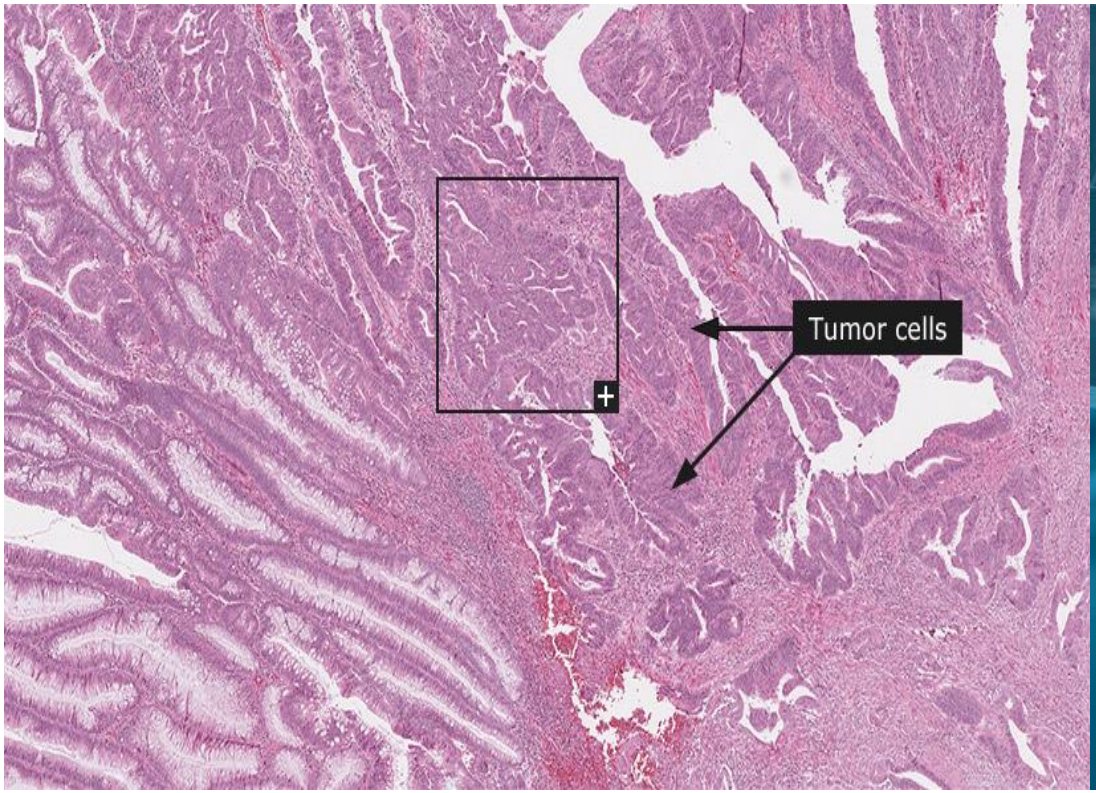
KCE REPORT 260

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

GUIDELINE ON THE MANAGEMENT OF RECTAL CANCER: UPDATE OF CAPITA SELECTA – PART 4: ADJUVANT THERAPY AFTER NEOADJUVANT THERAPY



KCE REPORT 260
GOOD CLINICAL PRACTICE

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GUIDELINE ON THE MANAGEMENT OF RECTAL CANCER: UPDATE OF CAPITA SELECTA – PART 4: ADJUVANT THERAPY AFTER NEOADJUVANT THERAPY

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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
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ABBREVIATIONS

ABBREVIATION	DEFINITION
AHRQ	Agency for Healthcare Research and Quality
AR	Abdominal resection
CI	Confidence interval
CRT	Chemoradiotherapy
CT	Computed tomography
ELRR	Endoluminal locoregional resection
EMVI	Extramural venous invasion
ERUS	Endorectal ultrasound
ESGE	European Society of Gastrointestinal Endoscopy
ESMO	European Society for Medical Oncology
FU	Fluorouracil
GDG	Guideline Development Group
GIN	Guidelines International Network
HR	Hazard ratios
IKNL	Integraal Kankercentrum Nederland
KCE	Belgian Health Care Knowledge Centre
LR	Local recurrence
LRFS	Local recurrence free survival
LTME	Laparoscopic total mesorectal excision
MA	Meta-analysis
MFS	Metastasis-free survival
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network

NICE	National Institute for Health and Care Excellence
NIHDI (RIZIV/INAMI)	National Institute for Health and Disability Insurance
OR	Odds ratio
OS	Overall survival
PET-CT	Positron emission tomography - computed tomography
PICO	Population-intervention-comparator-outcome
PROCARE	Project on Cancer of the Rectum
QoL	Quality of life
RCT	Randomised controlled trial
RQ	research question
RR	Risk ratio
SEER	Surveillance, Epidemiology and End Results
SR	Systematic review
TAE	Transanal excision
TEM(S)	Transanal endoscopic microsurgery
TME	Total mesorectal excision

SCIENTIFIC REPORT

WHEN SHOULD ADJUVANT CHEMOTHERAPY BE CONSIDERED IN PATIENTS WHO RECEIVED NEOADJUVANT RADIO(CHEMO)THERAPY?

1 INTRODUCTION

The question whether patients with rectal cancer, who have previously received neoadjuvant CRT and surgery, benefit from adjuvant chemotherapy remains uncertain. Therefore current guidelines recommend different strategies. The NCCN recommends that adjuvant treatment, preferably oxaliplatin based, should be considered for a maximum total duration of six months in patients with stage III (N0), stage I-IV (N1-2) or stage IV and/or locally unresectable or medically inoperable tumours, who were given neoadjuvant CRT and transabdominal resection. [1] The European Society for Medical Oncology (ESMO) states that for rectal cancer stage III (and 'high-risk' stage II) adjuvant chemotherapy can be given, even though the level of scientific evidence for sufficient benefit is much lower than for colon cancer.[2] Similarly, NICE recommends to consider adjuvant chemotherapy for patients with high‑risk stage II and all stage III rectal cancer in order to reduce the risk of local and systemic recurrence.[3] On the contrary, the Dutch guidelines by IKNL state that there is no indication for such treatment in rectal cancer.[4] Additionally, a recent trial suggests differences in effect of adjuvant chemotherapy after neoadjuvant chemotherapy depending on the type of chemotherapy used.[5]

The aim of this RQ is to assess the effect of adjuvant chemotherapy in patients with rectal cancer who were previously treated with neoadjuvant CRT and surgery compared with no adjuvant chemotherapy in terms of OS, DFS and quality of life QoL.

2 METHODS

A systematic literature search for SRs and RCTs was carried out in CENTRAL, MEDLINE and EMBASE on March 25th, 2015. Search strategies can be found in the Appendix. Additional hand searches were performed in reference lists of retrieved publications. SRs and RCTs that compared the effect of adjuvant chemotherapy with no adjuvant chemotherapy in patients who underwent curative resection for rectal cancer and had been treated with neoadjuvant chemotherapy or that compared different types of adjuvant chemotherapy were included. Trials that included both rectal and colorectal cancer were eligible if the results for rectal cancer patients were provided separately. Primary outcomes included DFS, OS and QoL in patients with non-metastatic rectal cancer of all stages. Non-randomised trials were not assessed.

From the RCTs the following information was extracted: basic patient characteristics (age, tumour stage), preoperative treatment, postoperative treatment and delivery form, tumour localisation with respect to the anal verge, accrual period, study design, timing of randomisation, follow-up period, results for OS, DFS and QoL and corresponding hazard ratios (HR) with 95% CI and p-values, relapse, side-effects/adverse events (see tables in Appendix). We expected to apply standard meta-analysis methods[6] to evaluate the overall effect of adjuvant chemotherapy on DFS and OS. The main outcome measure was the HR between the risk of event in the treatment arm (adjuvant chemotherapy) and the control arm (no adjuvant chemotherapy) with the 95% CIs used as a measure of estimate uncertainty. QoL assessments were included only if assessed by acknowledged QOL scoring systems such as SF-36 or EORTC-QLQ C-30.

3 EVIDENCE DESCRIPTION

3.1 Systematic reviews

Five recent reviews and meta-analyses were assessed in full text.[7-11] A flow-chart of the full study selection for SR is presented in the Appendix. None of these SRs were included for the reasons described below. A Cochrane review by Petersen et al.[8] published in 2012 assessed the effect of postoperative adjuvant in rectal cancer operated for cure. Although of high quality, this review was excluded because the results are based on trials were patients were assigned to adjuvant or no adjuvant chemotherapy after surgery mostly without having received neoadjuvant treatment. A review by Bujko et al. from 2010[9] included RCTs exploring adjuvant chemotherapy against observation in patient previously treated with preoperative CRT. Because we were aware of a number of more recently published trials not included in this review, we considered it outdated, excluded it and only used the reference list to identify potentially missed RCTs. Petrelli et al.[10] performed a SR, searched up to May 1st, 2014 and identified two RCTs (PROCTOR-SCRIPT trial,[12] CHRONICLE trial[13]), one pooled analysis of five RCTs and ten retrospective studies. This review was excluded due to considerable data inconsistencies and because several of the trials in the pooled RCT analysis (that was included as such) did not assess the correct comparison. However, because the search was performed recently, the reference list was assessed for potentially missed RCTs. We also assessed the pooled analysis by Valentini[11] that was included in the Petrelli review. This review was excluded due to the design used (nomograms for predicting local recurrence). Finally, Breugom et al.[7] performed a meta-analysis of individual patient data and retrieved individual patient data from four RCTs (the I-CNR-RT trial,[14] PROCTOR-SCRIPT trial,[12] CHRONICLE trial[13] and EORTC 22921 trial[15]) amounting to data from a total of 1 196 patients with (y)pTNM stage II or III disease. However, because the meta-analysis was based only on available individual data not all relevant trials were included e.g. individual OS data from the QUASAR trial could not be obtained and no sensitivity analysis was performed assessing the impact of the lack of available study data. This review was excluded because the authors' pooled studies with very diverse chemotherapy regimens and the relevance of the results for current practice is therefore unclear.

3.2 Randomized controlled trials

Fourteen RCTs were selected based on title and abstract. Five of these were duplicates and are not described further. Nine trials were assessed in full text. A flow-chart of the full study selection for RCTs is presented in the Appendix. A Chinese study,[16] was excluded because it was available only in abstract form, suffered from severe methodological issues and failed to state which type of chemotherapy was used. A German trial was excluded because it compared different types of preoperative chemotherapy.[17] Finally, one study was excluded because it was not a randomized trial.[18]

Six RCTs were included. These RCTs used a variety of chemotherapy regimens and delivery forms. Four of the included trials, i.e. the EORTC 22921 trial,[15] the QUASAR trial,[19] the I-CNR-RT trial[14] and the PROCTOR-SCRIPT trial,[12] assessed adjuvant fluorouracil (FU)-based chemotherapy compared with observation. The CHRONICLE trial[13] used a combination of adjuvant FU-based chemotherapy delivered orally (capecitabine) and infusion delivered oxaliplatin and compared this treatment with an observation group. Finally, the ADORE trial[5] compared a group receiving bolus injections of FU and leucovorin with a group receiving oxaliplatin infusions and bolus injections of FU and leucovorin. The six included trials and their findings are described in evidence tables (see Appendix).

3.3 Overall and disease-free survival

Because not all the identified trials were included in previously published MAs we intended to conduct a MA for the main outcomes. However, pooling was considered inappropriate by the GDG due to the heterogeneous way studies were conducted, with differences in inclusion criteria and a large variety in administration forms and dosages of adjuvant chemotherapy. Some studies used a suboptimal and/or outdated form of adjuvant therapy. The ADORE trial[5] used a more optimal administration form and dose of chemotherapy but did not include an observation group.

The individual trials generally reported a small and non-significant effect of adjuvant chemotherapy for OS and for DFS. The 5 yr OS reported by EORTC 22921 trial,[15] QUASAR trial[19] I-CNR-RT trial[14] and PROCTOR-SCRIPT trial[12] ranged from 66.9% to 80.4% following adjuvant chemotherapy and from 63% to 74% with observation. Three studies[12, 14, 15] reported % vs a 5 yrs DFS ranging from 58% to 63.6% following adjuvant chemotherapy and from 52% to 60.8% with observation. The CHRONICLE trial [13] reported a 3 yrs OS of 78% in the chemotherapy group and 74% in the observation group. The difference in 3 yrs DFS was not significant: 78% vs. 71% (p=0.56). Outcomes tend to be better after chemotherapy but given the lack of statistical significance the results from the individual studies are inconclusive can regarding a potential benefit of adjuvant chemotherapy in rectal cancer patients after neoadjuvant treatment and surgery in terms of OS or DFS. According to GRADE the level of evidence was very low (see profile table in Appendix).

However, some patients may respond better to chemotherapy. A subgroup analysis in the EORTC study shows that patients responding to preoperative chemotherapy (yp T0-T2) had a significant advantage when treated with adjuvant chemotherapy, compared to patients who did not receive adjuvant chemotherapy in terms of both OS (HR=0.64; 95%CI: 0.42-0.96) and DFS (HR=0.63; 95%CI: 0.44-0.90.[15] Such subgroups could not be extracted from the other publications.

3.4 Quality of life

QoL was not measured[12-15] or only in selected patients.[19]

4 CONCLUSIONS AND RECOMMENDATIONS

Conclusions

- The available evidence on the effect of adjuvant chemotherapy is based on different chemotherapy regimens.
- RCT s demonstrate no significant benefit on 5 yr OS and 5 yr DFS of adjuvant chemotherapy for patients with rectal cancer who received neoadjuvant chemotherapy (low level of evidence)
- A subgroup of patients who responded to neoadjuvant chemotherapy may benefit from adjuvant chemotherapy.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Although the GDG did not find it appropriate to extrapolate evidence from colorectal cancer to rectal cancer; in clinical practice similar treatment regimens are often used. Better criteria are needed to define a subgroup of patients who may benefit from adjuvant chemotherapy. ESMO consensus July 2015 states the following: • based on colon cancer trials and based on the increased relevant of distant metastases as cause of treatment failure and death, adjuvant chemotherapy should be considered for stage II and III patients • the type of neoadjuvant RT does not influence this recommendation
Quality of evidence	RCTs used different treatment regimens Two studies closed prematurely due to poor accrual [12, 13]- none of the studies obtained sufficient power.
Costs (resource allocation)	Cost was not considered in this study
Patients values and preferences	The literature suggests that most patients judge a moderate survival benefit to be sufficient to make adjuvant therapy worthwhile[20]

Recommendations

- Based on the current available evidence, no recommendation can be made in favour or against the use of adjuvant chemotherapy in patients with rectal cancer who received RCT.

Since no recommendation was made no strength of recommendation was assigned.

APPENDIX

Table 1 – Evidence on adjuvant chemotherapy from primary studies

Study	Patients	Design	Results	Comments
EORTC 22921 (Bosset, 2006) [15]	1 011 patients younger than 81 yrs, clinically staged T3–4 tumours within 15 cm from the anal verge; accrual 1993–2003. Median follow up for the first publication providing 5 yrs results was 5.4 yrs.	2 x 2 factorial randomisation to preoperative radiotherapy alone versus preoperative CRT (radiation with bolus 5-FU and leucovorin) and postoperative CT (4 courses of 5-FU and leucovorin every 21 days) versus no postoperative chemotherapy; patients were stratified according to the distance from the tumour to the anal verge. All patients received surgery.	**5-yr OS:** adjuvant chemotherapy compared to no adjuvant chemotherapy; OS was 67% in the postoperative chemotherapy group and 63% in the control group, HR = 0.85 (95% CI 0.68–1.04), p = 0.12 **5-yr DFS:** 58% in the postoperative chemotherapy group and 52% in the control group, HR = 0.87 (95% CI 0.72–1.04), p = 0.13. **Side-effects** There was no significant difference in the incidence of late side effects among the 2 treatment groups.	Trial did not find a statistically significant benefit of adjuvant chemotherapy regardless of whether patients had been given preoperative CRT or preoperative radiation alone. In subgroup analysis, patients responding to preoperative treatment (yp T0-T2) had a significant advantage if received adjuvant chemotherapy (compared to patients who did not receive adjuvant chemotherapy) in terms of both OS (HR=0.64; 95%CI: 0.42-0.96) and DFS (HR=0.63; 95%CI: 0.44-0.90) In a companion paper, results reported at 10 yrs follow-up were similar to those at 5-yrs.
PROCTOR-SCRIPT (Breugom, 2014) [12]	470 patients aged ≥ 18 yrs with rectal adenocarcinoma stage T2-T3, located within 15 cm from anal verge; patients received pre-operative CRT and surgery; accrual 2000-2013 (trial closed due to poor accrual). Median of survivors was 5 yrs.	Patients were randomised to observation or adjuvant chemotherapy and stratified according to centre, residual tumour (R0/R1), time between last irradiation and surgery and preoperative treatment.	**5-yr OS:** Survival rates was 79.2% in the observation group and 80.4% in the chemotherapy group (HR 0.93, 95% CI 0.62–1.39; p= 0.73) **5-yr DFS:** 55.4% for the observation group and 62.7% for the chemotherapy group (HR 0.80, 95% CI 0.60–1.07; p = 0.13) **5-yr overall recurrence:**	The per protocol analysis did not differ significantly from the intention to treat analysis

			Cumulative incidence for overall recurrence was 40.3% in the observation group and 36.2% in the chemotherapy group (HR 0.88, 95% CI 0.64–1.20; p = 0.43)	
I-CNR-RT (Sainato, 2014) [14]	655 patients younger than 76 yrs with locally advanced rectal cancer, clinically staged T3–4, tumours within 15 cm from anal verge; all patients had preoperative CRT (radiation with bolus 5-FU and leucovorin); accrual 1992-2001; median follow-up was 63.7 mo	Randomisation to postoperative chemotherapy (six courses of bolus 5-FU and leucovorin every 3 weeks) versus no postoperative chemotherapy	**5 yr OS:** no statistically significant difference in OS (66.9% in the postoperative chemotherapy group versus 67.9% in the control group, p=0.879) (HR 1.04, 95% CI 0.77-1.41) **5-yr DFS:** no statistically significant difference in disease-free survival (63.6% in the postoperative chemotherapy group versus 60.8% in the control group, p=0.416) (HR 0.98, 95%CI 0.72-1.32) **Relapse** (LR and DM): no statistically significant difference in LR (7.4% in the postoperative chemotherapy versus 8.7% in the control group) no statistically significant difference in DM (24.3% in the postoperative chemotherapy versus 23.9% in the control group)	Out of the 296 patients randomized in Arm B and expected to receive adjuvant chemotherapy, 83 (28%) never started the treatment, 40 (13.5%) completed 2 cycles, and 173 (58.4%) received cycles 3 to 6. Omission of chemotherapy was due to toxicity, disease progression and in most cases to individual refusal. No difference was found between the 2 arms in the OS and DFS values, analysed according to the pathological stage, the presence of involved nodes and the type of surgery.
CHRONICLE (Glynne-Jones, 2014) [13]	113 patients over 18 yrs with locally advanced rectal cancer (all tumour stages) located within 15 cm from the anal verge; patients received pre-operative chemoradiation (min 45Gy) and fluoropyrimidine based followed by surgery; accrual 2004-2008; median follow-up was 44.8 mo	After surgery patients were randomised to either chemotherapy (a combination of capecitabine and oxaliplatin,6 courses) or to observation	**3-yr OS:** The 3-yr OS for XELOX patients (adjuvant group) were 89% versus 88% in the observation group (HR for OS = 1.18; 95% CI 0.43–3.26; p = 0.75). **3-yr DFS:** The 3-yr DFS rate was 78% with XELOX patients and 71% with observation (HR for DFS = 0.80; 95% CI 0.38–1.69; p = 0.56]. **Side-effects (toxicity):**	Of the 800 patients planned for enrolment only 113 patients were randomised after 4 yrs, and *the trial was terminated* based on poor accrual, thus trial is underpowered. Only 48% of patients assigned to postoperative chemotherapy completed all planned 6 cycles. The imbalances on some of the baseline characteristics is due to change because patients were stratified using nodal status and surgeon (82

			Fifty (92.6%) of XELOX patients received at least one cycle of treatment— authors define these as the safety population. Twenty (40.0%) of the safety population reported grade 3 or higher toxicity. Three (6.0%) reported a grade 4 toxicity (sensory neuropathy (n = 2) and diarrhoea (n = 1)). There was one treatment-related death from diarrhoea. Nine patients reported an adverse events during follow-up. Six XELOX patients reported 8 late toxicities: bowel obstruction (n = 1), malignant fistula (n = 1), neuropathy (n = 2), impaired bladder function (n = 1), pulmonary embolism (n = 1), pain (n = 1), and blepharospasm (n=1). Three patients in the observation arm reported 3late toxicities: angina (n = 1), back pain (n = 1), and poor bowel control (n = 1).	surgeons to 113 patient created many randomisation “cells”)
QUASAR (Quasar group, 2007) [19]	Uncertain indication for chemotherapy (mostly stage II); colon cancer (2291 patients=71%) and rectal cancer (948 patients=29%); of the rectal cancer patients, 203 had preoperative radiotherapy and 264 had postoperative radiotherapy; stratification was carried out with respect to tumour site, preoperative radiotherapy or not and planned postoperative radiotherapy or not; for patients receiving preoperative radiation, the schedule of radiation and whether chemotherapy was simultaneously added to radiation as well clinical and pathological stages	Randomisation to postoperative chemotherapy (5-FU and leucovorin for 6 mo, some patients also received levamisole) versus no postoperative chemotherapy	**5-yr OS:** 78% in the postoperative chemotherapy group and 74% in the control group, HR of death 0.77 (95% CI 0.54–1.00), p = 0.05 **Recurrence:** HR for recurrence 0.68 (95% CI 0.52–0.88), p = 0.004	Only 20% of rectal cancer patients received preoperative radiation. The benefit oin terms of OS or reduction of incidence of recurrence was much the same irrespective of whether patients were given preoperative radiation, postoperative radiation, or no radiation

	were not given: Accrual 1993–2003; Median follow-up was 5.5 yrs;			
ADORE (Hong, 2014) [5]	Patients 18 yrs or older with histologically confirmed adenocarcinoma of the rectum (tumour less than 12 cm from the anal verge or below peritoneal reflection), pathological stage II or III disease with no microscopic residual tumour. All had undergone preoperative chemotherapy with fluoropyrimidine monotherapy followed by total mesorectal excision. Median follow-up was 38.2 mo (IQR 26.4–50.6)	Both groups (n=321) were randomised to chemotherapy, one group received FU and leucovorin (n=161) and the other group oxaliplatin (FOLFOX) (n=160)	**3-yr OS:** OS was 85.7% (95% CI 80.3–91.1) in the FU plus leucovorin group and 95.0% (91.6–98.4) in the FOLFOX group; HR 0.46 (95%CI 0.21 - 0.97) **3-yr DFS:** DFS was 71.6% (95% CI 64.6–78.6) in the FOLFOX group and 62.9% (95% CI 55.4–70.4) in the FU plus leucovorin group (hazard ratio 0.657, 95% CI 0.434–0.994; p=0.047). **QoL:** **EORTC-QLQ-C30 at** **3-yrs:** Appetite loss scale had deteriorated in the FOLFOX group with a more than 10-point difference from baseline (p=0·0002). The chemotherapy side-effects scale had also deteriorated from baseline in the FOLFOX group (p=0·012); score change was less than ten points (threshold for clinically significant difference). No significant difference between groups with in changes in global health status or other functioning and symptom scales. **Adverse events/side-effects:** Any grade neutropenia, thrombocytopenia, fatigue, nausea, and sensory neuropathy were significantly more common in the FOLFOX group. No significant difference in the frequency of these events at grade 3 or 4. The most common grade 3 or worse adverse	141 (95%) of 149 patients in the FU plus leucovorin group and 141 (97%) of 146 in the FOLFOX group completed all planned cycles of adjuvant treatment.

													events were neutropenia (38 [26%] of 149 patients in the FU plus leucovorin group vs 52 [36%] of 146 patients in the FOLFOX group), leucopenia (eight [5%] vs 12 [8%]), febrile neutropenia (four [3%] vs one [<1%]), diarrhoea (four [3%] vs two [1%]), and nausea (one [<1%] vs two [1%]).

Table 2 – Grade table: Should adjuvant CT (fluorouracil and oxaliplatin) be used for rectal cancer after neoadjuvant therapy and surgery?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant CT (flouroracil and oxaliplatin)	Control	Relative (95% CI)	Absolute		
Overall survival (follow-up 3 yrs; assessed with: HR (direct evidence))												
1	randomized trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	-	- 0%	HR 1.18 (0.43 to 3.26)	- -	⊕OOO VERY LOW	IMPORTANT
Disease-free survival (follow-up 3 yrs; assessed with: HR (direct evidence)												
1	randomized trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	- -	- 0% 0%	HR 0.80 (0.38 to 1.69)	- - -	⊕OOO VERY LOW	CRITICAL

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