Increasing the Interval Between Neoadjuvant Chemoradiotherapy and Surgery in Rectal Cancer

A Meta-Analysis of Published Studies

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Objectives: The aim of this meta-analysis was to demonstrate whether a longer interval between the end of neoadjuvant chemoradiotherapy (CRT) and surgery is associated with a better rate of pathological complete response (pCR) in rectal cancer.

Background: The standard of care in locally advanced rectal cancer is preoperative, long course (5-fluorouracil-based) CRT. After this neoadjuvant CRT, surgical exploration is undertaken 6 to 8 weeks later.

Methods: PubMed, EMBASE, Web of Science, and The Cochrane Library (CENTRAL) were searched systematically for prospective or retrospective studies reporting oncological results for intervals longer or shorter than 6 to 8 weeks between the end of CRT and surgery, in rectal cancer. The primary endpoint, reported as relative risk (RR), was the rate of pCR. Secondary endpoints were overall survival (OS), disease-free survival (DFS), R0 resection rates, sphincter preservation, and wound/anastomotic complications. A meta-analysis was performed, using the fixed- or random-effects model, with Review Manager 5.1.

Results: Thirteen trials, including 3584 patients, were identified, and overall, an interval longer than 6 to 8 weeks from the end of neoadjuvant CRT and surgery significantly improved the pCR (RR = 1.42, 95% confidence interval: 1.19–1.68; P < 0.0001). Pathological complete responses increased from 13.7% to 19.5% in the longer interval group, and the OS, DFS, R0 resection rates, sphincter preservation, and complication rates were similar in the 2 groups.

Conclusions: A longer waiting interval (more than the classical 6–8 weeks) from the end of preoperative CRT increases the rate of pCR by 6% in rectal cancer, with similar outcomes and complication rates. These results should be validated prospectively in a randomized trial.

Keywords: chemoradiotherapy, interval, neoadjuvant, pathologic complete response, rectal cancer, surgery

The treatment of locally advanced rectal cancer, that is stage cT3–4 or cN+ disease, consists of a course of neoadjuvant [5-fluorouracil (5FU)-based] chemoradiotherapy (CRT) for a total dose of 45 to 50.4 Gy in 25 daily fractions to the tumor and pelvic lymph nodes, followed by a radical total mesorectal excision (TME) of the rectum (plus or minus further adjuvant chemotherapy). The Dutch trial1 confirmed the beneficial effects of adding a short course (5 Gy for 5 days) of radiotherapy (RT) to TME surgery, which led to a lower (10-year overall) recurrence rate with similar survival rates for the RT group. Conversely, the German CAO/ARO/AIO 94 trial2 compared pre- and postoperative (prolonged course: 50.4 Gy in 28 fractions) CRT, showing better local control, even with a similar overall survival (OS) with the former strategy, at a median follow-up of 134 months.

The aims of preoperative treatment in rectal cancer are to obtain pathological downstaging, permit R0 resection, and increase local control and outcomes. It is particularly well known that obtaining a pCR after the neoadjuvant treatment is a valid surrogate of disease-free survival (DFS), as a recent meta-analysis of neoadjuvant CRT trials well established.3 With similar conclusions, 2 other meta-analyses of published trials in 2012 are presented.4,5 Conversely, tumor shrinkage per se was not necessarily associated with a better anterior resection rate in a review of 10 randomized trials comparing any form of neoadjuvant RT with none.6 The possibility of delaying the time between the end of CRT and surgery, beyond the classical 6- to 8-week interval, is a possibility for increasing pathological downstaging after RT, and data from recent retrospective cohort studies have shown that a delay of surgery beyond 6 to 8 weeks resulted in a better rate of pCR.7,8,9,11

For these reasons, a pooled analysis of studies was undertaken in which data were reported for pCR and outcomes after surgery performed at different intervals from the end of neoadjuvant CRT. The aim was to assess whether patients for whom surgery is delayed beyond the classical 6 to 8 weeks from the end of CRT had improved pCR rates, R0 resection rates (R0%), DFS and OS (if available), sphincter preservation, and wound/anastomotic complications, when compared with patients who underwent surgery within 6 to 8 weeks after the end of preoperative treatment.

Materials and Methods

Literature Search

A comprehensive literature search (up to May 10, 2013) was carried out using PubMed, EMBASE, the Cochrane Register of Clinical Trials, and the ISI Web of Science, restricted to articles published in English, using the following search keywords: “surgery or surgical resection or TME or anterior resection or abdominoperineal” AND “rectal cancer or rectal carcinoma” AND “preoperative or neoadjuvant or chemoradiotherapy or radiochemotherapy or radiotherapy or radiation or chemoradiation” AND “interval or delay or time or timing.” The reference lists of all included studies were also searched.

Study Selection Criteria

Published studies were included if they (i) used a retrospective or prospective study design; (ii) evaluated the association between the interval from the end of CRT and surgery (≥6–8 weeks) or pCR (defined as ypT0N0M0 after neoadjuvant 5FU-based prolonged course CRT) in rectal adenocarcinoma; (iii) presented odds ratio, relative risk (RR), or hazard ratio estimates [with 95% confidence interval (CI)], standard errors, or number of events necessary to calculate these for the outcome of interest (such as pCR rate, OS, relapse-free survival or DFS, other than the R0 resection rate, sphincter preservation, and wound complications/anastomotic leaks (if available), in
addition to $P$ values); and (iv) included at least 10 patients treated with rectal cancer. When multiple publications from the same study or institution were available, the publication with the largest number of cases and most applicable information was used. Studies including neoadjuvant radiotherapy only, short course RT, or observation alone after neoadjuvant CRT were excluded.

Two readers (F.P. and S.B.) independently determined the eligibility of each article for inclusion and extracted data. Discrepancies between readers were resolved into the team.

### Data Extraction

The following information was recorded for each eligible trial: authors’ names, year of publication, duration of follow-up, total number of patients, median age, percentage of patients achieving pCR, systemic therapy regimen delivered with RT, clinical TNM stage at presentation, and endpoint data available (percentages and number of events).

The methodological quality of observational comparative studies was assessed by the Newcastle-Ottawa scale (NOS). A score of 0 to 9 was assigned to each study. Conversely, the quality of randomized trials was assessed through the Jadad score (score assigned ranged from 0 to 5 for each study).

### Statistical Analysis

Pathologic CR was the primary outcome measure, and OS, DFS, R0 resection rate, sphincter preservation, and wound complications/anastomotic leaks were the secondary endpoints. When different intervals between CRT and surgery were presented, any event occurred in general beyond 8 weeks was compared with all events occurring less than 8 weeks in the interval. For example, if the 6 to 8, 8 to 10, and 10 to 12 weeks’ intervals were reported, the events occurred in the 8 to 10 and 10 to 12 weeks’ intervals were pooled and compared with 6 to 8 weeks’ interval. The summary statistics of patients achieving pCR after neoadjuvant CRT with RRs and 95% CI were calculated using the fixed-effect model/Mantel-Haenszel (M-H) method, when there was minimal heterogeneity in the variables among the studies, and the DerSimonian–Laird method (random effect model) when there was significant heterogeneity ($\chi^2$ for heterogeneity < 0.1). If events of interest were not reported by the authors, they were extrapolated directly from the survival curves or survival rates. Each publication was weighted as a function of the inverse variance of each effect size, and $\chi^2$ and $I^2$ test methods were utilized for the between-study heterogeneity of the RRs. Statistically significant differences were defined as less than 0.1 for the $\chi^2$ test and greater than 50% for the $I^2$ test. Forest plots were generated using standard techniques to summarize the included studies, with horizontal lines representing 95% CI, the area of each square representing the weighting, and the positions of each square demonstrating the RR point estimate. The overall summary estimate under fixed effects with its CI was shown, and the vertical line was at the null value ($RR = 1.0$). Publication bias was evaluated for pCR analysis through Egger’s linear regression, Begg’s rank correlation, and funnel plots, and a $P < 0.05$ for Egger’s or Begg’s tests was considered representative of significant statistical publication bias. The funnel plots displayed the RR associated with the pCR in each study, with each RR being reported on a log scale against its standard error. The vertical line indicated the pooled estimate of the overall RR, with the sloping lines representing the expected 95% CI for a given standard errors. All statistical analyses were performed with the Review Manager 5.1 [Review Manager (RevMan) computer program, version 5.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008] and Comprehensive Meta-Analysis software (version 2.2.064; July 27, 2011).

### RESULTS

The results of the literature search identified 5065 papers based on the search words, and among these (based on the criteria described earlier), 13 publications9–20 were eligible for inclusion in this meta-analysis (Fig. 1).

The Table 1 provides details about the 13 studies that were included in the meta-analysis, and of the 3584 patients included (all studies were available for the pCR endpoint), 19.5% and 13.7% had achieved pCR in the longer and shorter intervals between the end of CRT and surgery, respectively. All patients, except in 5 trials which included some patients treated with concomitant irinotecan (n = 3) or oxaliplatin (n = 2) in addition to 5FU, underwent neoadjuvant 5FU-based CRT. The number of patients ranged from 33 to 1593, and all were retrospective or prospective cases, except one phase II nonrandomized trial. Median follow-up ranged from 27 months to 4.9 years, with clinical staging, in general, being locally advanced (mainly cT3–4 and cN0/N+). Interval comparisons among publications were as follows: >8 versus <8 weeks in n = 3 trials, <8 versus 8–9 versus 10–11 versus >11 in n = 1 trial; >7 versus <7 weeks in n = 2 trials, >6 versus <6 weeks in n = 3 trials, 6–8 versus 11–13 weeks in n = 1 trial, 7–9 versus 6 weeks in n = 1 trial, 4–8 versus 10–14 in n = 1 trial, and <6 versus 6–8 versus >8 in n = 1 trial.

No randomized trial was included, so the quality of studies was assessed through the NOS scale. Overall, there is an average medium quality of 5 of 9 stars in all studies (range 3–6).

![FIGURE 1. PRISMA 2009 flow diagram for selection of included studies.](https://www.annalsofsurgery.com)
TABLE 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Study</th>
<th>Median Age (Shorter vs Longer, yrs)</th>
<th>Median Follow-up (Shorter vs Longer, mo)</th>
<th>Clinical Stage (Shorter vs Longer)</th>
<th>Neoadjuvant RT</th>
<th>Chemotherapy</th>
<th>CTRT-S Interval, wk</th>
<th>NOS Quality (Stars)</th>
<th>pCR Longer vs Shorter, %</th>
<th>OS</th>
<th>DFS</th>
<th>R0</th>
<th>Sphincter Preservation</th>
<th>Wound/Anastomotic Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein/2003</td>
<td>Prospective series</td>
<td>33 (19 + 14)</td>
<td>51 vs 53</td>
<td>NA</td>
<td>cT3N0/cT4N1</td>
<td>EBRT</td>
<td>45–54 Gy</td>
<td>5/9</td>
<td>21 vs 14</td>
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<td>(continued)</td>
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<tr>
<td>Moore/2004</td>
<td>Retrospective analysis</td>
<td>155 (73 + 82)</td>
<td>60 (all pts)</td>
<td>NA</td>
<td>cT3N0/cT4N1</td>
<td>EBRT</td>
<td>50.4 Gy</td>
<td>≤ 44 vs &gt; 44 d</td>
<td>90% in both</td>
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<tr>
<td>Tran/2006</td>
<td>Retrospective analysis</td>
<td>48 (16 + 32)</td>
<td>62.3 vs 58.1</td>
<td>Stage cII-cIII (98% in both)</td>
<td>EBRT</td>
<td>5FU ci</td>
<td>≤ 8 vs 8 weeks</td>
<td>5/9</td>
<td></td>
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<tr>
<td>Lim/2008</td>
<td>Prospective series</td>
<td>397 (217 + 180)</td>
<td>55.3 vs 57.5</td>
<td>cT4–4 (98% in both)</td>
<td>EBRT</td>
<td>5FU + LV bolus/X + CPT11</td>
<td>28–41 vs 42–56 d</td>
<td>5/9</td>
<td>5FU ci (54.8%), 5FU bolus (20%), oral 5FU (7.6%)</td>
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<tr>
<td>Tarlinsky/2008</td>
<td>Retrospective analysis</td>
<td>132 (48 + 84)</td>
<td>59 vs 64</td>
<td>Stage u-stage II (81 vs 75%)</td>
<td>EBRT</td>
<td>5FU ci or oral 5FU</td>
<td>≤ 7 vs &gt; 7</td>
<td>5/9</td>
<td>3.45 vs 15</td>
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<tr>
<td>Habr-Gama/2008</td>
<td>Retrospective analysis</td>
<td>250 (121 + 129)</td>
<td>56.9 vs 60</td>
<td>Stage cII-cIII (88 vs 92%)</td>
<td>EBRT</td>
<td>5FU + LV + CPT11</td>
<td>≤ 12 vs &gt; 12</td>
<td>6/9</td>
<td>7.6% vs 11</td>
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<tr>
<td>Garcia-Aguilar/2011</td>
<td>Phase II trial</td>
<td>136 (66 vs 70)</td>
<td>61 vs 56</td>
<td>Stage cII-cIII 100%</td>
<td>EBRT</td>
<td>5FU ci (+ mFOLFOX6 2 cycles in (longer interval)</td>
<td>6–8 vs 11–13</td>
<td>5/9</td>
<td>5FU ci (36.8%), X5FU + other (43.2%), none (17.8%), R (2.1%)</td>
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<tr>
<td>de Campos-Lohans/2011</td>
<td>Retrospective analysis</td>
<td>177 (83 + 94)</td>
<td>54.1 vs 57</td>
<td>Stage cII-cIII 100%</td>
<td>EBRT</td>
<td>5FU ci</td>
<td>&lt;8 vs ≥8</td>
<td>5/9</td>
<td>3.11 vs 16.2</td>
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<tr>
<td>Evans/2011</td>
<td>Retrospective analysis</td>
<td>95 (18 + 32 + 45)</td>
<td>68 (all pts)</td>
<td>cT3–4 (93.7%), cNO/N+(17.8/2%)</td>
<td>EBRT (long course 83.2%, short course 16.8%)</td>
<td>X (36.8%), X5FU + other (43.2%), none (17.8%), R (2.1%)</td>
<td>&lt;6 vs 6–8 vs &gt;8</td>
<td>5/9</td>
<td>17.7 vs 10</td>
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<tr>
<td>Wolthuis/2012</td>
<td>Retrospective analysis</td>
<td>356 (201 + 155)</td>
<td>64 vs 62</td>
<td>Stage cII-cIII</td>
<td>EBRT</td>
<td>5FU ci</td>
<td>≤ 7 vs &gt;7</td>
<td>6/9</td>
<td>2.84 vs 15.9</td>
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<tr>
<td>Author/Year</td>
<td>Type of Study</td>
<td>No. Patients</td>
<td>Median Age Shorter vs Longer, yrs</td>
<td>Median Follow-up Shorter vs Longer, mo</td>
<td>Clinical Stage Shorter vs Longer</td>
<td>Neoadjuvant RT</td>
<td>Chemotherapy</td>
<td>CTRT-S Interval, wk</td>
<td>NOS Quality (Stars)</td>
<td>pCR Longer vs Shorter, %</td>
<td>OS</td>
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<tr>
<td>Una Cidon/2012</td>
<td>Retrospective analysis</td>
<td>115 (57 + 58)</td>
<td>67 vs 66</td>
<td>NA</td>
<td>Stage II-II (100%)</td>
<td>EBRT 50.4 Gy</td>
<td>X</td>
<td>&lt;6 vs ≥6</td>
<td>3/9</td>
<td>36 vs 20.8</td>
<td>(P = 0.035)</td>
<td>✓</td>
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<tr>
<td>Sloothak/2013</td>
<td>Retrospective analysis</td>
<td>1593 (312 + 511 + 406 + 364)</td>
<td>63 vs 63 vs 64 vs 64</td>
<td>NA</td>
<td>cT3-4 (85%), cN+(80.2%)</td>
<td>EBRT 50 or 50.5 Gy</td>
<td>X†</td>
<td>&lt;8 vs 8–9 vs 10–11 vs &gt;11§</td>
<td>6/9</td>
<td>14.2 vs 10.2</td>
<td>(P = 0.013)</td>
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<tr>
<td>Fang/2013</td>
<td>Prospective series</td>
<td>106 (32 + 74)</td>
<td>NA</td>
<td>32.2 vs 35.6 wks</td>
<td>92%</td>
<td>cT3-4N0.1</td>
<td>EBRT 50.4 Gy</td>
<td>5–6 vs &gt;6</td>
<td>4/9</td>
<td>12.2 vs 18.8</td>
<td>(P = 0.37)</td>
<td>✓</td>
<td>(P = 0.64)</td>
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</table>

ci indicates continuous infusion; cII-cIII, clinical stage II-III; CPT11, irinotecan; EBRT, external beam radiotherapy; NA, not available; m, not significant; R, raltitrexed; X, capecitabine.

* n = 28 patients received 5FU 225 mg/m²/d and n = 15 received + CPT11 10 mg/m²/d.
† <6 and 6–8 weeks’ intervals were grouped for analysis.
‡ In few patients 5FU ± oxaliplatin.
§ 8–10–11–>11 were grouped for analysis.
¶ Interval CTRT-S was the only predictor of pCR after multivariate analysis adjusted for age at surgery, gender, tumor location, pretreatment EUS staging, preoperative radiation dose, and neoadjuvant-surgery time interval.
||Interval CTRT-S > 8 wk was the only predictor of pCR after multivariate analysis adjusted for age, sex, tumour height, interval CTRT-S, preoperative RT or CT, and type of surgery.
Primary Endpoint: pCR in Longer Versus Shorter Interval

All included trials provided pCR data (n = 3584 patients), and the RR and 95% CI for each study and the summary RR are shown in Figure 2. The overall summary estimated RR was 1.42 (95% CI: 1.19–1.68), P < 0.0001). Heterogeneity testing revealed that I² = 2% and the P for heterogeneity = 0.43, using a fixed-effect model. The risk difference was 5% (P = 0.008).

Secondary Endpoints: OS, DFS, R0 Resection, Sphincter Preservation, and Wound/Anastomotic Complications

Survival events in the included studies were calculated, when available, at fixed time points (as reported in the publications) with median follow-up of observations ranged from 2.3 to 4.99 years (n = 7 studies with follow-up length available).

Six trials provided OS data (n = 1360 patients), and the RR and 95% CI for each study and the summary RR are shown in Figure 3. The overall summary estimated RR was 0.85 (95% CI: 0.58–1.12; P = 0.19). Heterogeneity testing was moderate with I² = 61% and the P for heterogeneity = 0.02, using the random effect model.

The data for DFS were available in n = 7 trials (Fig. 4), and the overall summary estimated RR was 0.81 (95% CI: 0.58–1.12; P = 0.19). Heterogeneity testing was moderate with I² = 61% and the P for heterogeneity = 0.02, using the random effect model.

The R0 resection rate was provided in 6 trials (n = 2723 patients; RR = 1, P = 0.65). Sphincter preservation was similar in the longer versus shorter interval (n = 8 trials), and the RR was 0.94 (P = 0.13). Finally, the wound complications and anastomotic leak events were derived from n = 7 trials and were similar (RR = 0.83, P = 0.27).

Publication Bias

The funnel plot (Fig. 5) shows no evidence of remarkable asymmetry, and the result from Begg’s test was not significant (P = 0.42); therefore, the Egger’s test P value was significant (P = 0.41). Using the Trim and Fill method, and after the “one study removed” procedure, the final results remained unchanged.

DISCUSSION

Obtaining a pCR after preoperative treatment is often considered synonymous with a cure in various solid tumors including breast, bladder, and rectal cancer. In these cancers, the eradication of all cancer cells is dramatically associated with improved outcomes as confirmed by meta-analyses published in the literature and by controlled trials.3–5,21,22 In a recent Cochrane meta-analysis of 5 randomized trials, neoadjuvant CRT was found to significantly increase the rate of pathological complete response (pCR: P < 0.0001), although this did not translate into a higher sphincter preservation rate or survival compared to neoadjuvant RT alone.23

The pivotal German trial,2 led by Sauer et al, that compared pre- versus postoperative CRT (prolonged course: 50.4 Gy in 28 fractions) in locally advanced rectal cancer (mainly ctT3-4 or cN+ disease), showed a rate of pCR of 8% in the neoadjuvant arm, with an overall rate of postoperative complications at 36% (in the preoperative treatment group, compared to 34% in the postoperative treatment group). The rate of anastomotic leakage of any grade was also similar. In this trial, the interval between the end of CRT and surgery was 6 weeks. In the Dutch trial, the TME technique was performed within 1 week of the end of RT,1 and in the German trial (in patients who were assigned to neoadjuvant treatment), surgery was planned 6 weeks after the completion of CRT.2 The Lyon R90-01 trials demonstrated that a delay in surgery of up to 6 to 8 weeks increased the clinical tumor response and pathological downstaging of rectal cancer, compared to surgery performed 2 weeks after the completion of exclusive RT (39 Gy in 13 fractions).24 Morbidity, local relapse, survival, and sphincter preservation were not affected, and in particular, patients in the longer interval group had either more pCR or fewer residual tumor cells when compared to patients in the 2-week interval group (26 vs 10.3%, P = 0.0054).

In this meta-analysis, for the first time in the literature, all published data comparing oncological and surgical results of longer versus shorter (or standard) intervals between neoadjuvant CRT and surgery were included.

FIGURE 2. Forest plot for pathologic complete response rate meta-analysis.
surgery in rectal cancer was pooled together. The RR of obtaining a pCR, waiting more than 6 to 8 weeks from the end of CRT, was increased by 42%, and in particular, was 6% higher in the experimental cases. Overall outcomes of all patients in the longer interval groups were similar to the standard cases, and so were some complications, R0 resection rate, and sphincter preservation.

These results are relevant from several points of view. First, obtaining a higher rate of pCR is desirable in patients with locally advanced rectal cancer because it is associated with better OS when compared to any residual disease, and in particular with node-positive disease. Second, from a radiation oncologist viewpoint, the occurrence of greater downstaging and waiting additional weeks before operating could reduce acute complications of treatment and possibly increase and better modulate the dose of radiotherapy with the modern techniques now available. And third, from a surgical point of view, waiting longer than 2 months after CRT does not seem detrimental to patient survival, nor worse in terms of complication rates (with similar R0 and sphincter conservation rates).

These results appear to be robust, with no heterogeneity for the pCR analysis, which is the primary endpoint. Historically, the first strategy for increasing pathological downstaging after neoadjuvant RT was increasing the duration of radiation, as opposed to the addition of chemotherapy. In the recently published Trans-Tasman trial 01-4,25 a short course of RT (5 Gy with 5 fractions), followed by surgery (3–7 days after), and 6 months of adjuvant 5FU chemotherapy, was compared to a longer course of CRT (50.4 Gy, 1.8 Gy/fraction, in 5.5 weeks, with continuous infusional 5FU at 250 mg/m2 per day), surgery after 4 to 6 weeks, and 4 courses of adjuvant chemotherapy. In this trial, approximately 13% reached a ypT0N0M0 stage in the longer RT group when compared with 1% in the shorter course of RT. When comparing the 2, the long course CRT showed a trend toward less local recurrences in distal cancer, but similar survival rates. In particular, none of the pCR patients in the long course group recurred locally. An additional randomized trial came to similar conclusions.26 The intensification of systemic treatment has not lead (as of today) to a better outcome. In fact, the addition of a second agent (such as oxaliplatin) to the 5FU-based CRT resulted in an increase in the odds of pCR by 20% (absolute difference of 2.5% in favor of the 5FU + oxaliplatin association), and less perioperative metastases with a similar R0 resection rate.27 However, the oxaliplatin group
suffered of an increased G3-4 toxicity risk, even with a similar rate of surgical complications, but an 8% lower probability of full-dose RT delivery. In our meta-analysis, 5 trials included a fraction of patients treated with irinotecan or oxaliplatin in addition to 5FU. After the exclusion of these trials, the RR of the pCR was even higher (1.82, \( P < 0.00001 \); data not shown).

A debate exists concerning the nonoperative strategy of patients with locally advanced rectal cancer completely downstaged after a course of preoperative CRT, and the apparently low rate of local recurrence and the satisfactory outcome seem intriguing. A recent review of 30 published studies, however, mitigated any early enthusiasm. These results suggested that patients who were observed, but subsequently failed to sustain a complete response, may actually do worse than those who underwent immediate surgery. This policy, if potentially suitable for small and distal rectal cancer, should not (for now) be extrapolated to more advanced tumors. Prospective studies with more uniform inclusion criteria are required to evaluate the risks and benefits of such a strategy. In this scenario, waiting more than the classical 6 to 8 weeks from the end of CRT could be useful, because it could permit (by itself) the cure of a nonlocally advanced, distal, rectal carcinoma if the primary tumor obtains a pathological complete regression. This would be the ideal case to observe with no surgical resection, but only with strict endoscopic monitoring. Obviously, this is the potential scenario of a prospective clinical trial. Currently, a Royal Marsden trial (NCT01047969) is ongoing in patients with locally advanced rectal cancer, or cancer needing abdominoperineal resection, with the aim to estimate the rate of patients who can safely omit surgery, and who are still in complete response (with no detectable local disease).

This meta-analysis has some limitations, but it has some strengths as well. First, this is a study-level meta-analysis of non-randomized trials; therefore, the pCR correlation with surgical delay cannot be adjusted in a multivariate analysis with other clinicopathological variables. Second, the outcome (DFS and OS) of pCR patients, even if likely better than those without pCR as literature tell us, cannot be directly assessed in this meta-analysis due to lack of individual patient data. Third, the number of patients operated on in the delayed group could have been chosen using a surgical decision, for example, to mitigate excessive acute radiation toxicities.

On the contrary, this is the first published systematic analysis that evaluated pCR, survival, and surgical outcomes of patients with rectal cancer that underwent surgery later than the conventional 6 to 8 weeks from the end of neoadjuvant CRT. The population included in this study is relatively consistent in terms of drug schedules and clinical stage at inclusion, and the low heterogeneity and highly significant results were obtained with minimal evidence of bias for pCR analysis.

This meta-analysis calculated a 42% higher risk of obtaining pCR, and a trend for improved DFS and OS with similar radical resection rates and complications, when a longer interval between RT and surgery was chosen. These results are better than those obtained with the addition of oxaliplatin to the 5FU-based CRT, with the advantage of avoiding excessive toxicity and costs. The addition of biological agents is currently being investigated but is far from gaining significant short-term improvements. In addition, a further dose of brachytherapy has not been shown to increase the pCR rate. Deciding among the currently available predictors of pCR in rectal cancer is an ongoing setting of research, and the role of PET, for example, has been largely investigated with molecular correlations in particular.

As of today, obtaining the information that all cancer cells have been eradicated does not necessarily mean that radical surgery can be avoided in cases of rectal cancer. It is likely only a prognostic information that establishes that any residual risk (likelihood of locoregional and distant relapse) has been dramatically removed.

CONCLUSIONS
Awaiting further effective treatments and randomized trials, waiting for surgery longer than the classical 6 to 8 weeks after preoperative CRT significantly increase pCR, without a significantly detrimental outcome, and with similar wound and anastomotic complications.

REFERENCES


