Neoadjuvant Treatment Strategies: Advanced Radiation Alternatives

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Abstract

Keywords

- rectal cancer
- chemoradiation therapy
- short course
- long course
- IMRT

Long-course chemoradiation therapy (CRT) has been the standard approach for locally advanced rectal tumors. Neoadjuvant CRT is associated to improved local disease control, with less toxicity when compared with adjuvant CRT, as well as the chance for pathologic complete response. The CRT regimens have improved over the past years. This article will examine selected controversies, including novel chemoradiation regimens, duration of radiation (short vs. long course), and radiation techniques such as intensity-modulated radiation therapy (IMRT).

The most common neoadjuvant therapy for uT3 to T4 and/or node-positive clinically resectable rectal cancer is chemoradiation followed by surgery. Patients who received preoperative therapy in the German Rectal Cancer phase III trial had a significant decrease in the rates of local failure, acute toxicity, chronic toxicity, and a significant increase in the rate of sphincter preservation in patients who were felt to need to undergo abdominoperineal resection (APR) before treatment.^{1,2}

This article will examine selected controversies, including novel chemoradiation regimens, duration of radiation (short vs. long course), and radiation techniques such as intensity-modulated radiation therapy (IMRT).

Novel Chemoradiation Regimens

Both cytotoxic and targeted chemotherapeutic agents have been incorporated into preoperative chemoradiation regimens. Many of the phase I/II regimens report higher pathologic complete response (pCR) rates compared with historical rates observed with fluorouracil (5-FU) alone.

Phase III Trials

Five randomized trials have examined the impact of addition of oxaliplatin to 5-FU or capecitabine-based chemoradiation on response rates and acute toxicity in patients with cT3–4 and/N+ rectal cancer (►Table 1). The STAR-01 trial randomized 747 patients to preoperative chemoradiation with

50.4 Gy + continuous infusion (CI) 5-FU +/- oxaliplatin (60 mg/m² weekly).³ There was a significant increase in grade 3+ toxicity with oxaliplatin (24 vs. 8%, $p < 0.001$) with no improvement in the pCR rate (15 vs. 16%). In the ACCORD 12/0405 PRODIGE trial, 598 patients were randomized to preoperative chemoradiation with 50.0 Gy plus capecitabine + oxaliplatin (CAPOX) versus 45.0 Gy plus capecitabine.⁴ There was a similar significant increase in grade 3+ toxicity with oxaliplatin (25 vs. 11%, $p < 0.001$) with no improvement in the pCR rate (19 vs. 14%). Oxaliplatin did not improve 3-year local recurrence (6 vs. 4%) or survival (88 vs. 83%).⁵

The NSABP R-04 trial was a 4-arm trial of CI 5-FU versus capecitabine-based preoperative chemoradiation (50.4 Gy) with or without oxaliplatin.⁶ A total of 1,606 patients with cT3 and/or N+ disease were randomized. The addition of oxaliplatin (to either 5-FU or capecitabine) was associated with a significantly higher incidence of grade 3+ diarrhea (15 vs. 7%, $p = 0.0001$) with no improvement in the incidence of pCR (21 vs. 19%) or sphincter-sparing surgery (60 vs. 64%).

The German CAO/ARO/AIO-04 randomized 1,265 patients with cT3–4 and/or N+ disease to the preoperative arm of CAO/ARO/AIO-94 (50.4 Gy + 5-FU) versus 50.4 Gy/5-FU + oxaliplatin (50 mg/m² weekly).^{1,2} In contrast with the STAR-01, ACCORD, and NSABP R-04 trials, patients who received oxaliplatin-based chemoradiation had a significant improvement in pCR (17 vs. 13%, $p = 0.031$) and no corresponding

Table 1 Oxaliplatin-based preoperative chemoradiation: phase III randomized trials

Trial/Treatment	# Pts	RT (Gy)	% pCR	% LF	% Gr 3 + toxicity	% 3 y survival
STAR ³						
CI 5-FU	379	50.3/1.8	16	–	8	–
CI 5-FU/oxaliplatin	368	50.4/1.8	15	–	24 (<0.001)	–
ACCORD12/ 0405 PRODIGE ^{4,5}						
Capecitabine	295	45/1.8	14	6 (3 y) 11	–	
Capecitabine/oxaliplatin	291	50/1.8	19	4	25 (<0.001)	–
NSABP R-04 ⁶						
CI 5-FU or capecitabine	622	50.4/1.8	19	–	7	–
CI 5-FU or capecitabine + oxaliplatin	631	50.5/1.8	21	–	15 (0.0001)	–
CAO/ARO/AIO-94 ^{1,2}						
CI 5-FU	637	50.4/1.8	13	–	20	71
CI 5-FU/oxaliplatin	628	50.4/1.8	17 ($p = 0.031$)	–	24	76 ($p = 0.03$)

Abbreviations: CI, continuous infusion; FU, fluorouracil; Gr, grade; LF, local failure; pCR, pathologic complete response rate; Pts, patients; RT, radiation dose/fraction size.

increase in acute grade 3+ toxicity (23 vs. 22%). There was also a corresponding significant increase in the 3-year disease-free survival (DFS, 76 vs. 71%, $p = 0.03$). The preliminary results of the fifth trial (PETACC-6) did not result in any improvement in tumor downstaging or anal sphincter preservation.

Since four of the five randomized trials reported an increase in acute toxicity with no benefit in the pCR rate, the current standard is not to include oxaliplatin with 5-FU/capecitabine-based preoperative chemoradiation regimens. However, local control and survival data for all the trials are not available, and this recommendation may need to be modified once these data are reported.

Phase I/II Trials

Other cytotoxic agents have been explored. The oral agent, S-1, has been combined with preoperative radiation therapy. A recent phase II trial from Jung et al reported similar acute toxicity as 5-FU-based long-course chemoradiation, but no increase in the pCR rate was observed.⁷ The SHOGUN trial of preoperative 50.4 Gy plus S-1 (80 mg/m²/day $\times$ 5) + oxaliplatin reported a 11% grade 3+ toxicity and a 27% pCR rate in 45 patients.⁸

When S-1 (60 mg/m²/day) was combined concurrently with 5 Gy $\times$ 5, retrospective data revealed acceptable grade 3+ toxicity.⁹ The mTOR inhibitor, rapamycin, was delivered 1 week prior to 5 Gy $\times$ 5; the toxicity was acceptable but the pCR rate was only 3%.¹⁰

The role of targeted biological agents, such as bevacizumab and cetuximab, is being defined. Phase I/II trials using preoperative chemoradiation with capecitabine and oxaliplatin (CAPOX) + bevacizumab revealed pCR rates of 18 to 24%.^{11,12} Two trials combining bevacizumab with preoperative folinic acid (leucovorin)–fluorouracil (5-FU)–oxaliplatin (FOLFOX)¹³ or capecitabine-based chemoradiation¹⁴ were stopped early due to excessive toxicity.

Although the report from Heidelberg of capecitabine–irinotecan (CAPEIRI)-based chemoradiation reported a pCR rate of 25%,¹⁵ other trials combining chemoradiation with cetuximab plus 5-FU, capecitabine, or CAPOX have more limited rates of 5 to 12%.^{16,17}

Patient selection for treatment based on KRAS expression is useful in patients with metastatic colorectal cancer.¹² Updated results from the neoadjuvant phase II EXPERT-C rectal cancer trial (50.4 Gy/CAPOX/cetuximab) revealed a survival benefit from the addition of cetuximab in a subset of patients with KRAS wild type versus mutant (92 vs. 65% 3-year survival, $p = 0.02$).^{18,19} Interestingly, the primary endpoint of the trial (pCR) was not changed (11 vs. 9%). A follow-up analysis reported that the molecular marker, rs61764370, could predict response²⁰ and the intensified chemoradiation strategy improved tumor-related symptoms and did not have a significant detrimental impact on quality of life.²¹ As an alternative, the SAAK 4/07 trial used panitumumab-based chemoradiation in patients with KRAS wild-type cancers.²²

The RTOG has reported two phase II randomized trials. The first, RTOG 0012, enrolled 106 patients who received preoperative chemoradiation with PVI 5-FU plus twice-a-day irradiation compared with FOLFIRI plus conventional once daily radiation. There were no significant differences in the rate of pCR (30 vs. 26%), local recurrence (16 vs. 17%), and a corresponding decrease in overall 5-year OS (61 vs. 75%), respectively.²³ Grade 3+ toxicity rates were 42 and 55%, respectively.

The second RTOG trial compared preoperative chemoradiation with CAPEIRI versus CAPOX in 101 patients with cT3–4 disease (RTOG 0247).²⁴ Although not statistically significant, patients who received CAPOX had a higher pCR rate (21 vs. 10%) with similar hematologic (4 vs. 8%) and nonhematologic toxicity rates (29 vs. 24%). Neither of these preoperative regimens were moved into phase III.

Short-Course versus Long-Course Chemoradiation

Short-course radiation (5 Gy $\times$ 5) was established as a standard therapy by the Dutch CKVO and Swedish trials.^{25,26} Chemoradiation was established as a standard therapy by the German Rectal Cancer Trial CAO/ARO/AIO-94.^{27,28} These two trials could not be directly compared, since patients selected for treatment with short course included patients with cT1–3 disease, whereas 95% of the patients in the German trial had stage cT3 and/or N+ disease. Recently, randomized trials of short-course radiation therapy have included patients with stages cT3 and/or N+, thereby allowing a more relevant comparison between these two approaches.

Historically, short-course radiation therapy has not been recommended for patients with cT3 and/or N+ disease. This is due to its lack of sphincter preservation, inability to safely combine it with adequate doses of systemic chemotherapy, and associated acute toxicity.²⁹ However, these shortcomings may be mitigated by increasing the interval between the completion of radiation and surgery as well as delivering chemotherapy sequentially, as opposed to concurrently, with radiation.

Increasing Interval between Short-Course Radiation and Surgery

Investigators have been reluctant to recommend short-course radiation if the goal of preoperative therapy is to increase the chance of sphincter preservation. The Stockholm III trial is examining if increasing the interval between radiation and surgery improves sphincter preservation and reduces toxicity. Patients are randomized to 5 Gy $\times$ 5 followed by surgery 1 week later versus 5 Gy $\times$ 5 followed by surgery 4 to 8 weeks later versus 2 Gy $\times$ 25 (50 Gy) followed by surgery 4 to 8 weeks later. An interim analysis revealed that the pCR rate was increased in the short-course radiation arm when the delay to surgery was 4 to 8 weeks versus 1 week (2 vs. 12%, $p = 0.001$).³⁰ An additional interim analysis reported a significant increase in grade 3+ postoperative complications in patients who received 5 Gy $\times$ 5 followed by surgery 1 week later (53%) versus either 5 Gy $\times$ 5 (39%) or 50 Gy (41%).³¹ Final results are pending.

Addition of Sequential Chemotherapy

Due to its large fraction size, it is not recommended to combine short-course radiation with concurrent chemotherapy. The KROH 10–01 trial, reported by Yeo and colleagues, treated 73 patients with cT3–4 disease with 5 Gy $\times$ 5 using IMRT and concurrent chemotherapy (a modified regimen of 5-FU 400 m² and leucovorin 20 mg/m²) followed by surgery 4 to 8 weeks later.³² The pCR rate was only 1.4% and the acute grade 3+ toxicity was 38%. Given these suboptimal results, sequential chemotherapy, either before or after short course radiation, may offer a more favorable outcome.

The sequential approach is based on data from Garcia-Aguilar and colleagues in patients treated with chemoradiation.³³ They reported a randomized phase II trial of 144 patients with cN+ rectal cancer who received either pre-

operative chemoradiation (50.4 Gy + continuous infusion 5-FU) followed by surgery 6 weeks later or initial chemoradiation, and if there was a clinical response, mFOLFOX6 was followed by surgery 11 weeks later. The pCR rate was increased in the mFOLFOX arm (25 vs. 18%) with no associated increase in postoperative complications (40% in each arm). These preliminary data suggested that delivering additional chemotherapy and delaying surgery in patients who respond to preoperative chemoradiation were not detrimental to the response or surgical complication rates.

The Dutch Colorectal Group has tested the role of sequential chemotherapy following short-course radiation. A total of 50 patients with primary rectal cancer (8% T2, 76% T3, 16% T4) and synchronous resectable metastasis (84% liver, 10% lung, 6% both) were enrolled into a phase II trial of short-course radiation followed 2 weeks later by six cycles of CAPOX + bevacizumab.³⁴ After a 6 to 8 weeks rest, they underwent resection of the primary and resection and/or ablation of the metastasis. For the total patient group, 72% had a R0 resection at all sites; however, the 2-year relapse rate was 64%. The overall 2-year survival was 80%. Limiting the analysis to the pelvis, 26% achieved a pCR and with a median follow-up of 32 months, the local recurrence rate was 6%.

This approach serves as the experimental arm of the Dutch RAPIDO phase III trial. Eligibility includes at least one of the following criteria on pelvic magnetic resonance imaging (MRI): overgrowth to an adjacent organ or structure, cT4b, extramural vascular invasion (EMVI +), N2, MRF +, enlarged lateral nodes, or > 1 cm (lat LN +). Patients are randomized between short course 5 $\times$ 5 Gy followed by six cycles of CAPOX chemotherapy and surgery versus long-course chemoradiation followed by surgery and eight cycles of postoperative CAPOX. The primary endpoint is 3 years DFS and data are pending.

In a US pilot trial, 44 evaluable patients were treated with short-course radiation followed by sequential chemotherapy.³⁵ They received five fractions (25 Gy to the involved mesorectum and 20 Gy to the pelvic nodes) followed by four cycles of mFOLFOX6. Postoperatively, 33 (75%) had ypT0–2 disease, including 13 (30%) who were ypT0 and 14 (32%) were ypN0.

The Dutch Colorectal Group is also testing the role of postoperative chemotherapy following short-course radiation. In the ongoing SCRIPTS CKTO 2003–16 phase III trial (Simply Capecitabine in Rectal cancer after Irradiation Plus TME surgery), patients with clinical stage II or III disease located below the level of S1/S2 or the inferior margin within 15 cm of the anal verge receive 5 Gy $\times$ 5 followed by total mesorectal excision (TME). Patients are then randomized postoperatively to either capecitabine versus observation.

Phase III Trials

Polish Trial 1

Bujko and colleagues randomized 316 patients with cT3 rectal cancers to short-course radiation versus chemoradiation.^{36,37} All tumors were above the anorectal ring and TME was performed for distal tumors only. Postoperative chemotherapy was optional. There was no radiation quality control review

Table 2 Randomized trials of preoperative short-course radiation versus chemoradiation

	Polish trial 1 ^{36,37}		Polish trial 2 ³⁸		TROG ³⁹	
Number of patients	316		515		326	
Clinical stage	T3–4		cT3–4		T3Nany (56% N0)	
SCRT	5 Gy × 5		5 Gy × 5, then FOLFOX		5 Gy × 5	
ChemoRT	50.4 Gy + bolus 5-FU/LV		50.4 Gy + 5FU/LV/oxaliplatin		50.4 Gy + PVI 5-FU	
Postop chemotherapy	Optional		Optional		Bolus 5-FU/LV (4–6 cycles)	
Results (%)	ChemoRT	SCRT	ChemoRT	SCRT	ChemoRT	SCRT
pCR	16	1 ^a	12	16	–	–
SP	58	61	–	–	–	–
CRM+	4	13 ^a	–	–	–	–
Compliance	69	98	–	–	–	–
Local failure	14	9 (4 y)	22	22	4	8 (3 y)
Survival	66	67 (4 y)	65	73 (3 y)	70	74 (3 y)
Gr 3–4			24	24 (early)	9	8 (late)

Abbreviations: ChemoRT, chemoradiation; CRM +, positive circumferential radial margins; FU, fluorouracil; Gr, grade; LV, leucovorin; pCR, pathologic complete response; PVI, protracted venous infusion; RT, radiation therapy; SCRT, short-course radiation therapy; SP

^aStatistically significant.

and TME was performed only for distal tumors. As seen in ► **Table 2**, compared with short-course radiation, patients who received chemoradiation had a higher pCR rate (16 vs. 1%) and a lower incidence of positive radial margins (4 vs. 13%, $p = 0.017$). However, there were no significant differences in sphincter preservation (58 vs. 61%), crude local recurrence (14 vs. 9%), disease-free survival (56 vs. 58%) and 4-year survival (66 vs. 67%). Of note, the surgeons who participated in this trial were not willing to change surgical technique from an APR to sphincter preserving based on the response to preoperative therapy. Although acute toxicity was significantly higher with chemoradiation (18 vs. 3%, $p < 0.001$), there was no difference in overall postoperative complications.

Polish Trial 2

In a follow-up trial, 515 patients with fixed cT3 or cT4 rectal cancer were randomized to preoperative short-course radiation (5 Gy × 5 followed 1 week later to FOLFOX4 and surgery 6 weeks later) versus long-course chemoradiation (50.4 Gy plus concurrent bolus 5-FU/LV/oxaliplatin followed by surgery 6 weeks later).³⁸ The primary endpoint was the R0 resection rate. In both arms, oxaliplatin was optional. The incidence of grade 3+ toxicity was similar (24%) as well as the rates of R0 resection (77 vs. 71%), and pCR (16 vs. 12%), respectively. With a median follow-up of 35 months, 3-year outcomes included overall survival (73 vs. 65%, $p = 0.055$), DFS (53 vs. 52%), and local failure (22 vs. 21%). Although there were no differences in local control, there was an overall trend to an improvement in 3-year survival.

TROG, AGITG, CSSANZ, RACS Intergroup Trial

A similar trial from Australia and New Zealand was reported from the Tasman Radiation Oncology Group (TROG).³⁹ A total

of 326 patients with ultrasound or MRI-staged cT3Nany adenocarcinoma located in the lower two-thirds of the rectum were randomized to short-course radiation versus chemoradiation. In contrast with the Polish trial, all patients received 6 months of postoperative adjuvant 5-FU/leucovorin chemotherapy. The median potential follow-up time was 5.9 years and the primary endpoint was a 3-year local recurrence.

Compared with short-course radiation, patients who received chemoradiation had a 3% lower cumulative local recurrence rate at 3 years (4.4 vs. 7.5%, $p =$ nonsignificant [NS]), and 2% at 5 years (5.7 vs. 7.5%, $p =$ NS). Similarly, there were no significant differences in distant failure, overall survival, or late radiation toxicity. A subset analysis of the 79 patients with distal tumors revealed a cumulative incidence of local recurrence of 12.5% for short-course radiation and there were no failures with chemoradiation.

Although a well-designed and performed trial, there were two criticisms of the trial. First, the number of patients was similar to the Polish I trial where the patient sample size was relatively small. Second, rather than powered to show equivalence, it was designed to have a 80% power to detect a difference in the projected 3-year local recurrence rate of 15% for short-course radiation compared with 5% for chemoradiation. Although the 3% lower incidence of local recurrence with chemoradiation versus short-course radiation did not reach statistical significance ($p = 0.24$), the 95% confidence interval (CI) for the difference included an 8% difference in favor of (i.e., 10 vs. 2%). Overall, the data suggested a small local control advantage for chemoradiation, especially for distal tumors.

In summary, the most common treatment for T3 and/or N+ rectal cancer is preoperative chemoradiation. Emerging data are challenging the chemoradiation approach.

Randomized trials comparing short-course radiation with chemoradiation are encouraging; however, longer follow-up is needed. The addition of sequential chemotherapy following short-course radiation is feasible and is being tested prospectively. The impact on outcome, acute and chronic toxicity, and sphincter preservation needs to be determined.

Radiation Techniques

IMRT

Computed tomography (CT)-based three-dimensional (3D) treatment planning for rectal cancer is the current standard of care. The use of IMRT, which is the standard for the treatment of anal cancer is being investigated for rectal cancer. IMRT treatment planning techniques can also decrease the volume of small bowel in the field when compared with 3D conformal techniques.⁴⁰

Wang et al reported a retrospective analysis of 260 patients who received 50.4 Gy in 22 fractions (2.3 Gy gross tumor volume [GTV], 1.9 Gy clinical target volume [CTV]) with IMRT and concurrent capecitabine.⁴¹ The grade 3+ acute toxicity was 6%; 29% had perineal wound complications. A recent prospective phase II trial from the NRG (RTOG 0822) examined the role of IMRT in rectal cancer.⁴² A total of 79 patients received concurrent CAPOX plus 45.0 Gy to the pelvis with IMRT followed by a 3D boost to 50.4 Gy. The incident of GI toxicity was 52% grade 2+ and 18% grade 3+. The trial failed to meet endpoint, since the incidence of Gr 2+ toxicity in RTOG 0247 (which used 3D radiation) was 40%. Therefore, neoadjuvant chemoradiation with IMRT is not routinely recommended.

Fractionation and Dose

Higher preoperative doses up to 60 Gy are associated with increased pCR rates; however, they may also significantly increase acute and long-term morbidity rates. The RTOG R-0012 phase II randomized trial compared twice daily the preoperative chemoradiation of up to 60 Gy (1.2 to 45.6 Gy with a boost of 9.6 to 14.4 Gy) with conventional fractionation (1.8 to 45 Gy with a boost of 5.4 to 9 Gy) plus 5-FU/irinotecan.²³ Both regimens resulted in a 28% pCR rate but were also associated with a more than 40% rate of grade 3 to 4 acute toxicity.

Hyperfractionated radiation has been examined in phase I and II trials.⁴³ In general, the pCR rates may be improved but at the expense of increased acute toxicity. Coucke and colleagues⁴⁴ treated 250 assessable patients with cT3–4 and/or N+ disease with 41.6 Gy at 1.6 Gy twice daily and reported a 92% actuarial 5-year local control rate but a survival rate of only 60%. The rate of acute grade 3+ toxicity was 42% in the 5-FU plus twice-a-day radiation arm of RTOG R-0012 (1.2 to 45.6 Gy with a boost of 9.6 to 14.4 Gy). Hyperfractionated and accelerated fractionated radiation, especially in combination with chemotherapy, remain investigational. Other investigational approaches, such as neutrons,⁴⁵ carbon ions,⁴⁶ and hyperthermia,^{47,48} have been examined. None have shown a clear advantage compared with conventional photons.

References

- Rödel C, Liersch T, Becker H, et al; German Rectal Cancer Study Group. 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(07):679–687
- Rödel C, Graeven U, Fietkau R, et al; German Rectal Cancer Study Group. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2015;16(08):979–989
- Aschele C, Cionini L, Lonardi S, 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(20):2773–2780
- Gérard JP, Azria D, Gourgou-Bourgade S, 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(10):1638–1644
- Gérard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. *J Clin Oncol* 2012;30(36):4558–4565
- O'Connell MJ, Colangelo LH, Beart RW, 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(18):1927–1934
- Jung M, Shin SJ, Koom WS, et al. A randomized phase 2 study of neoadjuvant chemoradiation therapy with 5-fluorouracil/leucovorin or irinotecan/S-1 in patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2015;93(05):1015–1022
- Matsusaka S, Ishihara S, Kondo K, et al. A multicenter phase II study of preoperative chemoradiotherapy with S-1 plus oxaliplatin for locally advanced rectal cancer (SHOGUN trial). *Radiother Oncol* 2015;116(02):209–213
- Beppu N, Matsubara N, Kakuno A, et al. Feasibility of modified short-course radiotherapy combined with a chemoradiosensitizer for T3 rectal cancer. *Dis Colon Rectum* 2015;58(05):479–487
- Buijsen J, van den Bogaard J, Jutten B, et al. A phase I-II study on the combination of rapamycin and short course radiotherapy in rectal cancer. *Radiother Oncol* 2015;116(02):214–220
- Willett CG, Duda DG, di Tomaso E, et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. *J Clin Oncol* 2009;27(18):3020–3026
- van Cutsem E, Lang I, D'haens G, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience. *J Clin Oncol* 2008;26(15 suppl):2
- Campbell PT, Newton CC, Dehal AN, Jacobs EJ, Patel AV, Gapstur SM. Impact of body mass index on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. *J Clin Oncol* 2012;30(01):42–52
- Resch G, De Vries A, Öfner D, et al; Austrian Breast and Colorectal Cancer Study Group. Preoperative treatment with capecitabine, bevacizumab and radiotherapy for primary locally advanced rectal cancer—a two stage phase II clinical trial. *Radiother Oncol* 2012;102(01):10–13
- Das P, Lin EH, Bhatia S, et al. Preoperative chemoradiotherapy with capecitabine versus protracted infusion 5-fluorouracil for rectal cancer: a matched-pair analysis. *Int J Radiat Oncol Biol Phys* 2006;66(05):1378–1383
- Chung KY, Minsky B, Schrag D, et al. Phase I trial of preoperative cetuximab with concurrent continuous infusion 5-fluorouracil and pelvic radiation in patients with local-regionally advanced rectal cancer. *J Clin Oncol* 2006;24(18 suppl):3560

- 17 Rödel C, Arnold D, Hipp M, et al. Phase I-II trial of cetuximab, capecitabine, oxaliplatin, and radiotherapy as preoperative treatment in rectal cancer. *Int J Radiat Oncol Biol Phys* 2008;70(04):1081–1086
- 18 Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). *J Clin Oncol* 2012;30(14):1620–1627
- 19 Sclafani F, Gonzalez D, Cunningham D, et al. TP53 mutational status and cetuximab benefit in rectal cancer: 5-year results of the EXPERT-C trial. *J Natl Cancer Inst* 2014;106(07):1–4
- 20 Sclafani F, Chau I, Cunningham D, et al. Prognostic role of the LCS6 KRAS variant in locally advanced rectal cancer: results of the EXPERT-C trial. *Ann Oncol* 2015;26(09):1936–1941
- 21 Sclafani F, Peckitt C, Cunningham D, et al. Short- and long-term quality of life and bowel function in patients with MRI-defined, high-risk, locally advanced rectal cancer treated with an intensified neoadjuvant strategy in the randomized phase 2 EXPERT-C trial. *Int J Radiat Oncol Biol Phys* 2015;93(02):303–312
- 22 Helbling D, Bodoky G, Goutschi O, et al. Neoadjuvant chemoradiotherapy with or without panitumumab in patients with wild-type KRAS, locally advanced rectal cancer (LARC): a randomized, multicenter, phase II trial SAKK 41/07. *Ann Oncol* 2013;24(03):718–725
- 23 Mohiuddin M, Paulus R, Mitchell E, et al. Neoadjuvant chemoradiation for distal rectal cancer: 5-year updated results of a randomized phase 2 study of neoadjuvant combined modality chemoradiation for distal rectal cancer. *Int J Radiat Oncol Biol Phys* 2013;86(03):523–528
- 24 Wong SJ, Winter K, Meropol NJ, et al. Radiation Therapy Oncology Group 0247: a randomized Phase II study of neoadjuvant capecitabine and irinotecan or capecitabine and oxaliplatin with concurrent radiotherapy for patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2012;82(04):1367–1375
- 25 Kapiteijn E, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345(09):638–646
- 26 van Gijn W, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011;12(06):575–582
- 27 Sauer R, Becker H, Hohenberger P, et al. Preoperative chemoradiotherapy as compared with postoperative chemoradiotherapy for locally advanced rectal cancer. *N Engl J Med* 2004;351:11–20
- 28 Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012;30(16):1926–1933
- 29 Stephens RJ, Thompson LC, Quirke P, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. *J Clin Oncol* 2010;28(27):4233–4239
- 30 Pettersson D, Lörinc E, Holm T, et al. Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer. *Br J Surg* 2015;102(08):972–978; discussion 978
- 31 Pettersson D, Glimelius B, Iversen H, Johansson H, Holm T, Martling A. Impaired postoperative leucocyte counts after preoperative radiotherapy for rectal cancer in the Stockholm III Trial. *Br J Surg* 2013;100(07):969–975
- 32 Yeo SG, Oh JH, Kim DY, et al. Preoperative short-course concurrent chemoradiation therapy followed by delayed surgery for locally advanced rectal cancer: a phase 2 multicenter study (KROG 10-01). *Int J Radiat Oncol Biol Phys* 2013;86(01):34–39
- 33 Garcia-Aguilar J, Smith DD, Avila K, Bergsland EK, Chu P, Krieg RM; Timing of Rectal Cancer Response to Chemoradiation Consortium. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. *Ann Surg* 2011;254(01):97–102
- 34 van Dijk TH, Tamas K, Beukema JC, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. *Ann Oncol* 2013;24(07):1762–1769
- 35 Myerson RJ, Tan B, Hunt S, et al. Five fractions of radiation therapy followed by 4 cycles of FOLFOX chemotherapy as preoperative treatment for rectal cancer. *Int J Radiat Oncol Biol Phys* 2014;88(04):829–836
- 36 Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. *Radiother Oncol* 2004;72(01):15–24
- 37 Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;93(10):1215–1223
- 38 Bujko K. Neoadjuvant chemoradiation for fixed cT3 or cT4 rectal cancer: results of a Polish II multicenter phase III study. *J Clin Oncol* 2016;34(4 Supp):489
- 39 Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol* 2012;30(31):3827–3833
- 40 Samuelian JM, Callister MD, Ashman JB, Young-Fadok TM, Borad MJ, Gunderson LL. Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2012;82(05):1981–1987
- 41 Wang L, Li ZY, Li ZW, et al. Efficacy and safety of neoadjuvant intensity-modulated radiotherapy with concurrent capecitabine for locally advanced rectal cancer. *Dis Colon Rectum* 2015;58(02):186–192
- 42 Hong TS, Moughan J, Garofalo MC, et al. NRG Oncology Radiation Therapy Oncology Group 0822: a phase 2 study of preoperative chemoradiation therapy using intensity modulated radiation therapy in combination with capecitabine and oxaliplatin for patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2015;93(01):29–36
- 43 Ceelen W, Boterberg T, Pattyn P, et al. Neoadjuvant chemoradiation versus hyperfractionated accelerated radiotherapy in locally advanced rectal cancer. *Ann Surg Oncol* 2007;14(02):424–431
- 44 Coucke PA, Notter M, Stamm B, et al; All Surgeons From Public Hospitals And Private Clinics. Preoperative hyper-fractionated accelerated radiotherapy (HART) in locally advanced rectal cancer (LARC) immediately followed by surgery. A prospective phase II trial. *Radiother Oncol* 2006;79(01):52–58
- 45 Duncan W, Arnott SJ, Jack WJ, Orr JA, Kerr GR, Williams JR. Results of two randomised clinical trials of neutron therapy in rectal adenocarcinoma. *Radiother Oncol* 1987;8(03):191–198
- 46 Yamada S, Kamada T, Yasuda S, et al. Phase I/II trial of carbon-ion therapy for patients with locally recurrent rectal cancer. *Proc ASCO* 2005;22:280s
- 47 van der Zee J, González González D, van Rhooen GC, van Dijk JD, van Putten WL, Hart AA; Dutch Deep Hyperthermia Group. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. *Lancet* 2000;355(9210):1119–1125
- 48 Juffermans JH, Hanssens PE, van Putten WL, van Rhooen GC, van Der Zee J. Reirradiation and hyperthermia in rectal carcinoma: a retrospective study on palliative effect. *Cancer* 2003;98(08):1759–1766