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PAN-EX: A pooled analysis of two trials of neoadjuvant chemotherapy followed by chemoradiotherapy in MRI-defined, locally advanced rectal cancer

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Abstract

Background: EXPERT and EXPERT-C were prospective phase II clinical trials of neoadjuvant chemotherapy (NACT) followed by chemoradiotherapy (CRT) in high-risk, locally advanced rectal cancer (LARC).

Design: We pooled individual patient data from these trials. The primary objective was overall survival (OS) in the intention-to-treat (ITT) population. Prognostic factors were also analysed.

Results: 269 patients were included. Of these, 91.1% completed NACT, 88.1% completed CRT and 240 (89.2%) underwent curative surgery (R0/R1). After a median follow-up of 71.9 months, 5-year progression-free survival (PFS) and OS were 66.4% and 73.3%, respectively. In the group of R0/R1 resection patients, 5-year relapse-free survival (RFS) and OS were 71.6% and 77.2%, respectively, with local recurrence occurring in 5.5% and distant metastases in 20.6% of cases. Significant prognostic factors after multivariate analyses included age, tumour grade and MRI extramural venous invasion (mrEMVI) at baseline, MRI tumour regression grade (mrTRG) after CRT, ypT stage after surgery and adherence to study treatment. mrTRG after NACT was associated with PFS (P=0.002) and OS (P=0.018) and appeared to stratify patients based on the incremental benefit from sequential CRT. Among the outcome measures considered, in the subgroup of R0/R1 resection patients, ypT and ypStage had the highest predictive accuracy for RFS and OS.

Conclusions: Administering NACT before CRT could be a potential strategy for high-risk LARC. In this setting, mrTRG after CRT is an independent prognostic factor while mrTRG after NACT should be tested as parameter for treatment selection in trials of NACT ± CRT. ypT stage may be a valuable surrogate endpoint for future phase II trials investigating intensified neoadjuvant treatments in similar patient populations.

Keywords: locally advanced rectal cancer; neoadjuvant chemotherapy; chemoradiotherapy; MR tumour regression grade; pooled analysis.

Key message: This analysis confirms that administering neoadjuvant chemotherapy (NACT) before chemoradiotherapy (CRT) could be a potential option for high-risk, locally advanced rectal cancer. In this setting, MRI tumour regression grade is an independent prognostic factor and, when assessed after NACT, may predict the probability and magnitude of incremental benefit from sequential CRT.

Introduction

Short-course radiotherapy (RT) or long-course chemoradiotherapy (CRT) followed by surgery are established treatments for locally advanced rectal cancer (LARC) (1). The increased ability to stratify patients by prognostic factors at baseline or response to neoadjuvant treatment has recently led to a reappraisal of this multimodality approach. Risk-adapted strategies have been investigated to reduce treatment-related toxicities and deterioration of quality of life (QoL) while maintaining satisfactory oncological outcomes. These include surgery alone for tumours with limited extramural invasion, neoadjuvant chemotherapy (NACT) alone for intermediate-risk tumours and omission of surgery after CRT-induced clinical complete response (CR) (2).

While treatment de-escalation is worth pursuing in low-risk tumours, patients with poor baseline prognostic features may benefit from intensified neoadjuvant treatments (3). Adding radiosensitising agents to fluoropyrimidines has largely failed to demonstrate superiority over standard CRT (4). Administering NACT before CRT, however, is an attractive option with the potential to improve the outcome of high-risk LARC. Increased tumour downsizing/downstaging, early treatment of micrometastases, good patient compliance and *in vivo* assessment of tumour sensitivity are some of the theoretical advantages of this approach. Nevertheless, its routine use has been prevented by the lack of randomised phase III trials.

PAN-EX is a pooled analysis of individual patient data from EXPERT and EXPERT-C, two phase II trials of NACT followed by CRT in high-risk LARC (5, 6). This study aims to provide detailed information on short- and long-term outcomes of the largest prospective series of patients treated with this intensified neoadjuvant treatment and to assess a number of prognostic factors.

Methods

Study and patient characteristics

All eligible patients enrolled in EXPERT and EXPERT-C were included. In both studies eligibility was limited to patients with ≥1 of the following on baseline high-resolution pelvic MRI: tumour ≤1 mm of the mesorectal fascia (MRF), extramural invasion >5 mm (T3c/d), T4, T3 at/below levators. N2 and extramural venous invasion (EMVI) were additional inclusion criteria in EXPERT and EXPERT-C, respectively. Study designs and treatment regimens are reported in Supplementary Figure 1. According to both EXPERT and EXPERT-C study protocols pelvic MRI scans had to be performed at baseline, within the last week of the first 12 weeks of NACT and 4 weeks after completion of CRT. These were reviewed independently by one radiologist (G.B.). Patients were followed-up for 5 years (5, 6). We have previously reported survival outcomes for the EXPERT and EXPERT-C studies after a median follow-up of 55 and 63.8 months, respectively (5, 7). The current analysis has been conducted using extended follow-up data (74.5 months for EXPERT and 71.3 months for EXPERT-C).

Prognostic variables

Clinical (trial, cetuximab treatment, age, sex, performance status), imaging-based (tumour location, T, N, MRF involvement, EMVI) and pathological variables (grading) at baseline, imaging-based variables indicating response to treatment (response by RECIST, T downstaging, N downstaging, MRI tumour regression grade [mrTRG], change of MRF status, change of EMVI status) and surgical/pathological variables (surgical procedure, circumferential resection margin [CRM] involvement, ypT, ypN, ypStage, T downstaging, N downstaging, pathologic TRG [pTRG], pCR) were assessed as predictors of outcome. Adherence to study protocol (as defined by administration of 4 cycles of NACT, ≥50 Gy of RT and 4 cycles of ACT) was evaluated in patients who underwent curative (R0/R1) resection. All variables were prospectively collected except mrEMVI, mrTRG and pTRG in EXPERT which were retrospectively assessed by one radiologist (G.B.) and two

pathologists (A.W./L.S.) blinded to clinical data. For consistency, whenever possible, baseline and post-treatment MRI scans from EXPERT were retrospectively reviewed by the same radiologist.

Tumour downstaging was defined as reduction of ≥1 level in T or N staging between baseline and post-CRT MRI or histopathological staging. mrTRG was defined as previously reported (8). pTRG was scored according to the Dworak system (9). Given that 88% concordance of tumour differentiation among paired specimens was found, in order to minimise the effect of random histological sampling, grade of resected tumour was used whenever the corresponding baseline biopsy was not available or tumour differentiation was discordant between paired samples.

Statistical analysis

The primary objective was overall survival (OS) in the intention-to-treat (ITT) population. Secondary objectives included: R0/R1 resection, CR, progression-free survival (PFS), local PFS (LPFS) and distant PFS (DPFS) in the ITT population; OS, recurrence-free survival (RFS), local RFS (LRFS) and distant RFS (DRFS) in R0/R1 patients; prognostic value of clinical, surgical/pathological and imaging-based factors as assessed at different time points; prognostic accuracy of short-term outcome measures.

Survival outcomes were calculated from respective trial start date and date of surgery in the ITT and R0/R1 population, respectively. LPFS and DPFS were defined as the time between trial start date and progression, local and distant, respectively. LRFS and DRFS were defined as the time between surgery and recurrence, local and distant, respectively. Patients alive and without evidence of tumour progression/recurrence at the time of the analysis were censored at last follow-up. For local and distant event endpoints patients who died without tumour progression/recurrence were censored at the time of death.

Kaplan Meier method, univariate and multivariate Cox regression models were used. Multivariate models were built to assess the prognostic significance of the above mentioned variables for all outcome measures in both the ITT and R0/R1 resection population. Variables with a *P*-value ≤0.1 from univariate analyses were entered into multivariate models (forward selection method) where only those with a *P*-value ≤0.05 following adjustment for other prognostic variables were considered statistically significant. The concordance index by Gönen & Heller was used to assess the accuracy of short-term outcome measures in predicting RFS and OS in R0/R1 patients (higher index=higher discriminatory power).

Results

269 patients were included. Table 1 and Supplementary Figure 2 show patient characteristics and progress through the study treatment. NACT and CRT were completed by 91.1% and 88.1% of patients, respectively. Tumour response after NACT, after CRT and histopathological findings are reported in Table 2. The median time from end of CRT to restaging pelvic MRI scan was 4.0 weeks (IQR: 3.7 - 4.7) with no difference between EXPERT and EXPERT-C. After a median of 6.6 weeks from completion of CRT, 240 patients (89.2%) underwent curative surgery and no viable tumour cells were found in 48 specimens (20.0%). 75 out of 212 assessable patients (35.4%) had complete/major tumour regression (pTRG3/4). ACT was started after a median of 8.0 weeks and completed in 67.7% of cases. Overall, 155/240 R0/R1 patients (64.6%) fully adhered to the study protocol.

After a median follow-up of 71.9 months, in the ITT population, 5-year PFS and OS were 66.4% (95%CI: 60.7-72.1) and 73.3% (95%CI: 68.0-78.6), respectively (Figure 1). Common sites of progression were lung (47.0% of cases), liver (33.3%), pelvis (21.2%), peritoneum (16.7%) and distant lymph nodes (12.1%). In R0/R1 patients, 5-year RFS and OS were 71.6% (95%CI: 65.9-77.3) and 77.2% (95%CI: 71.7-82.7), respectively. The first cause of treatment failure was local

recurrence in 5.5% (95%CI: 2.7-8.4) and distant metastasis in 20.6% (95%CI: 15.3-26.3) of cases. Prognostic factors after univariate analyses are reported in Supplementary Tables 1-8. Table 3 shows those that remained significant after multivariate analyses.

The prognostic value of mrTRG after each treatment phase was further investigated in the ITT population. Overall, 227 and 230 patients were assessable for mrTRG after NACT and CRT, respectively. mrTRG after NACT was associated with a statistically significant difference in PFS (*P*=0.002) and OS (*P*=0.018). In patients who achieved minimal tumour regression (mrTRG4/5) (*N*=156, 68.7%) 5-year PFS was 61.7% and 5-year OS was 70.6%. The same figures were 79.5% (HR=0.47, *P*=0.026) and 82.1% (HR=0.57, *P*=0.114) for patients with mrTRG3 (*N*=40, 17.6%) and 90.0% (HR=0.18, *P*=0.003) and 90.0% (HR=0.23, *P*=0.014) for patients with mrTRG1/2 (*N*=31, 13.7%), respectively (Figure 2, Table 4). After sequential CRT, while mrTRG1/2 retained its prognostic value, similar outcomes were observed between patients with mrTRG4/5 and those with mrTRG3. mrTRG1/2 was observed in 28/38 (73.7%) and 34/153 (22.2%) of patients who achieved mrTRG3 and mrTRG4/5 after NACT, respectively. Only the former had statistically significantly better survival compared with the group of patients with intermediate/poor regression (mrTRG3-5) after CRT (HR PFS=0.30, *P*=0.009; HR OS=0.34, *P*=0.037) (Table 4, Figure 3).

Further to the Cox regression analyses we calculated the c-index for a number of short-term outcome measures to assess their prognostic accuracy in R0/R1 patients (Supplementary Table 9). 191 patients were assessable for the variables considered. Among these, ypT0-2 (Supplementary Figure 3) and ypStage 0-1 appeared to have the highest predictive accuracy for RFS (c-index: 0.6238 and 0.6252, respectively) and OS (c-index: 0.6094 and 0.6132, respectively).

Discussion

A number of interesting findings have emerged from this analysis. We have confirmed that

administering systemic chemotherapy before CRT is associated with good patient compliance, high rates of tumour response/downstaging and microscopically radical resection. Encouraging rates of both local and distant tumour control were also observed especially considering the high-risk patient population. In line with previous studies, survival was better for those patients who completed the full course of study treatment (10).

Assessment of toxicity and QoL was not included in this study and one could argue that the potential advantages of intensifying neoadjuvant therapies may come with the price of a detrimental effect on these important outcome measures. However, we have previously shown that toxicity was not an issue (5, 6). Moreover, in a recent analysis of the EXPERT-C trial (which accounted for 61% of the PAN-EX population) QoL and bowel function did not appear to be significantly affected in both the short and the long term (11). Nevertheless, the absence of a control group of standard CRT limits the general applicability of our results and a definitive conclusion on the role of NACT in high-risk LARC can only be provided by randomised phase III trials.

Detection of risk factors and implementation of risk-adapted strategies are considered paramount in the management of RC especially following the routine adoption of MRI for tumour staging and assessment of response to treatment. In this context, the results of PAN-EX may provide valuable insights into the potential role of several factors in the decision-making process for LARC. Although all patients included in this analysis had high-risk tumours by study eligibility criteria, we were able to identify independent baseline prognostic variables such as age, tumour grade and mrEMVI that may be given consideration for use as stratification factors in future clinical studies conducted in similar populations. Furthermore, the availability of MRI scans taken after each phase of treatment allowed us to assess the prognostic value of dynamic, imaging-based, indicators of response at different time points. In line with our previous data in patients treated with standard CRT (8), we demonstrated that, even in the setting of an intensified neoadjuvant treatment, absence

of tumour signal/minimal residual tumour before surgery is a favourable prognostic factor. More interestingly, for the first time, we showed that mrTRG after systemic chemotherapy correlated with long-term outcome and could serve as a valuable tool to predict the probability of gaining incremental benefit from sequential CRT and to estimate the magnitude of this.

These results are of significant value if we consider that a strong interest has recently emerged for the investigation of preoperative strategies where the use of CRT is restricted to those patients who do not achieve a satisfactory response to upfront systemic chemotherapy (2). However, validated criteria to discriminate between responders and nonresponders to chemotherapy are lacking. Although the relatively small samples size and the design of PAN-EX (i.e., all patients received CRT) recommend caution in the interpretation of our findings, this study suggests that patients who achieve intermediate tumour regression (mrTRG3) after NACT may be more likely to benefit from the use of sequential CRT compared to those who achieve complete/good (mrTRG1/2) or poor (mrTRG4/5) tumour regression who may have only a marginal incremental survival advantage. Future studies are needed to confirm this hypothesis and also to investigate whether assessment of response to upfront systemic chemotherapy by using mrTRG could be used to select patients for ACT. It should be noted, however, that the relatively early timing of response assessment before surgery (i.e.,4 weeks after completion of CRT) might have had an impact on capturing the highest degree of tumour regression and possibly precluded a shift of patients towards more prognostically favourable mrTRG categories. Moreover, although previous studies support the contention that imaging-based assessment of tumour regression is reproducible with moderate to substantial inter-observer agreement, MRI scans in this study were reviewed by a highly experienced radiologist and generalisability of our results has to be confirmed.

The results of PAN-EX may also potentially challenge two important assumptions in LARC: the routine use of CRT in tumours involving/threatening the MRF and the choice of pCR as surrogate

endpoint for phase II trials. In our series approximately 35% of patients who had tumours <1 mm of the MRF at baseline were found to have a safe MRF after 3 months of NACT. These figures confirm the ability of chemotherapy to downsize the primary tumour and suggest that some of these high-risk patients may possibly proceed to surgery directly after systemic treatment and be spared from acute toxicities and long-term side effects of radiotherapy. However, validation of this hypothesis in studies investigating the correlation between imaging, histopathological findings and long-term outcomes is needed. Interestingly, when we analysed the prognostic value of a number of surgical/pathological variables in the curatively resected population, only ypT stage was found to independently predict survival. In an exploratory concordance analysis, ypT appeared also to have higher discriminatory power for long-term outcomes than pCR, this supporting the contention that alternative short-term outcome measures could perform better than pCR in assessing the impact on survival of novel intensified neoadjuvant treatment strategies in phase II LARC trials.

We acknowledge that our study has a number of limitations. EXPERT and EXPERT-C were sequential trials that spanned over a period of 7 years. Differences in terms of treatment and procedures between these trials as well as the improvement over time of the quality of imaging, surgery and pathology suggest that these patient populations are not entirely comparable. The retrospective assessment of some of the variables investigated may have introduced biases and, due to the large number of variables and outcome measures considered, the analysis of prognostic factors should be regarded as exploratory. Moreover, the lack of appropriate control groups makes our proposed interpretations of some of the study findings speculative in nature. However, the analysis of this largely homogeneous prospective series of high-risk LARC patients offers a unique opportunity to further explore the role NACT followed by CRT in this setting and provides a valuable platform for the generation of hypotheses to test in future prospective clinical trials. Biomarker analyses in this patient population are ongoing and will hopefully lead to another step forward in the adoption of risk-adapted treatment strategies for LARC.

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Disclosures

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Figure legends

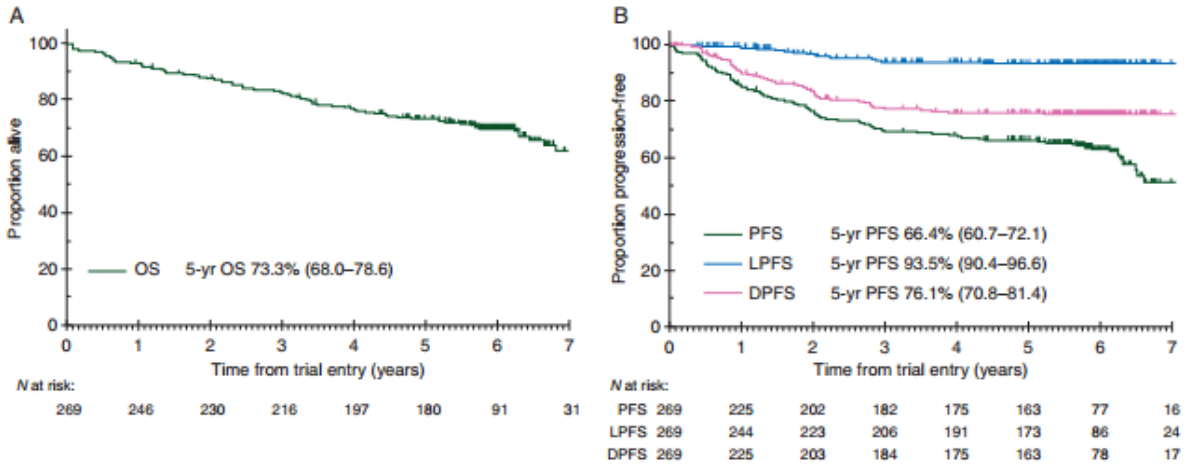

Figure 1. Survival outcomes in the ITT popularion. A) Overall survival; B) Progression-free survival (PFS), local progression-free survival (LPFS) and distant progression-free survival (DPFS).

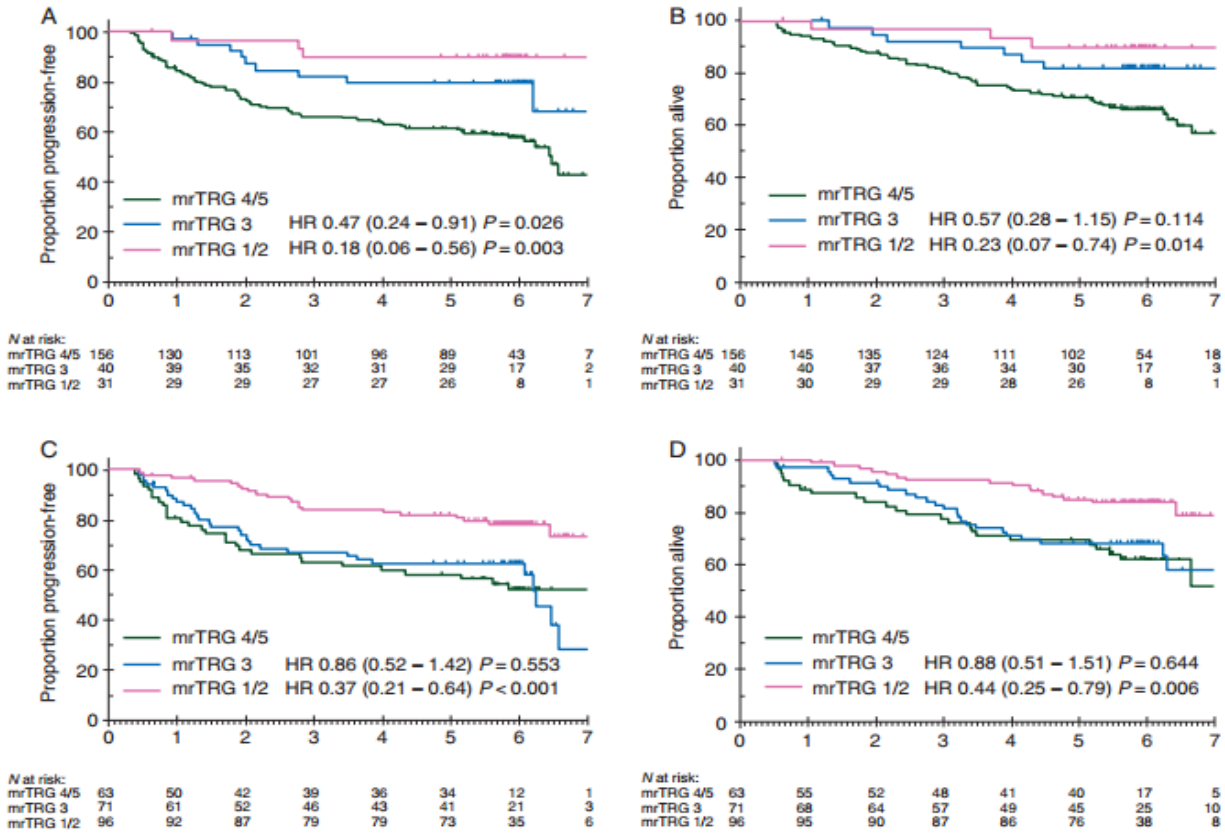

Figure 2. Survival outcomes by mrTRG. A) Progression-free survival by mrTRG after NACT; B) Overall survival by mrTRG after NACT; C) Progression-free survival by mrTRG after CRT; D) Overall survival by mrTRG after CRT

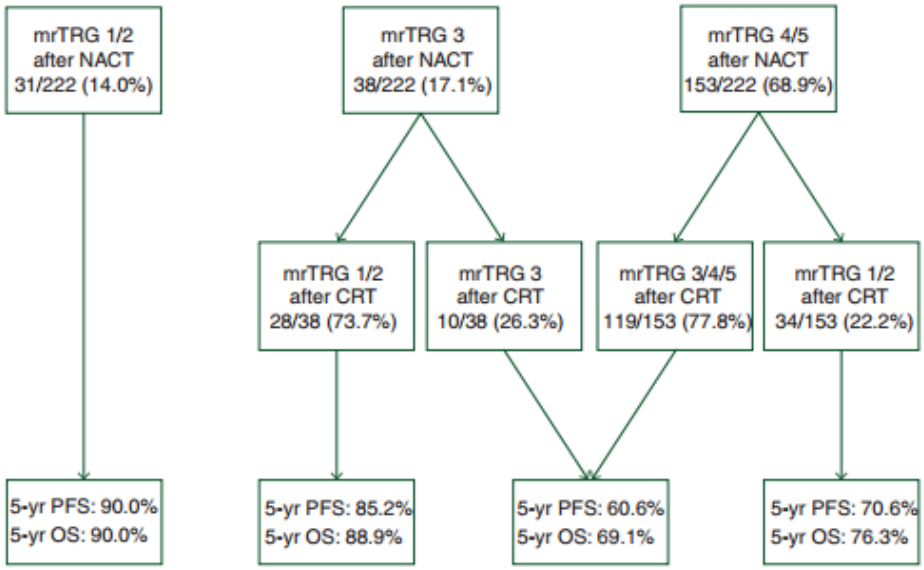

Figure 3. Changes of mrTRG from NACT to CRT in the assessable ITT population (*N*=222) and corresponding survival outcomes

Abbreviations: NACT: neoadjuvant chemotherapy; CRT: chemoradiotherapy; PFS: progression-free survival; OS: overall survival.

Table legends

	EXPERT (*n*= 105)		EXPERT-C (*n* = 164)		PAN-EX (*n* = 269)		*P* value
	n	%	*n*	%	*n*	%	
Gender							
Male	57	54.3	101	61.6	158	58.7	0.235
Female	48	45.7	63	38.4	111	41.3	
Age							
Median and range	64	36–82	63	28–80	63	28–82	0.625
WHO performance status							
0	34	32.4	78	47.6	112	41.6	0.015
≥1	71	67.6	86	52.4	157	58.4	
T stage							
2	3	2.9	4	2.4	7	2.6	0.177
3	84	80.0	120	73.2	204	75.8	
(T3c–T3d)	(60)	(57.1)	(103)	(62.8)	(163)	(60.6)	(0.354)
4	18	17.1	40	24.4	58	21.6	(0.159)
Length of tumour[a]							
Mean and standard deviation	53.7	18.2	56.6	16.5	55.6	17.1	0.185
N stage							
0	34	32.4	47	28.7	81	30.1	0.420
1	36	34.3	55	33.5	91	33.8	
2	35	33.3	62	37.8	97	36.1	
TNM stage							

1	3	2.9	3	1.8	6	2.2	0.460
2	31	29.5	44	26.8	75	27.9	
3	71	67.6	117	71.3	188	69.9	
Tumour location							
High	21	20.0	69	42.1	90	33.5	<0.001
Mid	40	38.1	72	43.9	112	41.6	
Low	42	40.0	23	14.0	65	24.2	
Missing	2	1.9	0	0	2	0.7	
Mesorectal fascia involved/at risk							
Yes	73	69.5	93	56.7	166	61.7	0.027
No	31	29.5	71	43.3	102	37.9	
Missing	1	1.0	0	0	0	0.4	
Tumour differentiation							
Well/moderately diff	90	85.7	139	84.8	229	85.1	0.885
Poorly diff/undiff	11	10.5	16	9.7	27	10.0	
Missing	4	3.8	9	5.5	13	4.9	
Extramural venous invasion							
Yes	73	69.5	118	72.0	191	71.0	0.946
No	29	27.6	46	28.0	75	27.9	
Missing	3	2.9	0	0	3	1.1	

[a] Available for 258 patients (94 in EXPERT and 164 in EXPERT-C).

Table 1. Baseline patient characteristics

	After NACT		After CRT		Surgery	
	n = 269	%	*n* = 269	%	*n* = 244	%
Response by RECIST						
CR	11	4.1	31	11.5	–	–
PR	157	58.3	183	68.0		
SD	76	28.3	30	11.2		
PD	3	1.1	5	1.9		
Unknown	22	8.2	20	7.4		
T downstaging						
Yes	47	17.5	77	28.6	138	56.6
No	180	66.9	152	56.5	106	43.4
Unknown	42	15.8	40	14.9	–	–
N downstaging						
Yes	83	30.9	108	40.1	130	53.3
No	145	53.9	117	43.5	114	46.7
Unknown	41	15.2	44	16.4	–	–
MRF/CRM						
Safe	136	50.6	164	61.0	233	95.5
(Safe after treatment when involved/at risk at baseline)	(48/139)	(34.5)	(76/138)	(55.1)	–	–
Involved/at risk	92	34.2	64	23.8	11	4.5
Unknown	41	15.2	41	15.2	–	–
EMVI						

Absent	96	35.7	126	46.8	–	–
(Absent after treatment when present at baseline)	(36/147)	(24.5)	(66/147)	(44.9)		
Present	124	46.1	86	32.0		
Unknown	49	18.2	57	21.2		
mrTRG						
1/2	31	11.5	96	35.7	–	–
3	40	14.9	71	26.4		
4/5	156	58.0	63	23.4		
Unknown	42	15.6	39	14.5		
pCR						
Yes	–	–	–	–	48	19.7
No					196	80.3
pTRG						
3/4	–	–	–	–	75	30.7
2					63	25.8
0/1					74	30.3
Unknown					32	13.1

NACT, neoadjuvant chemotherapy; CRT, chemoradiotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; MRF, mesorectal fascia; CRM, circumferential resection margin; EMVI, extramural venous invasion; mrTRG, magnetic resonance tumour regression grade; pCR, pathological complete response; pTRG, pathological tumour regression grade.

Table 2. Imaging-based response to neoadjuvant treatment in the ITT population (*n* = 269) and pathological findings at surgery in the resected (R0–2) population (*n* = 244)

ITT population	LPFS		DPFS		PFS		OS	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Baseline factors	*n* = 227		*n* = 253		*n* = 253		*n* = 253	
Age (≥70 years)	–	–	–	–	1.67 (1.10–2.55)	0.017	1.68 (1.08–2.62)	0.024
Tumour grade (G3/4)	–	–	3.13 (1.66–5.94)	<0.001	2.73 (1.63–4.56)	<0.001	3.51 (2.07–5.95)	<0.001
mrEMVI positive	–	–	2.30 (1.13–4.69)	0.022	1.85 (1.12–3.05)	0.016	–	–
Post-treatment imaging-based factors [a]	*n* = 183		*n* = 196		*n* = 194		*n* = 194	
mrTRG (1/2)	–	–	–	–	0.49 (0.30–0.81)	0.006	–	–
mrEMVI positive → negative	–	–	0.32 (0.16–0.64)	<0.001	–	–	–	–
R0/R1 population	LRFS		DRFS		RFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Baseline factors	*n* = 227		*n* = 227		*n* = 228		*n* = 230	
Tumour grade (G3/4)	–	–	3.84 (1.95–7.58)	<0.001	3.75 (2.13–6.01)	<0.001	4.50 (2.51–8.06)	<0.001
Post-treatment imaging-based factors [b]	*n* = 183		*n* = 183		*n* = 184		*n* = 207	
mrTRG (1/2)	–	–	0.35 (0.17–0.79)	0.011	0.48 (0.28–0.82)	0.008	0.56 (0.32–0.98)	0.044
Post-treatment surgical/pathological factors [b]	*n* = 232		*n* = 197		*n* = 199		*n* = 199	
ypT stage (0–2)	–	–	0.15 (0.06–0.38)	<0.001	0.22 (0.12–0.41)	<0.001	0.26 (0.14–0.49)	<0.001
R0 resection	0.06 (0.02–0.22)	<0.001	–	–	–	–	–	–
Adherence to study treatment [c]	–		–		*n* = 199		*n* = 199	
Completion of study treatment	–	–	–	–	0.43 (0.25–0.74)	0.002	0.37 (0.21–0.65)	0.001

The number in each multivariate model varies according to the number of patients for whom the significant univariate variables were available for.

[a] Adjusted for significant baseline prognostic factors.

[b] Adjusted for significant baseline prognostic factors and adherence to study treatment.

[c] Adjusted for significant baseline and post-treatment surgical/pathological prognostic factors.

PFS, progression-free survival; RFS, recurrence-free survival; LPFS, local progression-free survival; DPFS, distant progression-free survival; LRFS, local recurrence-free survival; DRFS, distant recurrence-free survival; OS, overall survival; ITT, intention-to-treat population; HR, hazard ratio; CI, confidence interval; G, grade; EMVI, extramural venous invasion; mr, magnetic resonance; TRG, tumour regression grade; R0, microscopically negative resection margins; R1, microscopically positive resection margins.

Table 3. Significant prognostic factors after multivariate analyses

	n events/ subjects	5-year PFS (95% CI)	HR (95% CI)	*P* value	*n* events/ subjects	5 year OS (95% CI)	HR (95% CI)	*P* value
mrTRG post-NACT								
4/5	71/156	61.7 (54.1–69.3)	1.0	(0.002)	62/156	70.6 (63.3–77.9)	1.0	(0.018)
3	10/40	79.5 (66.8–92.0)	0.47 (0.24–0.91)	0.026	9/40	82.1 (70.1–94.1)	0.57 (0.28–1.15)	0.114
1/2	3/31	90.0 (79.2–100)	0.18 (0.06–0.56)	0.003	3/31	90.0 (79.2–100)	0.23 (0.07–0.74)	0.014
mrTRG post-CRT								
4/5	30/63	58.2 (45/9–70.5)	1.0	(0.001)	26/63	69.4 (57.8–81.0)	1.0	(0.015)
3	31/71	62.7 (51.3–74.1)	0.86 (0.52–1.42)	0.553	28/71	68.2 (57.2–79.2)	0.88 (0.51–1.51)	0.644
1/2	23/96	82.0 (74.2–89.8)	0.37 (0.21–0.64)	<0.001	20/96	85.1 (77.8–92.4)	0.44 (0.25–0.79)	0.006
mrTRG 3/4/5 post-CRT	59/129	60.6 (52.2–69.0)	1.0	(0.001)	52/129	69.1 (61.1–77.1)	1.0	(0.018)
mrTRG 4/5 post-NACT → mrTRG 1/2 post-CRT	14/34	70.6 (55.3–85.9)	0.67 (0.37–1.21)	0.183	12/34	76.3 (62.0–90.6)	0.78 (0.41–1.47)	0.438
mrTRG 3 post-NACT → mrTRG 1/2 post-CRT	5/28	85.2 (71.9–98.5)	0.30 (0.12–0.74)	0.009	4/28	88.9 (77.1–100)	0.34 (0.12–0.94)	0.037
mrTRG 1/2 post-NACT	3/31	90.0 (79.2–100)	0.17 (0.05–0.53)	0.002	3/31	90.0 (79.2–100)	0.23 (0.07–0.72)	0.012

PFS, progression-free survival; OS, overall survival; ITT, intention-to-treat population; HR, hazard ratio; CI, confidence interval; mrTRG, magnetic resonance tumour regression grade; NACT, neoadjuvant chemotherapy; CRT, chemoradiotherapy.

Table 4. Survival outcomes by mrTRG post-NACT (*n* = 227) and mrTRG post-CRT (*n* = 230) in the ITT population