally advanced rectal cancer are quite heterogeneous in the route of drug administration (oral versus intravenous), type of infusion (bolus versus continuous), drug doses scheduled and use or not of folic acid as biochemical modulator. At best, induction of pT0 responses rates are modest, with a controversial value in identifying patients with a potential better long-term outcome [41, 42], but with minor impact in local treatment management practice.

A definitive evidence that chemoradiation is superior in terms of tumoricidal effect than radiotherapy alone in rectal cancer has been recently reported by Bosset et al. [43]. The results of the EORTC 22921 randomized trial showed a pT0 incidence of 5.3% versus 13.7% (P < 0.001). Downstaging was also significantly superior in chemoradiation patients (P < 0.0001).

Oxaliplatin alone or in combination with fluoropirimidines has been tested in neoadjuvant treatment schemes of simultaneous chemoradiation, in an effort to explore the radiopotentiation properties of these agents [18, 44–47]. Unequivocal evidence of response categories of downstaged pT0–1 specimens are reported in the range of 28% to 58% (table 6), which should be interpreted as increased activity compared with fluoropirimidine exclusive sensitized chemoradiation [19, 47–52]. Neoadjuvant systemic chemotherapy with oxaliplatin containing regimen immediately followed by chemoradiation, offers the opportunity to induce local effects (significant damage in oxali-sensitive cells and tumor down sizing), that might be further exploited by chemoradiation.

Results of neoadjuvant capcitabine and oxaliplatin followed by synchronous chemoradiation (capecitabine) in magnetic resonance image-defined poor-risk rectal cancer has been recently reported by Chau et al. [53]. In the Royal Marsden experience, among 67 available specimens for pathologic assessment, pT0–1 specimens were 34% and only microscopic foci were seen through the muscularis propria in an additional 24% of cases. The dominant treatment-induced grade 3–5 toxicities observed during neoadjuvant chemotherapy exclusively were diarrhea (12%) and cardiac/thromboembolic events (10%); during chemoradiation skin reaction was registered in 43% of patients, and neutropenia in 6%.

The present report mimics strategy and results just described. Neoadjuvant FOLFOX-4 was acceptably tolerated (incidence of grade 3 or superior of 6% to the complete treatment program) and pT0–1 specimen rate of 44%. It has been reported that downstaging and downsizing effects as monitors of rectal cancer response to local treatment are related to time to surgery [31]. In our two patient cohorts (chemoradiation with tegafur or neoadjuvant FOLFOX followed by chemoradiation with tegafur), time to surgery from the beginning of neoadjuvant therapy differs from 10 to 14 weeks (Figure 1), which may have contributed, in part, to the local rectal cancer response differences observed. Rödel et al., have recently reported that tumor regression after preoperative chemoradiation might be of prognostic interest. In an exploratory analysis performed in 385 patients treated in the CAO/ARO/AIO-94 trial (preoperative chemoradiation arm) 5 year disease-free survival was 86% in patients with specimens with no viable tumor cell, compared with 63% if tumor regression was less than 50% in the pathological evaluation (P = 0.006) [54].
**Microscopic foci in additional 24% of specimens.**

**or pTmic.

Oxa, oxaliplatin.

**References**


**Table 6. Incidence of pT0-1 post-resection specimens after preoperative chemoradiation with oxaliplatin containing regimens**

<table>
<thead>
<tr>
<th>Author [Ref]</th>
<th>Patients no.</th>
<th>Chemotherapy</th>
<th>RT (Gy)</th>
<th>pT0 + pT1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carraro et al. [48]</td>
<td>12</td>
<td>Oxa 25 mg/m² × 4 days weeks 1 and 5 5FU/lV</td>
<td>50.4</td>
<td>3 + 2 (41%)</td>
</tr>
<tr>
<td>Rödel et al. [49]</td>
<td>31</td>
<td>Oxa 50 mg/m² days 1, 8, 22 and 29 Capecitabine</td>
<td>50.4</td>
<td>6 + 12 (58%)</td>
</tr>
<tr>
<td>Gerard et al. [50]</td>
<td>40</td>
<td>Oxa 130 mg/m² day 1 and 20 SFU/lV</td>
<td>50</td>
<td>6 + 12* (45%)</td>
</tr>
<tr>
<td>Aschele et al. [18]</td>
<td>25</td>
<td>Oxa 60 mg/m² weekly × 6 5FU</td>
<td>50.4</td>
<td>7 + 6* (52%)</td>
</tr>
<tr>
<td>Gambacorta et al. [45]</td>
<td>30</td>
<td>Oxa 130 mg/m² Days 1, 19 and 38 Ralitrexed</td>
<td>50</td>
<td>9 + 8* (50%)</td>
</tr>
<tr>
<td>Machiels et al. [19]</td>
<td>40</td>
<td>Oxa 50 mg/m² weekly × 5 w Capecitabine</td>
<td>45</td>
<td>5 + 6* (32%)</td>
</tr>
<tr>
<td>Francois et al. [51]</td>
<td>30</td>
<td>Oxa 30–80 mg/m² weekly 5-FU</td>
<td>45</td>
<td>4 + 4* (28%)</td>
</tr>
<tr>
<td>Glynne-Jones et al. [52]</td>
<td>16</td>
<td>Oxa 130 mg/m² Days 1 and 29 Capecitabine escalated</td>
<td>45</td>
<td>5 + ? (28%)</td>
</tr>
<tr>
<td>Chau et al. [53]</td>
<td>67</td>
<td>Oxa 130 mg/m² + Capecitabine (neoadjuvant) + Capecitabine</td>
<td>45</td>
<td>18 + 5* (34%)</td>
</tr>
</tbody>
</table>

Oxa, oxaliplatin.

*or pTmic.

**Microscopic foci in additional 24% of specimens.

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