Conclusion
Both clinical and endoscopic proctitis showed a correlation with brachytherapy CTV dose. A higher CTV D90 was associated with an increased risk of severe late proctitis. A large CTV volume and D2cc were associated with an increased risk of developing an ulcerative lesion at the site of the tumor.

OC-0281 Time interval between chemoradiation and surgery and postoperative complications in rectal cancer

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Purpose or Objective
A prolonged time interval between neoadjuvant chemoradiation and surgery in locally advanced rectal cancer allows more downsizing of the tumour and increases the probability of complete tumor response and organ sparing treatment. A prolonged time interval may at the same time lead to more fibrosis in the operation field and increase the risk of surgical complications. This study examines the association of a prolonged time interval between chemoradiation and surgery and the risk of surgery-related complications in rectal cancer patients.
Material and Methods
Within the Dutch Surgical Colorectal Audit cohort, we selected rectal cancer patients treated with chemoradiation and surgery between 2007 and 2017. Time interval was categorized into 6-7 weeks, 8-9 weeks, 10-11 weeks, 12-13 weeks, and 14-20 weeks between completion of chemoradiation and surgery. Outcomes of interest were intraoperative, postoperative (all), and postoperative surgical complications within 30 days following resection. Multivariable logistic regression was used to test the association between groups of time interval and surgery-related complications adjusted for age, sex, comorbidity, previous abdominal surgery, mean body mass index, ASA classification, clinical tumour and nodal stage, tumour location, surgical approach, surgical procedure, extended tumour (T4) resection and whether a stoma or anastomosis was received. The 8-9 weeks group was used as reference in the models.
Results
In total, 5740 patients were included of whom 874 (15.2%) received surgery after 6-7 weeks, 1619 (28.2%) after 8-9 weeks, 1611 (28.1%) after 10-11 weeks, 984 (17.1%) after 12-13 weeks and 652 (11.4%) after 14-20 weeks. The groups were similar in age, sex and mean body mass index. Patients with a history of abdominal surgery, a high clinical tumour and nodal stage (T4/N2), a low rectal tumour, and a high ASA classification (ASA III) tended to have a longer time interval. Rate of intraoperative complications increased from 1.8% to 6.1% in the shortest (6-7 weeks) to the longest (14-20 weeks) interval group, postoperative complications increased from 32.6% to 42.2% and postoperative surgical complications from 15.1% to 27.9% (Table). Adjusted for all potential confounders, time interval was not significantly associated with a higher risk of intraoperative, postoperative and postoperative surgical complications.

	Intraoperative complications		
Time interval	*N (%)*	*OR (95% CI)*	*p-value*
6-7 weeks (N=874)	16 (1.8)	0.6 (0.3-1.0)	0.225
8-9 weeks(N=1619)	66 (4.1)	Ref.	
10-11 weeks (N=1611)	82 (5.1)	1.1 (0.8-1.6)	0.647
12-13 weeks (N=984)	58 (5.9)	1.1 (0.8-1.7)	0.515
14-20 weeks (N=652)	40 (6.1)	1.1 (0.7-1.7)	0.808
	Postoperative complications		
Time interval	*N (%)*	*OR (95% CI)*	*p-value*
6-7 weeks (N=874)	285 (32.6)	0.9 (0.7-1.1)	0.211
8-9 weeks(N=1619)	586 (36.2)	Ref.	
10-11 weeks (N=1611)	574 (35.6)	0.7 (0.8-1.1)	0.748
12-13 weeks (N=984)	385 (39.1)	1.1 (0.9-1.4)	0.237
14-20 weeks (N=652)	275 (42.2)	1.2 (1.0-1.4)	0.124
	Postoperative surgical complications		
Time interval	*N (%)*	*OR (95% CI)*	*p-value*
6-7 weeks (N=874)	132 (15.1)	0.9 (0.6-1.3)	0.567
8-9 weeks(N=1619)	317 (19.6)	Ref.	
10-11 weeks (N=1611)	337 (20.9)	1.1 (0.8-1.4)	0.597
12-13 weeks (N=984)	241 (24.5)	1.1 (0.8-1.5)	0.491
14-20 weeks (N=652)	182 (27.9)	1.2 (0.8-1.6)	0.417

Conclusion
Compared to a time interval of 8 to 9 weeks between completion of chemoradiation and surgery, prolonging the interval does not significantly increase the risk of intraoperative and postoperative complications, nor postoperative surgical complications. These findings suggest that a prolonged time interval, to increase the chance on a complete tumour response, is safe in terms of surgery-related complications.

OC-0282 Complete response after short-course radiotherapy versus chemoradiation in advanced rectal cancer

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Purpose or Objective
Older or frail patients with locally advanced rectal cancer (LARC), who are not fit enough to receive neoadjuvant chemoradiation (CRT), are often offered short-course radiotherapy with delayed surgery (SCRT-delay). They thus receive a lower total radiation dose, no chemotherapy and a shorter treatment period. These patients may therefore have a lower chance on a complete response and, as such, on organ-sparing approaches. The purpose of this study was to compare the pathological complete response (pCR) rate between neoadjuvant CRT and SCRT-delay in patients with LARC.
Material and Methods
In the population-based Netherlands Cancer Registry, all stage III rectal cancer patients, diagnosed between 2008 and 2014, who underwent CRT or SCTR-delay and surgery were selected. Delayed time until surgery was defined as a minimum of four weeks between completion of neoadjuvant therapy and date of surgery. pCR (ypT0N0) was compared between the treatment groups using, adjusting for other determinants of pCR by multivariable analyses.
Results
386 patients (9.6%) underwent SCRT-delay and 3,659 patients (90.4%) underwent CRT. The pCR-rate in the SCRT-delay group was significantly lower compared to the CRT-group (6.4% vs. 16.2%, p<0.001), also when adjusted for clinical tumor stage, clinical nodal stage and time interval to surgery (Odds ratio 0.3, 95%CI 0.2-0.5, p<0.001). Also, the SCRT-delay group achieved less near-pCR (ypT0-1N0), tumor and nodal downstaging and had a higher positive lymph-node ratio.

	SCRT-delay N= 391 (%)	CRT N= 3,659 (%)	p-value
pCR (ypT0-N0)	25 (6.4)	592 (16.2)	< 0.001
Near-pCR (ypT0–1 N0)	43 (11.0)	755 (20.6)	<0.001
Tumor downstaging (ypT<cT)	182 (46.8)	2,079 (58.1)	<0.001
Nodal downstaging (ypN<cN)	225 (58.1)	2,618 (72.4)	<0.001
pT-stage			< 0.001
0	31 (7.9)	673 (18.4)	
1	21 (5.4)	210 (5.7)	
2	99 (25.3)	934 (25.5)	
3	206 (52.7)	1,581 (43.2)	
4	32 (8.2)	183 (5.0)	
Missing	2 (0.5)	78 (2.1)	
pN-stage			< 0.001
0	215 (55.0)	2,413 (65.9)	
1	109 (27.9)	805 (22.0)	
2	63 (16.1)	400 (10.9)	
Missing	4 (1.0)	41 (1.1)	
Lymph node ratio , mean±SD	0. 12±0.2	0.09±0.2	< 0.001
Missing	4 (1.0)	49 (1.3)	

Table 1. Differences in pathological outcomes between short-course radiotherapy and delayed surgery (SCRT-delay) and chemoradiation (CRT).

% pCR	SCRT-delay N(%)	CRT N(%)	SCRT vs. CRT OR adjusted (95%CI)	p-value
Overall	25 of 391 (6.4)	592 of 3,659 (16.2)	0.3 (0.2-0.5)	<0.001
Tumor stage				
cT2-3	21 of 311 (6.8)	505 of 2,912 (17.3)	1.8 (1.3-2.4)	<0.001
cT4	4 of 80 (5.0)	87 of 747 (11.6)	Ref.	
Nodal stage				
cN1-2	23 of 349 (6.6)	557 of 3,409 (16.3)	0.9 (0.5-1.4)	0.527
cN0	1 of 37 (2.7)	24 of 192 (12.5)	Ref.	
Time interval				
<7weeks	6 of 106 (5.7)	82 of 533 (15.4)	0.9 (0.7-1.2)	0.506
8-9 weeks	6 of 87 (6.9)	171 of 1,090 (15.7)	1.0 (0.8-1.2)	0.843
10-11 weeks	4 of 72 (5.6)	180 of 1,034 (17.4)	1.1 (0.9-1.4)	0.454
>12 weeks	9 of 126 (7.1)	159 of 1,002 (15.9)	Ref.	

Table 2. Probability on pathological complete response (pCR) in patients undergoing short-course with delayed surgery (SCRT-delay) or chemoradiation (CRT).

Conclusion

Replacing chemoradiation with short-course radiotherapy and delayed surgery results in a lower chance on pCR in patients with stage III rectal cancer LARC compared to neoadjuvant CRT. Novel neoadjuvant treatment strategies for LARC patients not fit enough for CRT are needed in order to increase their eligibility for organsparing treatments.

OC-0283 Prognostic value of serum NPY hypermethylation in neoadjuvant chemoradiotherapy for rectal cancer

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Purpose or Objective

Long-term prevention of metastatic disease remains a challenge for locally advanced rectal cancer patients undergoing neoadjuvant chemoradiotherapy (CRT). Establishment of robust prognostic factors predictive of metastatic progression may allow for better patient selection for systemic treatment intensification. Circulating tumour specific DNA (ctDNA) based on hypermethylation of the NPY gene (meth-ctDNA) has previously been proposed as a universal marker of colorectal cancer. We hypothesised that meth-ctDNA could be a prognostic marker in the neoadjuvant setting and examined this in a secondary, explorative analysis of a prospective clinical trial.

Material and Methods

Serum samples were prospectively collected as part of a phase III trial of radiotherapy dose escalation for locally advanced rectal cancer. Main trial results have previously been reported. In summary, patients with MRI-staged T3-4N0-2M0 rectal cancer and threatened circumferential resection margin received 50.4Gy in 28 fractions with concomitant oral UFT and L-leucovorin, plus an additional 10Gy tumour boost in the experimental arm. Baseline serum samples were available for 146 patients (out of 224 treated on trial). DNA was purified from 2-4 ml serum, bisulfite converted and analysed by droplet digital PCR. Samples were considered positive for meth-ctDNA if >2 positive droplets/sample, and fractional abundance of meth-ctDNA was calculated.

Overall survival (OS) and rate of distant metastases were compared between meth-ctDNA positive and negative patients using log-rank tests. Other prognostic factors (clinical T and N stage, age for OS) and treatment arm were controlled for in multivariate Cox regression analysis. The importance of quantitative load was examined by considering the fractional abundance of meth-ctDNA.

Results

Patient characteristics were representative of the main trial population (median age 64 years, 64% male patients, 19% T4 tumours, 87% N positive). Thirty patients out of 146 had meth-ctDNA in baseline serum samples, with no correlation with clinical T and N stages (p=0.8 and p=0.6, respectively). Median follow-up was 10.6 years (interquartile range, IQR, 9.2-11.5 years) for OS and 5.1 years (IQR 3.7-6.0 years) for freedom from distant metastases. Patients with meth-ctDNA had significantly worse OS at 5 years (47% vs 69%, p=0.02), Figure 1a, even when controlling for other prognostic factors (HR=2.08, 95% CI 1.23-1.51, p=0.007). This difference appeared mainly driven by disparity in the rate of distant metastases (55% vs 72% at 5 years, p=0.01), Figure 1b, with HR=2.20 (1.19-4.07, p=0.01) in multivariate analysis. Increased quantitative load was highly significant for worse outcomes (p<0.0001 and p=0.001, for OS and distant metastases, respectively).

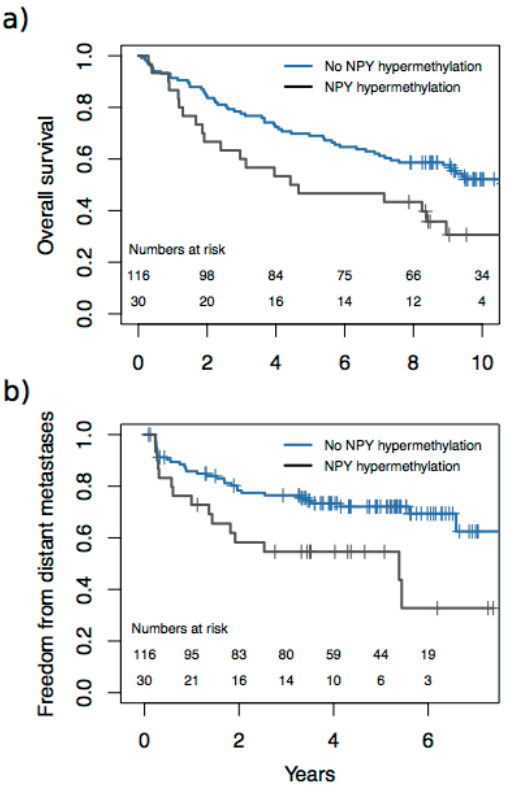

Figure 1: Overall survival (a) and freedom from distant metastases (b) for patients with locally advanced rectal cancer treated with preoperative chemoradiotherapy. Black curves indicate patients with hypermethylated circulating tumour specific DNA (meth-ctDNA) detected in baseline blood serum samples; black curves indicate patients with no meth-ctDNA.