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Original research article

# Neoadjuvant chemotherapy with or without oxaliplatin after short-course radiotherapy in high-risk rectal cancer: A subgroup analysis from a prospective study

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ABSTRACT

*Aim:* To evaluate the role of oxaliplatin in neoadjuvant chemotherapy delivered after short-course irradiation.
*Background:* Using oxaliplatin in the above setting is uncertain.
*Patients and methods:* A subgroup of 136 patients managed by short-course radiotherapy and 3 cycles of consolidation chemotherapy within the framework of a randomised study was included in this post-hoc analysis. Sixty-seven patients received FOLFOX4 (oxaliplatin group) while oxaliplatin was omitted in the second period of accrual in 69 patients because of protocol amendment (fluorouracil-only group).
*Results:* Grade 3+ acute toxicity from neoadjuvant treatment was observed in 30% of patients in the oxaliplatin group vs. 16% in the fluorouracil-only group ($p = 0.053$). The corresponding proportions of patients having radical surgery or achieving complete pathological response were 72% vs. 77% (odds ratio [OR] = 0.88; 95% confidence interval [CI]: 0.39–1.98; $p = 0.75$) and 15% vs. 7% (OR = 2.25; 95% CI: 0.83–6.94; $p = 0.16$), respectively. The long-term outcomes were similar in the two groups. Overall and disease-free survival rates at 5 years were 63% vs. 56% ($p = 0.78$) and 49% vs. 44% ($p = 0.59$), respectively. The corresponding numbers for cumulative incidence of local failure or distant metastases were 33% vs. 38% (hazard ratio [HR] = 0.89; 95% CI: 0.52–1.52; $p = 0.68$) and 33% vs. 33% (HR = 0.78; 95% CI: 0.43–1.40; $p = 0.41$), respectively.
*Conclusion:* Our findings do not support adding oxaliplatin to three cycles of chemotherapy delivered after short-course irradiation.


## 1. Introduction

We have recently published the results of a phase III randomised trial performed in patients with rectal cancer and threatened mesorectal fascia that compared short-course radiotherapy in

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combination with three cycles of consolidation chemotherapy vs. neoadjuvant long-course chemoradiation.[1,2] Although oncological outcomes were similar after these two neoadjuvant treatments, short-course radiotherapy/consolidation chemotherapy is considered to be a valid option because of its several advantages over long-course chemoradiation, i.e., lower early toxicity, convenience and lower cost. Therefore, short-course radiotherapy combined with consolidation chemotherapy consisting of 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) is recommended by the European Society for Medical Oncology guidelines as an alternative management to neoadjuvant long-course chemoradiation.[3] However, the utility of oxaliplatin as a component of consolidation chemotherapy given after short-course radiotherapy has not been evaluated. It is worth exploring this issue because several randomized studies have shown that the addition of oxaliplatin to fluoropyrimidine-based neoadjuvant long-course chemoradiation resulted in increased toxicity with no benefit in long-term oncological outcomes.[4–13] Therefore, the utility of oxaliplatin in the setting of short-course radiotherapy/consolidation chemotherapy can be questioned. However, consolidation chemotherapy after short-course radiotherapy is delivered in full systemic doses. Thus, distant micrometastases can be eradicated. Moreover, the results of the MOSAIC randomised study demonstrated that the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy improves survival in colon cancer.[14] Thus, oxaliplatin may also provide some benefit in the neoadjuvant short-course radiotherapy/consolidation chemotherapy setting.

The exploration of the utility of oxaliplatin was possible in our trial.[15] During the first part of accrual, giving oxaliplatin was mandatory in the two study arms. However, evidence about the lack of a benefit of adding oxaliplatin to fluoropyrimidine neoadjuvant long-course chemoradiation was published during a study.[4,5] Therefore, in the second part of the accrual, oxaliplatin delivery was left to the discretion of the local investigator. If a decision to continue or to skip oxaliplatin was made, it had to be enforced in all subsequently enrolled patients in the two arms. This created an opportunity for the comparison of treatment outcomes with or without oxaliplatin. We previously made this comparison using the two pooled arms, which showed no benefit of adding oxaliplatin to fluoropyrimidine chemotherapy over fluoropyrimidine chemotherapy alone in terms of radical surgery and pathological complete response (pCR) rates.[14] Currently, using the updated patients' material, we aimed at evaluating the impact of oxaliplatin addition on early as well as long-term outcomes in the short-course radiotherapy/consolidation chemotherapy arm.

## 2. Material and methods

The study details were published previously.[1,2,16] In short, the eligibility criteria were as follows: primary cT4 or palpably fixed cT3 lesion or a locally recurrent rectal cancer (i.e., patients with high probability of positive surgical margin), pathologically proven adenocarcinoma, ≤75 years of age and World Health Organization (WHO) performance status ≤2. The threatened mesorectal fascia diagnosed by magnetic resonance imaging (MRI) was not used as an eligibility criterion because of the long waiting time in Poland for this examination during the study accrual. Between 2008 and 2014, the patients were randomly assigned to receive either preoperative 5 × 5 Gy irradiation over 5 consecutive days with three cycles of sequential FOLFOX4 or preoperative long-course chemoradiation with oxaliplatin, bolus 5-fluorouracil and leucovorin. Surgery in both arms was scheduled about 6 weeks after the completion of neoadjuvant treatment. The decision for delivery of adjuvant chemotherapy and its schedule was left to the discretion of the attending physician. The trial was registered with ClinicalTrials.gov (NCT00833131).

Only patients assigned to the short-course radiotherapy/consolidation chemotherapy were included in the current analysis. The FOLFOX4 regimen was defined as oxaliplatin 85 mg/m$^2$ on day 1, leucovorin 200 mg/m$^2$/day on days 1 and 2, and 5-fluorouracil bolus 400 mg/m$^2$/day followed by continuous infusion 600 mg/m$^2$/day on days 1 and 2, repeated every 2 weeks (oxaliplatin group). The protocol was amended on January 2012 to allow for omitting oxaliplatin, but the schedule of delivering 5-fluorouracil and leucovorin remained unchanged, i.e., de Gramont schedule (fluoropyrimidine-only group).

Expertise and surgical skills are needed to perform major, often exenterative, resections of fixed cT3, cT4 or locally recurrent tumours. Moreover, there is a large variation in standards and outcomes between institutions.[17] Therefore, to minimize the institutional influence as a confounding factor, we included only 14 institutions in our main intention-to-treat analysis where patients were treated during both periods of accrual and received consolidation chemotherapy with oxaliplatin before protocol amendment and without oxaliplatin after amendment. That means we included only a subgroup of 136 patients (67 from the oxaliplatin group and 69 from the fluorouracil-only group) out of the total group of 261 eligible patients (Fig. 1). The remaining 125 patients were excluded, mostly because they were treated at hospitals where oxaliplatin had been given for two study periods.

In addition, we performed two following sensitivity analyses in the total group of patients randomised to the short-course radiotherapy/consolidation chemotherapy arm: i.e., an intention-to-treat analysis of 261 patients (183 in the oxaliplatin group and 78 in the fluorouracil-only group) and a per-protocol analysis of 249 patients (178 from the oxaliplatin group and 71 from the fluorouracil-only group) (Fig. A1).

We compared categorical data using the chi-square test or Fisher's exact test and continuous data using Student's *t* test or the Mann–Whitney *U* test. The follow-up duration was measured from randomisation. The binary logistic multivariable regression model was used in the analyses of odds of having radical surgery or achieving pCR. Survival was estimated by the Kaplan–Meier method. Local failure, distant failure, or death was an event for disease-free survival (DFS) estimation. The multivariable Cox's proportional hazards model was used to compare differences in overall survival (OS) and DFS. Local failure was defined either as no tumour resection or as $R_2$ resection or as local recurrence after $R_{0\text{-}1}$ resection. Local failure and distant metastases were recorded when they occurred at any time, i.e., not only as the first event. The analysis of local or distant failure was reported as a cumulative incidence considering death as a competing risk. The differences were compared in the multivariable analysis using a competing risk regression. All tests were two-sided. The data were analysed with IBM SPSS Statistics software (version 20 for Linux; IBM SPSS Inc., Armonk, NY, USA) and R software (www.r-project.org).

## 3. Results

Pretreatment pelvic MRI examination was less frequently performed in the oxaliplatin group (Table 1). Their tumours were more advanced and WHO performance score worse compared to the fluorouracil-only group. Of the patients who had tumour resection, adjuvant chemotherapy was given in 40% of the oxaliplatin group vs. 43% of the fluorouracil-only group. In the oxaliplatin group, adjuvant chemotherapy included oxaliplatin more often than in the fluorouracil-only group (Table 2). The types of chemotherapy delivered for recurrences are unknown because these data were not collected.

Grade 3 or higher acute toxicity occurring during the whole neoadjuvant treatment was observed in 30% (20 of 67) of the

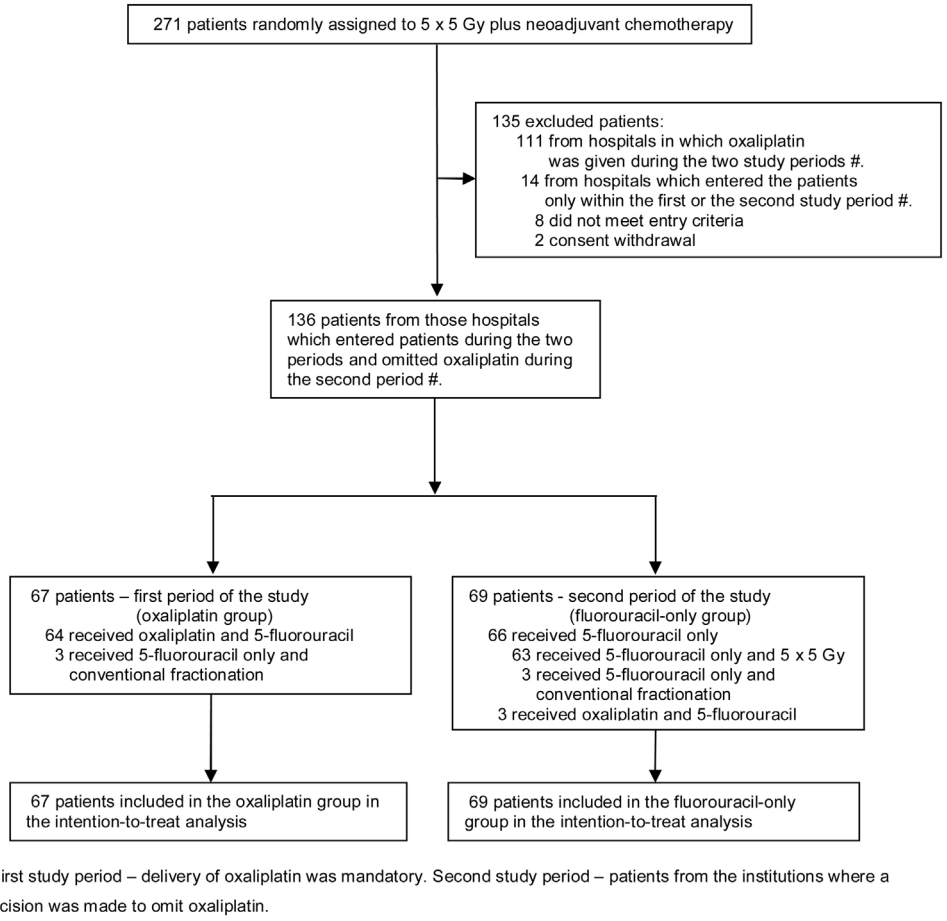


**Fig. 1.** Flow diagram.

**Table 1**
Patient characteristics.

| | Oxaliplatin group n = 67 (%) | Fluorouracil-only group n = 69 (%) | p-value |
|---|---|---|---|
| Gender | | | 0.30 |
| Female | 24 (36%) | 19 (28%) | |
| Male | 43 (64%) | 50 (72%) | |
| Age in years, median (IQR) | 60.5 | 60.6 | 0.83 |
| Pre-treatment pelvic MRI | | | 0.025 |
| Yes | 38 (57%) | 51 (75%) | |
| No | 29 (43%) | 17 (25%) | |
| No data | | 1 | |
| Type of tumour | | | 0.042 |
| Fixed cT3 | 16 (24%) | 29 (42%) | |
| cT4 | 47 (70%) | 39 (57%) | |
| Recurrent | 4 (6%) | 1 (1%) | |
| WHO performance score | | | 0.021 |
| 0 | 21 (31%) | 38 (55%) | |
| 1 | 42 (63%) | 28 (41%) | |
| 2 | 4 (6%) | 3 (4%) | |
| Distance between tumour and the anal verge in cm | | | 0.29 |
| 0-5 | 40 (60%) | 35 (51%) | |
| >5-10 | 27 (40%) | 34 (49%) | |
| >10-15 | 0 | 0 | |

Numbers in the table denote number of patients (%) unless otherwise stated.
IQR - interquartile range.

patients in the oxaliplatin group vs. 16% (11 of 69) in the fluorouracil-only group ($p = 0.053$). There was one (1.5%) toxic death related to the neoadjuvant treatment in the oxaliplatin group and one (1.5%) in the fluorouracil-only group. Chemotherapy dose reduction or cycle delay was more often needed in the oxaliplatin group than in the fluorouracil-only group (Table 2). The interval between completion of chemotherapy and surgery was 6 days shorter in the oxaliplatin group than in the fluorouracil-only group. The proportion of patients having radical surgery (defined as tumour resection with >1 mm negative circumferential margin and negative distal bowel margin) was 72% (48 of 67) in the oxaliplatin group vs. 77% (53 of 69) in the fluorouracil-only group (odds ratio

**Table 2**
Intention-to-treat analysis of events.

| | Oxaliplatin group n = 67 | Fluorouracil-only group n = 69 | P-value |
|---|---|---|---|
| Consolidation chemotherapy dose reduction or cycle delay | | | 0.016 |
| No | 31 (46%) | 46 (67%) | |
| Yes | 36 (54%) | 23 (33%) | |
| Interval between completion of chemotherapy and surgery in weeks, median (IQR) | 5.2 (4.7–6.4) | 6.0 (5.2–7.4) | 0.009 |
| Adjuvant chemotherapy | | | 0.78 |
| No | 31 (60%) | 29 (57%) | |
| Yes | 21 (40%) | 22 (43%) | |
| No data | 4 | 5 | |
| No applicable, no tumour resection | 11 | 13 | |
| Type of adjuvant chemotherapy | | | 0.001 |
| Oxaliplatin-based | 14 (70%) | 3 (15%) | |
| Fluoropyrimidine-based | 6 (30%) | 17 (85%) | |
| No data | 5 | 7 | |
| No applicable, no chemotherapy or no tumour resection | 42 | 42 | |
| Vital status | | | |
| Alive | 36 (54%) | 38 (55%) | |
| Dead | 31 (46%) | 31 (45%) | |
| Local failure or distant metastases or death (disease-free survival events) | | | |
| No | 30 (45%) | 30 (44%) | |
| Yes | 37 (55%) | 39 (56%) | |
| Locoregional status | | | |
| Locoregional control | 44 (66%) | 43 (62%) | |
| No tumour resection or $R_2$ resection | 11 (16%) | 13 (19%) | |
| Pelvic recurrence alone after radical resection | 5 (8%) | 6 (9%) | |
| Pelvic recurrence + distant metastases after radical resection | 7 (10%) | 7 (10%) | |
| Distant metastases | | | |
| No | 45 (67%) | 45 (65%) | |
| Yes | 22 (33%) | 24 (35%) | |

Numbers in the table denote number of patients (%) unless otherwise stated.
IQR - interquartile range.
P-value was not given for long-term oncological events because statistical tests were performed taking into account time of events occurrence (Kaplan-Meier and cumulative incidence analyses).

[OR] = 0.88; 95% confidence interval [CI]: 0.39–1.98; $p = 0.75$), after accounting in the multivariable analysis for institution and imbalance in the proportion of patients in respect to their cT-category and WHO performance score. The corresponding numbers for pCR (ypT0N0) were 15% (10 of 67) vs. 7% (5 of 69) (OR = 2.25; 95% CI: 0.83–6.94; $p = 0.16$) in the intention-to-treat analysis and 18% (10 of 56) vs. 9% (5 of 56) in the patients having their tumour resected.

The median follow-up was 7.7 years (minimum = 6.6 years; interquartile range [IQR] = 7.1–8.8 years) in the oxaliplatin group and 5.6 years (minimum = 4.6 years; IQR = 5.0–6.3 years) in the fluorouracil-only group. None of the patients was lost to follow-up regarding vital status. The missing information in this respect was completed from the national registry. The row proportions of events are shown in Table 2. No differences were observed in the long-term oncological outcomes between the oxaliplatin and fluorouracil-only groups. At 5 years, OS was 63% (95% CI: 52%–74%) in the oxaliplatin group vs. 56% (95% CI: 44%–68%) in the fluorouracil-only group (log-rank $p = 0.78$) (Fig. 2). The corresponding numbers for DFS were 49% (95% CI: 37%–61%) vs. 44% (95% CI: 32%–56%) (log-rank $p = 0.59$) (Fig. 3). The proportional hazard assumption for analysed groups was violated for both OS and DFS. For this reason, the Cox's model was stratified by oxaliplatin delivery. The analysis did not demonstrate that institution, cT-category and WHO performance score have an impact on OS or DFS. Hence, we considered Kaplan–Meier estimations and log-rank *p*-values presented above as a valid measure of association between oxaliplatin delivery and survival.

The cumulative incidence of distant metastases at 5 years was 33% in the oxaliplatin group vs. 33% in the fluorouracil-only group (Fig. 4). After considering institution and imbalance in respect to cT-category and WHO performance score in the multivariable analysis, hazard ratio [HR] was 0.78 (95% CI: 0.43–1.40; $p = 0.41$). The corresponding numbers for cumulative incidence of local failure were 33% vs. 38% (Fig. A2) (HR = 0.89; 95% CI: 0.52–1.52; $p = 0.68$).

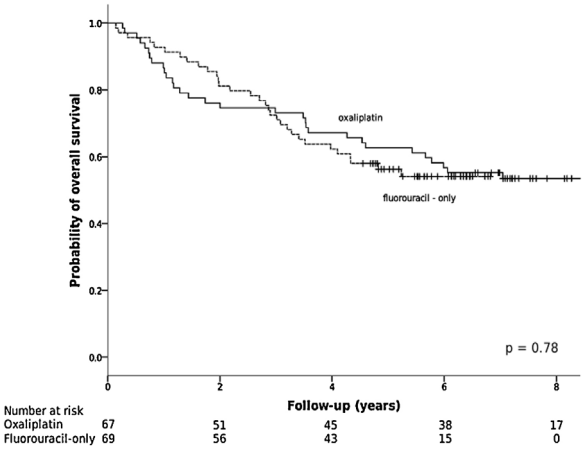


**Fig. 2.** Overall survival.

The results of the sensitivity intention-to-treat analysis performed in the total group of patients assigned to the short-course radiotherapy/consolidation chemotherapy arm were not much different from those presented above (Tables A1 and A2). The proportion of patients having radical surgery was 79% in the oxaliplatin group vs. 74% in the fluorouracil-only group ($p = 0.44$). At 5 years, OS was 61% (95% CI: 54%–68%) in the oxaliplatin group vs. 56% (95% CI: 45%–67%) in the fluorouracil-only group (log-rank $p = 0.69$) (Fig. A3). The corresponding numbers for DFS were 48% (95% CI: 41%–55%) vs. 45% (95% CI: 34%–56%), (log-rank $p = 0.62$), respectively (Fig. A4). The cumulative incidence of distant metastases was 34% vs 31% (HR = 1.09; 95% CI: 0.69–1.73; $p = 0.72$), respectively (Fig. A5). Finally, the numbers for local failure were 31% vs 37% (HR = 0.82; 95% CI: 0.54–1.25; $p = 0.35$), respectively (Fig. A6). The similar per-protocol analysis demonstrated that the results were

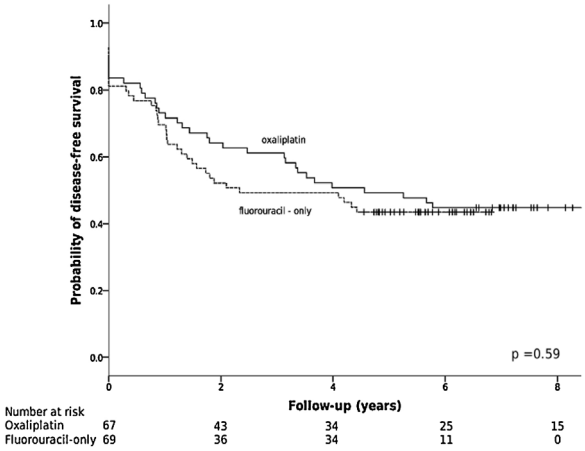


**Fig. 3.** Disease-free survival. The curves do not start at 1 because the lack of tumour resection or $R_2$ resection was considered to be a local failure at time 0.

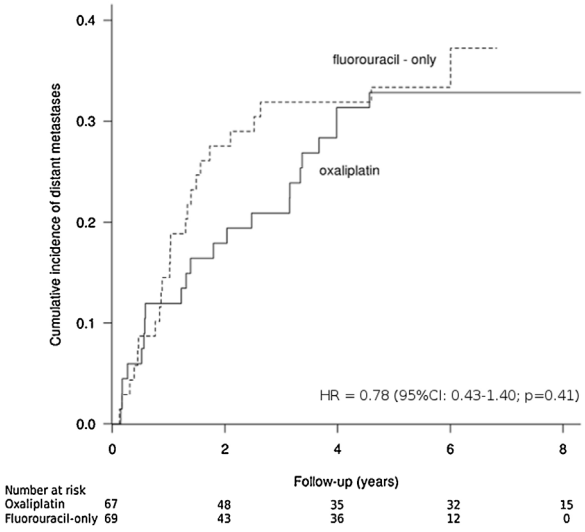


**Fig. 4.** Cumulative incidence of distant metastases. Competitive risk analysis.

only slightly different from those presented above for intention-to treat analyses (data not shown).

## 4. Discussion

Our analysis suggests that the addition of oxaliplatin to three cycles of consolidation fluoropyrimidine chemotherapy after short-course irradiation does not result in clinically meaningful long-term oncological benefit. In addition, the use of oxaliplatin increases acute toxicity. For the above reasons, our results suggest omitting oxaliplatin from consolidation chemotherapy delivered after short-course irradiation to avoid unnecessary adverse effects. To our knowledge, this is the first study exploring the utility of oxaliplatin as a component of neoadjuvant chemotherapy combined with neoadjuvant radiotherapy.

Similarly, the absence of survival benefit from oxaliplatin addition was demonstrated by most of the randomised trials comparing long-course chemoradiation given with or without oxaliplatin[4–12] and by a meta-analysis of these trials.[13] An extrapolation of this finding to the setting of three cycles of neoadjuvant chemotherapy given after short-course radiotherapy supports our suggestion.

However, the pCR rate was numerically about twofold higher in the oxaliplatin group than in the fluorouracil-only group (15% vs. 7%, respectively; $p = 0.16$). A higher rate of pCR after using oxaliplatin was also demonstrated by the meta-analysis comparing long-course chemoradiation given with or without oxaliplatin (18.3% vs 14.8%, respectively; $p = 0.002$).[13] Notably, despite the improvement in the pCR rate observed after the addition of oxaliplatin, no subsequent improvement in oncological long-term outcomes was observed, which provides further evidence showing that the pCR rate is not a surrogate endpoint for survival.[18] Nevertheless, because a higher rate of disease sterilization is expected, the addition of oxaliplatin to fluoropyrimidine consolidation chemotherapy is worth considering if the treatment uses a watch-and-wait strategy.

Neoadjuvant chemotherapy combined with neoadjuvant radio(chemo)therapy is gaining attention.[19–23] Neoadjuvant chemotherapy has two aims: to enhance a local efficacy of radiotherapy and to more effectively eradicate distant micrometastases compared to adjuvant chemotherapy. Chemotherapy focused on the enhancement of local efficacy is given for a short period of time,[2,23] whereas chemotherapy that is focused on distant micrometastases eradication (named as total neoadjuvant chemotherapy) is given for a prolonged period.[22] Three cycles (6 weeks) of oxaliplatin may not reduce the rate of distant metastases, as suggested by our analysis, but if oxaliplatin was to be given for a prolonged period of time, such an effect could be revealed. Two other randomised trials explored short-course radiotherapy combined with sequential neoadjuvant oxaliplatin-based chemotherapy lasting 12 weeks in the STELLAR trial[20] and 18 weeks in the RAPIDO trial.[22] The final publications of these trials should show whether neoadjuvant oxaliplatin-based chemotherapy is beneficial if given for a prolonged period of time.

Oxaliplatin delivery was not randomised in our study and the results are based on unplanned analysis in the subgroups, which are not equal in their baseline characteristics. Many patients did not have a pelvic MRI. Moreover, the risk of type II error (false negative result) is high because the sample size was small. Therefore, the level of evidence for our finding is low. Hence, our results are useful only for hypothesis generation. However, a sensitivity analysis of the larger sample size provided results consistent with the main analysis, which strengthens our suggestion that the addition of oxaliplatin did not result in clinically meaningful improvement in long-term outcomes. Another limitation is the shorter follow-up time in the fluoropyrimidine-alone group than in the oxaliplatin group. Furthermore, it is unknown whether chemotherapy given for recurrences were similar in the two groups. The absence of quality control for the neoadjuvant treatment, surgery and pathology should also be acknowledged. The strength of our analysis is the treatment of the patients in the framework of the prospective study with rigorous protocol requirements for treatment and follow-up. Despite the above limitations, we believe that our findings are of value for clinical practice.

## 5. Conclusion

Our results do not support adding oxaliplatin to three cycles of consolidation chemotherapy delivered after short-course irradiation. However, the addition of oxaliplatin may be beneficial if the treatment goal is a watch-and-wait strategy for patients achieving clinical complete response.

### Declaration of Competing Risk

None

### Declaration of interest

None

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.rpor.2020.08.002.

## References

1. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. *Ann Oncol*. 2016;27:834–842, http://dx.doi.org/10.1093/annonc/mdw062.
2. Ciseł B, Pietrzak L, Michalski W, et al. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. *Ann Oncol*. 2019;30(8):1298–1303, http://dx.doi.org/10.1093/annonc/mdz186.
3. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. ESMO Guidelines Committee, Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv263, doi: 10.1093/annonc/mdy161.
4. Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol*. 2011;29:2773–2780. DOI: 10.1200/JCO.201034.4911.
5. Gérard J-P, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, et al. Comparison of Two Neoadjuvant Chemoradiotherapy Regimens for Locally Advanced Rectal Cancer: Results of the Phase III Trial ACCORD 12/0405-Prodige 2. *J Clin Oncol*. 2010;28:1638–1644. DOI: 10.1200/JCO.200925.8376.
6. Allegra CJ, Yothers G, O'Connell MJ, Beart RW, Wozniak TF, Pitot HC, et al. Neoadjuvant 5-Fu or Capecytabine plus Radiation with or without Oxaliplatin in Recatal Cancer Patients: A Phase III Randomised Clincal Trial. *J Nat Cancer Inst*. 2015:107, pii: djv248, DOI: 10.1093/jnci/djv248.
7. Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, et al. Neoadjuvant Modified FOLFOX6 With or Without Radiation Versus Fluorouracil Plus Radiation for Locally Advanced Rectal Cancer: Final Results of the Chinese FOWARC Trial. *J Clin Oncol*. 2019;37:3223–3233. DOI: 10.1200/JCO.18.0230.9.
8. Jiao D, Zhang R, Gong Z, Liu F, Chen Y, Yu Q, et al. Fluorouracil-based Preoperative Chemoradiotherapy With or Without Oxaliplatin for Stage II/III Rectal Cancer: A 3-year Follow-Up Study. *Clin J Cancer Res*. 2015;27:588–596. DOI: 10.3978/j.issn.1000-9604.2015.12.05.
9. O'Connell MJ, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, et al. Capecitabine and Oxaliplatin in the Preoperative Multimodality Treatment of Rectal Cancer: Surgical End Points From National Surgical Adjuvant Breast and Bowel Project Trial R-04. *J Clin Oncol*. 2014;32:1927–1934. DOI: 10.1200/JCO.201353.7753.
10. Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, et al. Preoperative Chemoradiotherapy and Postoperative Chemotherapy With Fluorouracil and Oxaliplatin Versus Fluorouracil Alone in Locally Advanced Rectal Cancer: Initial Results of the German CAO/ARO/AIO-04 Randomised Phase 3 Trial. *Lancet Oncol*. 2012;13:679–687. DOI: 10.1016/S1470-2045(12)7018.7-0.
11. Schmoll HJ, Haustermans K, Price T, Nordlinger B, Hofheinz R, Daisne J-F, et al. Preoperative Chemoradiotherapy and Postoperative Chemotherapy with Capecitabine and Oxaliplatin Vs. *Capecitabine Alone in Locally Advanced Rectal Cancer: Disease Free Survival at Interim Analysis. Ann Oncol*. 2014;25(Supplement 2):111. DOI: https://doi.org/10.1093/annonc/mdu193.17.
12. Valentini V, Gambacorta MA, Cellini F, Aristei C, Coco C, Barbaro B, et al. The INTERACT Trial: Long-term Results of a Randomised Trial on Preoperative Capecitabine-Based Radiochemotherapy Intensified by Concomitant Boost or Oxaliplatin, for cT2 (distal)-cT3 Rectal Cancer. *Radiother Oncol*. 2019;134:110–111. DOI: 10.1016/j.radonc.2018.11.023.
13. Hüttner FJ, Probst P, Kalkum E, Hackbusch M, Jensen K, Ulrich A, et al. Addition of Platinum Derivatives to Fluoropyrimidine-Based Neoadjuvant Chemoradiotherapy for Stage II/III Rectal Cancer: Systematic Review and Meta-Analysis. *J Natl Cancer Inst*. 2019;111:887–902, doi: 10.1093./jnci/djz081.
14. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27:3109–3116. DOI: 10.1200/JCO.200820.6771.
15. Wiśniowska K, Nasierowska-Guttmejer A, Polkowski W, et al. Does the addition of oxaliplatin to preoperative chemoradiation benefit cT4 or fixed cT3 rectal cancer treatment? A subgroup analysis from a prospective study. *Eur J Surg Oncol*. 2016;42:1859–1865, http://dx.doi.org/10.1016/j.ejso.2016.08.001.
16. Bujko K, Nasierowska-Guttmejer A, Wyrwicz L, et al. Neoadjuvant Treatment for Unresectable Rectal Cancer: An Interim Analysis of a Multicentre Randomized Study. *Radiother Oncol*. 2013;107:171–177, http://dx.doi.org/10.1016/j.radonc.2013.03.001.
17. Beyond TME Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. Br J Surg. 2013; 100:E1-33. DOI: 10.1002/bjs.9192_1.
18. Bonnetain F, Bosset JF, Gerard JP, Calais G, Conroy T, Mineur L, et al. What is the clinical benefit of preoperative chemoradiotherapy with 5FU/leucovorin for T3-4 rectal cancer in a pooled analysis of EORTC 22921 and FFCD 9203 trials: surrogacy in question? *Eur J Cancer*. 2012;48:1781–1790. DOI: 10.1016/j.ejca.2012.03.016.
19. Fokas E, Allgäuer M, Polat B, Klautke G, Grabenbauer GG, Fietkau R, et al. Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12. *J Clin Oncol*. 2019;37:3212–3222. DOI: 10.1200/JCO.19.0030.8.
20. Jin J, Liu S, Zhu Y, Wang W, Wang X, Wang J, et al. The Updated Results for the Phase 3 Study of 5×5Gy Followed By Chemotherapy in Locally Advanced Rectal Cancer (STELLAR trial). *Int J Radiat Oncol Biol Phys*. 2017;99:E157 (suppl; abstr2378).
21. Marco MR, Zhou L, Patil S, Marcet JE, Varma MG, Oommen S, et al. Consolidation mFOLFOX6 Chemotherapy After Chemoradiotherapy Improves Survival in Patients With Locally Advanced Rectal Cancer: Final Results of a Multicenter Phase II Trial. *Dis Colon Rectum*. 2018;61:1146–1155. DOI: 10.1097/DCR.0000000000001207.
22. Nilsson PJ, van Etten B, Hospers GA, Påhlman L, van de Velde CJ, Beets-Tan RG, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer–the RAPIDO trial. *BMC Cancer*. 2013;13:279. DOI: 10.1186/1471-2407-13-279.
23. Habr-Gama A, São Julião GP, Vailati BB, Sabbaga J, Aguilar PB, Fernandez LM, et al. Organ Preservation in cT2N0 Rectal Cancer After Neoadjuvant Chemoradiation Therapy: The Impact of Radiation Therapy Dose-escalation and Consolidation Chemotherapy. *Ann Surg*. 2019;269:102–107. DOI: 10.1097/SLA.0000000000002447.