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Preoperative concurrent chemoradiotherapy (CT-RT) improves local control in T3–4 rectal cancers. Results of the FFCD 9203 randomized trial

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Background: This trial was evaluating the potential benefit of concurrent chemoradiotherapy (CT) on a preoperative (preop.) schedule.
Material and methods: Eligibility criteria: resectable adenocarcinoma T3–4 Nx M0, accessible to digital examination <75 years, written informed consent. Randomization between RT alone (45 Gy/25 fractions/5 week) and CT-RT using bolus 5FU (350 mg/m^2) and Folinic Acid (FA) (20 mg/m) days 1–5 on week 1 an d5. Surgery was performed after an interval of 3–10 weeks. Adjuvant chemotherapy with 4 cycles of FU-FA was given to all patients. Primary end point was 5 year overall survival (0.5%) the hypothesis was to increase 0.5 from 52% to 62% with CT-RT.
Results: Between 1993/2003 out of 762 included patients 733 were eligible. Patients characteristics were well-balanced between arms. median age 63 years, T3:89% median time to surgery 5.3 weeks. Adjuvant FU-FA was given to 73% of pts in both arms. Median follow up time (May 2005) was 74 months. Results are given in Table below.
Conclusion: Preoperative CT-RT increases moderately acute toxicity, significantly improves local control but has no influence on sphincter preservation and survival. Preoperative CT-RT is recommended as standard treatment for the majority of T3–4 rectal cancer.

	RT (363)	CT-RT (370)	p. value
Preoperative toxicity grade 3–4	2.7%(10)	14.6% (54)	<0.05
Sterilisation operative sp.	3.7% (13)	11.7% (40)	<0.05
Sphincter saving surgery	51.7% (182)	52.6% (184)	NS
5 year local recurrence	16.5% (47)	8% (24)	S
5 year overall survival	66.6%	67.8%	NS

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Patients with R0 resection of T3–4 rectal cancer after preoperative radio- or radiochemotherapy: does anybody benefit of post-operative LV/5-FU chemotherapy? Further results of EORTC trial 22921

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Background: EORTC trial 22921 compared post-operative chemotherapy (postop-CT) with LV/5-FU to no adjuvant treatment in a 2-by-2 factorial trial with another randomization between preoperative radio- and radio-chemotherapy in patients with potentially resectable T3–4 rectal cancer. The trial showed a significant increase of the downstaging with preoperative radiochemotherapy but failed to demonstrate a significant impact of postop-CT on progression-free or overall survival, although a late difference seemed to emerge at around respectively 2 and 5 years after start of pre-operative treatment. We further explored the data with the aim of refining our understanding of the study results.
Material and methods: We considered 785 of the 1011 randomized patients in whom a R0 tumor resection was achieved and who were M0 at surgery. Using meta-analytic methods, we investigated the homogeneity of the effect of postop.-CT on the time to relapse or death after surgery (DFSs) in patient subgroups defined by pre-operative treatment and pathological tumor size (pT).
Results: Although there was no statistically significant impact of postop-CT on DFSs for the whole group (P > 0.5), the treatment effect was differed significantly between the pT1–2 and the pT3–4 patients (heterogeneity P = 0.009): only the pT1–2 patients seemed to benefit from postop-CT (P = 0.011). This effect seemed further influenced by the type of pre-operative treatment (heterogeneity P = 0.017). It appeared that only the patients in whom downstaging was obtained by pre-operative radiotherapy alone benefited significantly from postop-CT (HR=0.43; 95CI: 0.24–0.78; P = 0.005) whereas the benefit was only marginal if downstaging had been obtained by pre-operative radio-chemotherapy (HR=0.80; 95CI: 0.51–1.25, P = 0.328). Patients with pT3–4 did not benefit from postop-CT (P = 0.297). The same pattern was observed for overall survival.
Conclusions: The exploratory analyses suggest that only good prognosis patients (pT1–2) benefit from post-operative chemotherapy. This could explain why in the primary trial results, the progression-free survival and overall survival diverge only after the poor prognosis patients (pT3–4) have failed. The data further suggest that the patients in whom down-staging was obtained by pre-operative radiotherapy alone significantly benefit from postoperative chemotherapy whereas the benefit is not obvious if it was obtained by radio-chemotherapy. Patients with no downstaging did not benefit.

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An international phase II study of Capecitabine, Oxaliplatin, Radiotherapy and Excision (CORE) in patients with MRI-defined locally advanced rectal adenocarcinoma. Interim results

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Background: The CORE study aimed at evaluating the feasibility and efficacy of preoperative weekly oxaliplatin, capecitabine and concomitant radiotherapy (XELOX-RT) followed by TME surgery then adjuvant XELOX in patients with MRI-defined locally advanced rectal cancer. The primary efficacy endpoint was pCR rate.
Methods: MRI inclusion criteria were: tumour beyond mesorectal fascia, tumour $\leqslant$2 mm from mesorectal fascia or T3 tumour <5 cm from anal verge. Chemoradiation consisted of 45 Gy RT (1.8 Gy/dose) 5 days a week for 5 weeks, weekly oxaliplatin 50 mg/m^2 and capecitabine 825 mg/m^2 twice a day, each day of radiation only. Surgery had to be performed 6–8 weeks after completion of XELOX-RT. Patients achieving R0 R1 resection were planned to receive XELOX for 6 cycles. Central MRI and pathological review was planned.
Results: At the time of this analysis, efficacy data on 52 patients out of 87 enrolled are available. Baseline MRI staging showed: 7 T2, 4 T3a, 11 T3b, 17 T3c, 9 T3d and 4 T4. According to central review MRI, the radiological response rate (RECIST) was 73% (4 CRs, 34 PRs). 51 patients underwent surgery (36 low anterior, 14 abdomino-perineal TME and 1 anorectal excision). Using Quirke methodology, R0 (circumferential resection margins >1 mm) rate was 80% (n = 41). Pathological downstaging (ypT0-T2N0) rate was 25% (n = 13). After stringent analysis, pCR rate was 16% (n = 8). According to tumor regression grading, excellent response was noted in 37% and poor response in 61%. Preoperative safety data are available for 73 patients. The most common Grade 3/4 event was diarrhoea 16%. Sensory neuropathy incidence was 1% (G3), neutropenia 1% (G3), hand–foot syndrome 1% (G3). Data on treatment compliance are available for 68 patients, where 60 (88%) received full dose of RT without interruption and more than 80% of the planned chemotherapy dose. RT dose reduction was related to toxicity in only 4 patients in which XELOX-RT had to be stopped after 4 weeks due to diarrhoea (n = 3) or G3 anorexia and neutropenia (n = 1). There were no deaths under treatment.
Conclusion: This international study demonstrates significant tumour regression and a high rate of R0 resection using a CRT regimen of weekly preoperative oxaliplatin, 5 day/week capecitabine and 45 Gy RT with acceptable toxicity. The use of MRI-defined entry criteria and the Quirke pathological assessment is an essential component of this study and for future phase III trials. Updated results will be presented.