Phase III randomised trial

No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT)

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ABSTRACT

Background and purpose: To evaluate the effect of adjuvant chemotherapy (ACT) in locally advanced rectal cancer (LARC) after neoadjuvant chemoradiation (NACT-RT). The study was funded by the Italian National Research Council (CNR).

Methods: From September 1992 to January 2001, 655 patients with LARC (clinically T3–4, any N) treated with NACT-RT and surgery, were randomized in two arms: follow-up (Arm A) or 6 cycles of ACT with 5 fluorouracil (SFU)-Folinic Acid (Arm B). NACT-RT consisted of 45 Gy/28/f concurrent with SFU (350 mg/sqm) and Folinic Acid (20 mg/sqm) on days 1–5 and 29–33; surgery was performed after 4–6 weeks. Median follow up was 63.7 months. Primary end point was overall survival (OS).

Results: 634/655 patients were evaluable (Arm A 310, Arm B 324); 92% of Arm A and 91% of Arm B patients received the preoperative treatment as in the protocol; 294 patients of Arm A (94.5%) and 296 of Arm B (91.3%) underwent a radical resection; complete pathologic response and overall downstaging rates did not show any significant difference in the two arms. 83/297 (28%) patients in Arm B, never started ACT. Five year OS and DFS did not show any significant difference in the two treatment arms. Distant metastases occurred in 62 patients (21%) in Arm A and in 58 (19.6%) in Arm B.

Conclusions: In patients with LARC treated with NACT-RT, the addition of ACT did not improve 5 year OS and DFS and had no impact on the distant metastasis rate.

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Patients presenting locally advanced rectal cancer (LARC) are currently given neoadjuvant chemoradiotherapy (NACT-RT) and then submitted to surgery after a delay of 6–10 weeks. This procedure, combined with the surgical technique TME, has been proven to decrease the local recurrence rate to 4–8%, although at the expense of a higher acute toxicity. However, no improvement in the overall survival (OS) rate was observed, as the distant metastasis rate remained unchanged, ranging from 25% to 35% [1–7].

For this reason adjuvant chemotherapy (ACT), generally with a 5FU regimen, was proposed after NACT-RT, for LARC patients [1,8,9] with the hope of obtaining an improvement in OS or Disease Free Survival rate (DFS).

In the last few years, several studies have attempted to identify new prognostic factors [10–13] and nomograms [10,14] can predict long-term outcomes and can help us to decide about ACT after NACT-RT. Nonetheless, even today, there is no clear evidence that ACT was able to achieve advantages in OS and DFS after NACT-RT [15].
The present trials randomizing patients with LARC to receive either ACT or observation after the same NACT-RT treatment were designed in 1992 in parallel with the $2 \times 2$ factorial EORTC 22921 [1] trial by a group of Italian radiotherapists who, at the time, did not agree on entering LARC patients to preoperative radiotherapy alone. The study was funded by the Italian National Research Council (CNR), contract 92.021062PF39.

Methods

Study design and patient population

From September 1992 to December 2003, after the same NACT-RT regimen and surgery, 655 patients with LARC in 11 Italian Centres were randomized to receive follow up (Arm A) or adjuvant chemotherapy (Arm B). Inclusion criteria were a pathologically verified adenocarcinoma of the extraperitoneal portion of the rectum (within 15 cm from the anal margin), clinical stage T3–T4 (UICC criteria), age ≤75 years, Performance Status (WHO) 0 or 1, leucocyte count >3.000/L, platelet count >130.000/L, serum creatinine below 1.2 mmol/L. Exclusion criteria were: previous history of cancer (except basal cell carcinoma of the skin or situ carcinoma of the cervix), of angina pectoris, and of bowel diseases potentially affecting the tolerance to pelvic irradiation.

The extent of the tumour was evaluated by clinical examination (DRE), abdominal–pelvic tomography, rigid rectoscopy and chest X-ray; endorectal ultrasonography was optional, except for tumours not accessible to DRE. The tumour was clinically classified as T3 when fixed or partially fixed at DRE, or when the tumour was mobile but with fat invasion at endorectal ultrasonography and/or at CT scan. Tumours with invasion of any neighbouring structure or organ (peritoneum included) were classified as T4. The lymph nodes >10 mm in size, smooth-oval shaped and hypoechoic or black on ultrasound were considered involved.

All the participating centres were required to have the approval of their own ethics committee. Before randomization, all patients had to sign an informed consent. Randomization was carried out by calling the coordination centre on the telephone who extracted a sealed envelope. Randomization was performed without masking and stratification, after checking the eligibility criteria and before the beginning of NACT-RT.

Treatment

Radiotherapy

All patients were treated, in prone position, by a three or four conformed field’s technique. The target volume included the rectal tumour with a safety margin of 4–5 cm, the mesorectum, the obturatory and internal iliac nodes; the external iliac nodes were included only in T4 tumours. The anatomical borders were: posteriorly the posterior margin of the sacrum, anteriorly 2–3 cm behind the posterior margin of the pubic symphysis, laterally 1–2 cm beyond the bony margins of the pelvis, superiorly the promontorium and inferiorly 4–5 cm below the distal margin of the tumour. For tumours located in the distal rectum the anal canal was included but avoiding the perineal skin. Dose distribution was obtained in at least 3 axial CT sections. Total dose was 45 Gy (energy level of 4 MV or above were required) prescribed at the ICRU point, in 25 fractions of 180 cGy/day, 5 fractions/week.

Concurrent Chemotherapy

Chemotherapy, consisting of a combination of 5FU and Folinic Acid (LV), was administered from days 1 to 5 and from days 29 to 33 of the radiotherapy course. 5FU was administered by rapid intravenous infusion at the dose of 350 mg/m²/day in 100 ml of saline solution, 1 h before the radiotherapy session and LV at the dose of 10 mg/m²/day immediately before 5FU.

Surgery

Surgery was planned between 4 and 6 weeks after radiotherapy. The surgical procedure, AR (anterior resection), APR (abdomino-perineal resection) or TR (transanal resection), was decided by the surgeon and in most cases was based on the initial tumour extension and location. TME was not specifically recommended.

Pathologic evaluation

Surgical specimens were evaluated according to a standardized procedure. Their macroscopic and microscopic characteristics were registered in a specific patient’s form, reporting the pathologic stage (UICC classification), the number of examined and involved lymph nodes, and the status of the margins, the differentiation grade, and the presence of mucine.

Postoperative chemotherapy

Patients randomized in Arm B were scheduled to receive six cycles of chemotherapy with 5FU and LV, 3–5 weeks after surgery, according to the same regimen in the preoperative treatment.

Follow-up

All patients were followed up every 4 months for the first year, and then every 6 months thereafter until the fifth year and then once a year. The follow up visit included: clinical examination, abdominal ultrasound and CT scan (every six months for the first 3 years and then yearly). A colonoscopy was prescribed yearly. Local recurrence was defined as any tumour reappearance, clinically or histologically proven, occurring in the pelvis or the perineum.

Sample size

To detect an improvement of 10% in 5 year OS (assuming an OS of 65% for the observation and 75% for the ADC arm) with 90% power, and probability errors $\alpha$ of 5%, approximately 315 evaluable patients were required in each arm.

Statistical analysis

The primary endpoint was to compare the OS of the two randomization arms. Secondary endpoints were the comparison of the Disease Free Survival (DFS) and of the failure modality. All eligible patients were included in the analysis of OS and DFS according to the intention to treat principle. Compliance, pathologic response and surgical procedure in the two treatment arms were also analysed and correlated with OS, DFS and failure modality. The starting point for the analysis of survival and DFS was the date of the first radiotherapy session. DFS event was considered the first disease recurrence (local or distant) or death in the absence of such events. The local and distant relapse rate was calculated on the total number of patients who were resected. OS was estimated according to the Kaplan–Meier actuarial method. The log-rank test was used to compare the difference in survival curves. Data were analysed using SPSS/PC+11.5 statistical software. Randomization was done at clinical diagnosis centres without masking and stratification by centre and clinical stage.

Results

The last update of the study was carried out in April 2008 with a minimum follow up of 48 months (median follow-up 63.7 months). The relocation of the working place of the study coordinator delayed the preparation of the manuscript reporting the results.

634/655 patients were eligible; 310 were randomized to follow up (Arm A) and 324 to adjuvant chemotherapy (Arm B).
The baseline characteristics of the patients (Table 1) were well balanced in the two treatment arms, except for cN stage (cN+ were 76 in Arm A vs 112 in Arm B). The consort diagram of the study is reported in Fig. 1.

Overall 91.8% of patients (Arm A 92.5%; Arm B 91%), received the full preoperative treatment according to the protocol. Acute G3 or G4 toxicity, was reported in 24% of patients; diarrhoea, moist perineal desquamation and neutropenia, occurred in 12-1%, 8-4% and 8-0% respectively; 5 patients (0.78%) died during the preoperative treatment due to toxic effects.

Forty-four patients (Arm A 16; Arm B 28) did not receive any surgery or palliative procedure; the reasons are reported in the consort diagram (Fig. 1). A radical surgery was done in 590 patients (294 in Arm A and 296 in Arm B); the percentage of R1 resection was 10-2% in both arms. The distribution according to the surgical procedure (AR vs APR vs TR) was similar in the two treatment arms. The overall rate of perioperative complications was 14.7% (87 patients); fistula (54), pelvic abscess (16), thromboembolism (3), myocardial infarction (1), other (13). Six patients (1%) died within 1 month after surgery. Late small bowel complications requiring surgery were reported in 13 patients (Arm A 6; Arm B 7).

No microscopic residual disease (pCR) was reported in 105/590 (17.8%) operative specimens with no difference in the two treatment arms (Arm A 17%; Arm B 18.6%). pCR occurred in 18-1% of the patients clinically classified as cT3 and in 10% of those classified as cT4. The overall down-staging rate (ypT0-T2) was slightly higher in Arm A (57.5%) compared to Arm B (50.7%) (Table 2) but the difference was not statistically significant. Involved nodes were found in 148 patients (25-1%) with no difference in the two treatment arms (Arm A 25.5%; Arm B 24.7%). Patients clinically classified as cT4 had a higher incidence of involved nodes (whole series 39.2%, Arm A 40%, Arm B 38.4%).

Out of the 296 patients randomized in Arm B and expected to receive ACT, 83 (28%) never started the treatment, 40 (13.5%) completed 2 cycles, and 173 (58.4%) received cycles 3 to 6. The time interval between the end of NACT-RT and the beginning of ACT varied from 9 to 7 weeks (median 14.8 weeks). Omission of chemotherapy was due to toxicity, disease progression and in most cases to individual refusal.

As reported in Table 3 there was no difference in the 5 year OS (Fig. 2) and in the 5 year DFS (Fig. 3) between the two treatment arms, both taking into account the randomized total and the total of resected patients in each arm.

In resected patients, the 5-year OS rate was 70% in Arm A and 69.1% in Arm B (HR 1.045; 95% CI 0.775–1.410; p = 0.772). The 5-year DFS rate was 62.8% in Arm A and 65.3% in Arm B (HR 0.977; 95% CI 0.724–1.319; p = 0.882).

Also, no difference was found between the two arms in the OS and DFS values, analysed according to the pathological stage, the presence of involved nodes and the type of surgery (APR vs AR).

In both arms the absence of pathologic down-staging, the presence of involved nodes and the abdominoperineal resection were associated with worse values of OS and DFS. In Arm B the 5 year OS was not influenced by the number of ACT cycles delivered (68.9% in the patients group receiving <3 cycles vs 69.2% in those receiving 3 to 6 cycles, p = 0.238). No apparent benefit of ACT was found in patients with pathologically involved nodes: in the group of 89 ypN+ patients (Arm A plus Arm B receiving none or less than 3 cycles of ACT) the 5 year OS and DFS were 52% and 44.9% respectively, compared to 50-8% and 37.8% of the 53 patients ypN+ of Arm B actually given 3 or more cycles of ACT.

The total rate of local failures both isolated and combined with distant metastases was 6-4% in Arm A and 4.5% in Arm B. The occurrence of distant metastases was observed in 120 patients (20-3%) of the resected total with no difference in the two treatment arms (Arm A 62 and Arm B 58). The distribution of local recurrences and distant metastases according to the pathological response is reported in Table 4.

Discussion

In this trial the addition of ACT 5FU based, after NACT-RT in patients with LARC, did not result in any benefit in long term OS and DFS, and it did not change the incidence of distant metastases. NACT-RT, on the contrary, was very effective on local control resulting in a pCR in more than 15% of cases and had a locoregional relapse rate below 10%, confirming the results of the recent studies using a similar preoperative regimen [1–5,15].

The absence of any benefit of ACT in our study may be partly attributed to the low compliance to complete the planned number of chemotherapy cycles. This seems however to be an intrinsic problem of this regimen as the same difficulty was reported both in the EORTC trial [1] (where only 42.9% of patients received the 6 planned cycles of 5FU) and in the FFC trial [2] (where 30% of the patients did not complete the treatment). A similar low compliance to ACT after NACT-RT was also reported by the German Group [16] (compliance was around 80% including dose reduction) and in the phase III

Table 1 Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ARM A (no adjuvant CT)</th>
<th>ARM B (with adjuvant CT)</th>
<th>TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total enrolled − n</td>
<td>321</td>
<td>334</td>
<td>655</td>
</tr>
<tr>
<td>Lost before treatment − n (%)</td>
<td>11 (3.4%)</td>
<td>10 (3%)</td>
<td>21 (3.21%)</td>
</tr>
<tr>
<td>Evaluable − n</td>
<td>310</td>
<td>324</td>
<td>634</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>60.5</td>
<td>60.5</td>
<td>60.5</td>
</tr>
<tr>
<td>Sex − n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>208 (67.1%)</td>
<td>213 (65.7%)</td>
<td>421 (66.4%)</td>
</tr>
<tr>
<td>Females</td>
<td>102 (32.9%)</td>
<td>111 (34.3%)</td>
<td>213 (33.6%)</td>
</tr>
<tr>
<td>Distance to anal verge − n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 4 cm</td>
<td>52 (16.8%)</td>
<td>65 (20.1%)</td>
<td>117 (18.5%)</td>
</tr>
<tr>
<td>&gt;4 ≤ 8 cm</td>
<td>222 (71.6%)</td>
<td>210 (64.8%)</td>
<td>432 (68.1%)</td>
</tr>
<tr>
<td>&gt; 8 cm</td>
<td>36 (11.6%)</td>
<td>49 (15.1%)</td>
<td>85 (13.4%)</td>
</tr>
<tr>
<td>Clinical T Stage − n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT3</td>
<td>265 (85.5%)</td>
<td>279 (86.1%)</td>
<td>544 (85.8%)</td>
</tr>
<tr>
<td>cT4</td>
<td>45 (14.5%)</td>
<td>45 (13.9%)</td>
<td>90 (14.2%)</td>
</tr>
<tr>
<td>Clinical N Stage − n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN0</td>
<td>194 (62.6%)</td>
<td>168 (51.9%)</td>
<td>362 (57.1%)</td>
</tr>
<tr>
<td>cN+</td>
<td>76 (24.5%)</td>
<td>112 (34.6%)</td>
<td>188 (29.7%)</td>
</tr>
<tr>
<td>cNx</td>
<td>40 (12.9%)</td>
<td>44 (13.6%)</td>
<td>84 (13.2%)</td>
</tr>
</tbody>
</table>
Nordic study [17] (47/98 patients started the treatment and 20% only completed 8 cycles).

In the analysis of a large series of patients included in the NCCN Colorectal Cancer (CRC) Database [18], the patient’s refusal was confirmed as the most frequent reason for not completing ACT after NACT-RT.

The number of ACT cycles actually delivered in our trial did not result to have an effect on the OS; no difference was in fact observed in the 5 year survival of patients receiving none or less than 3 cycles of ACT compared to those receiving 3 or more cycles.

In their recent literature review, Bujko and Coll [15] analysed the results of 4 relevant randomized trials, including ours (forwarded as personal communication), addressing the question of the value of ACT in patients already undergoing NACT-RT [1,8,9,19]. ACT was in all trials represented by 5FU with very similar regimens; the EORTC trial [1] had a 2 × 2 factorial design randomizing patients to preoperative radiotherapy alone vs NACT-RT and to ACT vs no ACT; the QUASAR trial [8] included only patients in stage II (20% of them had received a preoperative radiotherapy without concomitant chemo); our trial [19] was the only one in which all patients received NACT-RT; the fourth trial [9] was in Chinese and presented several methodological biases making its evaluation very difficult. No 5 year OS benefit was apparent in the EORTC trial in the patients receiving ACT vs those not given any adjuvant treatment (67.2% vs 63.2% p = 0.12), regardless if they had been given preoperative radiotherapy or chemoradiation. In the first analysis of this trial, the OS and DFS Kaplan–Meier curves, seemed to diverge in favour of the patients who received ACT.

Table 2
Pathologic response in 590 resected patients.

<table>
<thead>
<tr>
<th>Baseline clinical stage</th>
<th>N° patients</th>
<th>ypT0</th>
<th>ypT1-2</th>
<th>ypT3-4</th>
<th>ypTx</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT3</td>
<td>254</td>
<td>46 (18%)</td>
<td>113 (44%)</td>
<td>92 (36%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>cT4</td>
<td>40</td>
<td>4 (100%)</td>
<td>6 (15%)</td>
<td>28 (70%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>total</td>
<td>294</td>
<td>169 (57%)</td>
<td>120 (40%)</td>
<td>120 (40%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>ARM B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT3</td>
<td>257</td>
<td>51 (19%)</td>
<td>88 (34%)</td>
<td>115 (44%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>cT4</td>
<td>39</td>
<td>4 (102%)</td>
<td>7 (17%)</td>
<td>28 (71%)</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>296</td>
<td>150 (50%)</td>
<td>7 (17%)</td>
<td>143 (48%)</td>
<td>3 (12%)</td>
</tr>
</tbody>
</table>
Moreover, ACT resulted in a better OS and a longer DFS, but only in the subgroup of patients achieving downstaging (ypT0-2) after preoperative treatment; however, Collette and Bosset [20] disclosed that this benefit mainly concerned the patient’s group treated with neoadjuvant RT alone.

The first hypothesis of the AA was that this benefit could be due to the fact the group of patients are those bearing better prognostic features and that, besides favouring the downstaging from preoperative treatment, could have increased the likelihood of a benefit from adjuvant CT [21].

But, very recently, the updated analysis of the EORTC 22921 trial [22], failed to confirm the benefit of ACT for ypT0-2 patients and the OS and DFS-curves are superimposed after a median follow-up of 10.4 years.

Also in our trial, in which all patients received NACT-RT, those achieving downstaging (ypT0–2) had a better overall survival and a lower local and distant metastasis rate, but they had no benefit from ACT.

In the QUASAR trial [8], patients randomized to receive ACT, had a lower incidence of recurrences (p < 0.004) and a lower risk of death (p < 0.05) compared to those randomized with no ACT; the absolute improvement in survival was 3.6% at 5 years. The conclusive statement of this study was that all patients with stage II rectal cancer should be offered ACT. This conclusion is however not very relevant to our question as none of the patients included in that study were given NACT-RT and only one out of four received preoperative radiations; furthermore recurrences were not classified as local or distant and whether the better survival was due to an effect of ACT on local control or on the distant metastasis rate was impossible to know.

In the last Asco meeting [23], Hong et al., reported the results of Adore phase II study in which 321 patients ypII (ypT3-4/ypN0) or ypIII (any ypT/ypN1-2) after NACT-RT with 5FU alone were randomized to receive adjuvant chemotherapy with 5FU or FOLFOX. After a median follow-up of 38.2 months, a 3-year DFS rate was better in the Folfox arm (p = 0.047), however this benefit was confirmed only for yp III stage.

No conclusion is possible because of the small number of patients enrolled, as well as the short follow-up. Also Bosset in his first analysis [1] had found an advantage in 3-year DFS for ACT, but, as discussed earlier, these data have not been confirmed after a median follow-up of 10.4 years [22].

In our trial, patients achieving pCR had the lowest incidence of both local recurrences and distant metastases and a better OS. The value of ACT in this subgroup cannot however be derived in our series due to the limited number of cases; also no information can be derived from the EORTC 22921 [1,22] as the outcome of patients achieving pCR is not reported separately. In the pooled

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Overall survival</th>
<th>Disease free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A (No ACT)</td>
<td>ARM B (+ACT)</td>
</tr>
<tr>
<td></td>
<td>N° patients %</td>
<td>N° patients %</td>
</tr>
<tr>
<td>Tot Randomized</td>
<td>310  67.9</td>
<td>324  66.9</td>
</tr>
<tr>
<td>Tot Resected</td>
<td>294  70</td>
<td>296  69.1</td>
</tr>
<tr>
<td>Pathol. Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT0-2</td>
<td>169  79.6</td>
<td>150  80.3</td>
</tr>
<tr>
<td>ypT3-4</td>
<td>120  56.0</td>
<td>143  56.9</td>
</tr>
<tr>
<td>ypN+</td>
<td>75   54.6</td>
<td>73   46.6</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miles</td>
<td>105  58.4</td>
<td>104  63.5</td>
</tr>
<tr>
<td>Ant. Res</td>
<td>175  78.0</td>
<td>177  72.4</td>
</tr>
<tr>
<td>Adjuvant CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 cycles</td>
<td>123  68.9</td>
<td>173  69.2</td>
</tr>
<tr>
<td>≥3 cycles</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3**

5-year OS and DFS.

![Fig. 2. Overall survival by arm in 590 resected patients.](image)

**Fig. 2.** Overall survival by arm in 590 resected patients.

![Fig. 3. Disease free survival by arm in 590 resected patients.](image)

**Fig. 3.** Disease free survival by arm in 590 resected patients.
analysis published by Capirci and Coll [24], collecting 566 patients resulting ypT0 after NACT-RT, 127 had received ACT; the hazard risk of cancer specific death was at 1.38 in these patients compared to those not receiving any postoperative treatment.

A similar result was also reported by Fiektau and Coll [25] in a more limited series of 72 patients ypN0 after NACT-RT, who presented the same 3 year DFS regardless of whether or not they received ACT (87.5% vs 87.7%). The absence of any benefit of ACT both in OS and DFS in patients staged ypN0 after NACT-RT was also confirmed by Collette and Bosset [21] in their reanalysis of the EORTC 2291 trial data (hazard ratio for ACT 1.04 for OS and 1.06 for DFS).

In our study no benefit of ACT was found even in the ypN+ patients. In the German study [26] the 5 year DFS after NACT-RT was respectively 85%, 65% and 18% in patients ypN0, ypN1 and ypN2; the main impact of pathological positive nodes was on the distant metastasis rate, occurring in 15%, 35% and 76% respectively.

The conclusions of our study have recently been supported by the results of the PROCTOR/SCRIPT Trial presented by A.J. Bregou et Al. at the 2013 European Cancer Congress [27]; the same Authors are currently carrying out a meta-analysis including their data along with those of our trial and that of the CHRONICLE (with a capecitabine/oxaliplatin regimen). The results of this meta-analysis currently in progress are strongly awaited.

In conclusion, the results of our trial and of the other trials [22,27] using a regimen of 5FU as ACT after NACT-RT in LARC, suggest that this regimen does not improve the OS of these patients and in particular does not reduce the incidence of distant metastases.

While some clinical or pathologic features may identify subgroups of patients more likely to receive a benefit from ACT cannot be clearly derived from the existing studies, including ours, due to the underpowered number of the patients included and the low compliance to adjuvant chemotherapy.

Also in the European Consensus Conference [28,7] no evidence was found in favour of adjuvant treatment in LARC patients after NACT-RT.

An aid to select patients who may benefit from ACT after NACT-RT, could derive from the application of the nomograms. The predictive model of Valenti and Coll [14], can be applied in LARC patients after NART-CT and surgery in order to assess the risk of local recurrences, distant metastases and OS; the score, derived from clinical and pathological data, can support the decision to submit the patient to ACT or only follow-up. The second nomogram [10], based on clinical and PET data (tumour dimension and uptake of radioactive isotopes in the tumour), could be used after NACT-RT and before surgery to establish the best surgical approaches including a wait-and-see policy. Also, at this time-point of the treatment, the appropriate use of PET and/or RM [29] could help identify those patients likely to benefit from a sequential radiation boost. In fact, Burbach [30], in his meta-analysis on fourteen studies that have used dose escalation >60 Gy, suggest an additional boost radiation in patients with near cCR (comparable to poor pathological response) [13] in order to achieve a cCR (associated with better prognosis) as anticipated a long time ago [31].

As well as the contribution of new radiotherapy technology should be taken into proper consideration in the new generation of nomogram developments [32].

In the future, when prospectively validated, the nomograms and imaging, could help provide a decision support for more individualized treatment approaches including ACT after NACT-RT.

A large number of studies based on new treatment strategies and on new drugs have been recently published or are ongoing [33–40], but no clear advance has yet emerged. One of the possible hypotheses to explain why 5FU was ineffective as ACT after NACT-RT in rectal cancer could be the long interval from the end of NACT-RT, during which metastatic dissemination is likely to occur; induction CT before concomitant CRT could be considered and phase 3 trials are currently ongoing [41].

Conflict of interest statement

The authors declare that they have no conflicts of interest concerning this article.

References


