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ABSTRACT

Background: A pathological complete response (pCR) following chemoradiation (CRT) or short-course radiotherapy (scRT) leads to a favourable prognosis in patients with rectal cancer. Total neo-adjuvant therapy (TNT) doubles the pCR rate, but it is unknown whether oncological outcomes remain favourable and whether the same characteristics are associated with pCR as after CRT.

Methods: Comparison between patients with pCR in the RAPIDO trial in the experimental [EXP] (scRT, chemotherapy, surgery, as *TNT)* and standard-of-care treatment [STD] (*CRT*, surgery, postoperative chemotherapy depending on hospital policy) groups. Primary and secondary outcomes were time-to-recurrence (TTR), overall survival (OS) and association between patient, tumour, and treatment characteristics and pCR.

Results: Among patients with a resection within six months after preoperative treatment, 120/423 (28%) [EXP] and 57/398 (14%) [STD] achieved a pCR. Following pCR, 5-year cumulative TTR and OS rates in the EXP and STD arms were 8% *vs.* 7% (hazard ratio 1.04, 95%CI 0.32–3.38) and 94% *vs.* 93% (hazard ratio 1.41, 95%CI 0.51–3.92), respectively. Besides the EXP treatment (odds ratio 2.70, 95%CI 1.83–3.97), pre-treatment carcinoembryonic antigen (CEA) <5, pre-treatment tumour size <40 mm and cT2 were associated with pCR. Distance from the anal verge was the only characteristic with a statistically significant difference in association with pCR between the EXP and STD treatment ($P_{interaction}$=0.042). pCR rates did not increase with prolonged treatment time.

Conclusions: The doubled pCR rate of TNT compared to CRT results in similar oncological outcomes. Characteristics associated with pCR are the EXP treatment, normal CEA, and small tumour size.

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1. Introduction

Patients diagnosed with locally advanced rectal cancer (LARC) are at risk for non-radical surgery, a locoregional recurrence (LRR) and distant metastases (DM). To decrease these risks, (neo)adjuvant treatment is administered. The most recent American guidelines recommend total neoadjuvant therapy (TNT) for LARC as an alternative to short-course radiotherapy (scRT) or chemoradiotherapy (CRT) with postoperative chemotherapy, and exclusively TNT for high-risk LARC [1]. Patients who achieve a pathological complete response (pCR) to CRT or scRT demonstrate superior prognosis with regard to DM, LRR and survival compared to patients without pCR (non-pCR) [2–4]. When TNT results in a pCR, the oncological outcomes are largely unknown.

Besides a favourable prognosis, a pCR enables a potentially rectal preserving watch and wait (W&W) approach, if the complete response (CR) is detected at reassessment. The approximately double pCR rates recently reported in the RAPIDO (28% *vs.* 14%), PRODIGE 23 (28% *vs.* 12%) and STELLAR trials (22% *vs.* 12%), demonstrate a potential for increased W&W [5–7]. As the baseline characteristics between the TNT and CRT groups within each trial were similar, specific patient, tumour or treatment characteristics may be associated with an increased chance to achieve a pCR after TNT rather than CRT. However, reports concerning such associations are limited and only investigated in moderately sized, mostly retrospective studies [8–13]. In the context of expanded indications for TNT and increased use of W&W, clarification of characteristics associated with response becomes increasingly important.

The primary aim of this substudy was to compare oncological outcomes between patients with pCR after TNT and CRT in the randomised RAPIDO trial. Secondary aims were to investigate whether specific patient, tumour and treatment characteristics were associated with achieving pCR after TNT rather than CRT. Although W&W was not a treatment option in the RAPIDO trial, some patients did not undergo planned surgery after neoadjuvant treatment. To ensure a complete overview, an additional aim of this substudy was to report CR rate (pCR in resected patients and sustained cCR in non-resected patients), outcomes after CR and associations between characteristics and CR.

2. Methods

2.1. Study design

The RAPIDO trial was a phase III randomised study (NCT01558921). Details were previously described [5]. Patients randomised to the experimental (EXP) treatment underwent scRT (5x5 Gy), followed by chemotherapy (six cycles CAPOX or nine cycles FOLFOX4) as TNT, and total mesorectal excision (TME). Standard-of-care (STD) treatment consisted of long-course radiotherapy (28–25x1.8–2.0 Gy) with concurrent capecitabine, followed by TME and postoperative chemotherapy (eight cycles CAPOX or 12 cycles FOLFOX4) when stipulated by hospital policy prior to trial initiation. Eligible patients had at least one high-risk features on magnetic resonance imaging (MRI): cT4a/b, cN2, extramural vascular invasion involvement (EMVI+), involved mesorectal fascia (MRF+) or enlarged (>10 mm) lateral lymph nodes (ELLN+) considered to be metastatic.

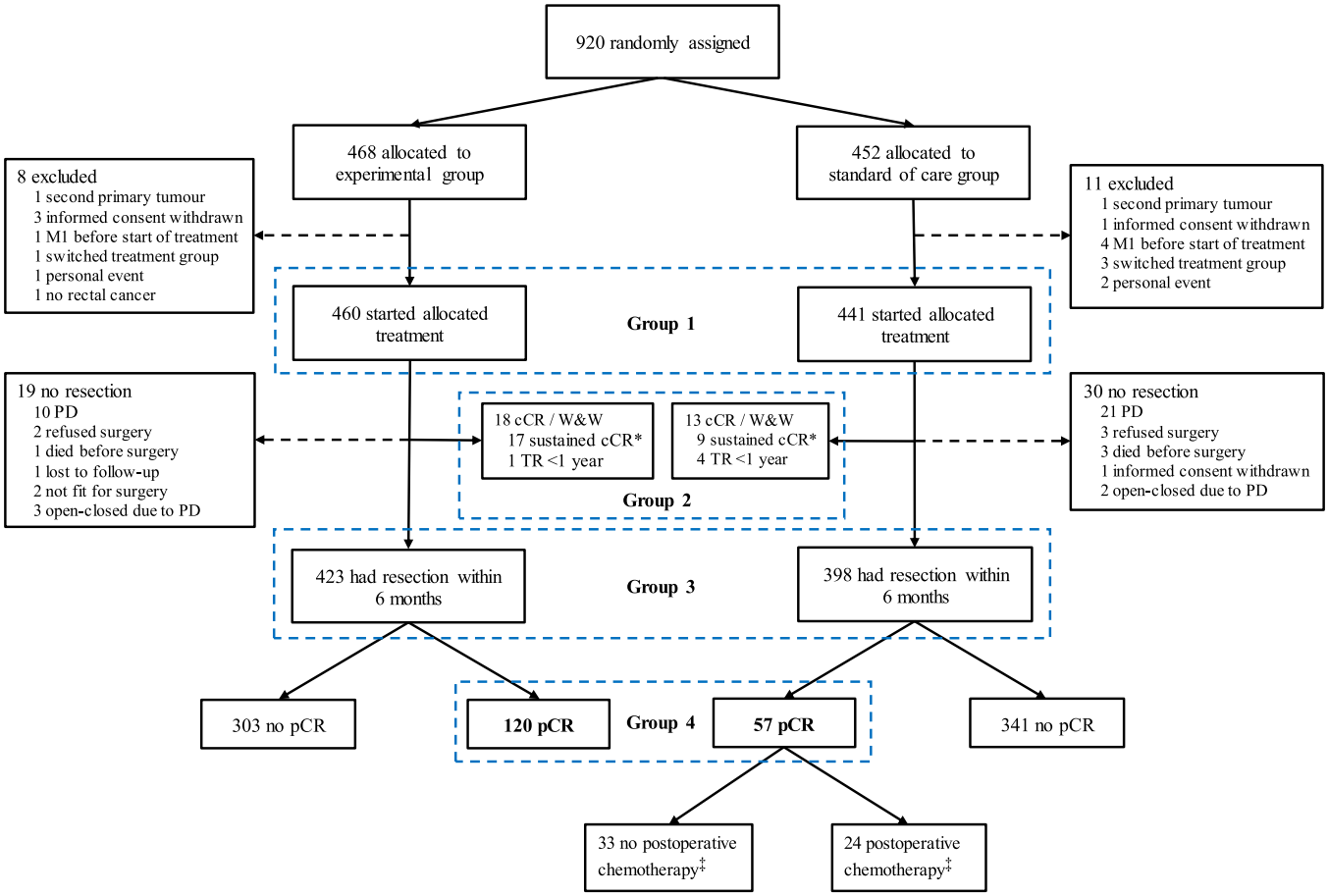

Fig. 1. Consort diagram. The complete response (CR) group was defined as: pCR + sustained cCR. *M1* Distant metastatic disease. *cCR* Clinical complete response. *W&W* Watch and wait policy. *PD* Progressive disease. *pCR* pathological complete response. *TR* Tumour regrowth. * Remained free of TR during at least 1 year since restaging. ‡ As predefined by hospital policy prior to initiation of the trial.

2.2. Procedures

Patients in the EXP treatment were scheduled for scRT in 5–7 days, followed by an 11–18-days interval to 18 weeks of chemotherapy and surgery within 2–4 weeks. When the protocol was followed strictly, the overall treatment time (OTT) was 22–26 weeks, defined as the interval between the first fraction of radiotherapy and surgery. Patients in the STD group were planned for 5.5 weeks of CRT, followed by surgery after 6–10 weeks, resulting in a protocolised OTT of 12–16 weeks.

The protocol for determining complete response by pathology included blocking of the whole tumor area and examining at least three levels for each block. A pCR was defined as absence of viable tumour in the resected specimen (ypT0N0). A central pathology review has not been completed, necessitating to use the pathology data of each local hospital. Clinical treatment response was assessed by restaging MRI 2 weeks prior to surgery. Although W&W was not incorporated in the RAPIDO protocol, a subset of patients who achieved clinical complete response (cCR) deviated from protocol and did not undergo planned surgery. Reasons for this were invariably recorded, but for the purpose of this study, they were considered to be included in a W&W programme aiming for organ preservation. The restaging assessments and decision for W&W were at the discretion of the local hospital. For additional analyses, patients with cCR who remained free of local regrowth for at least a year after restaging (sustained cCR) were combined with patients with pCR into a complete response (CR) group. The decision to use a one year cut-off was taken prior to these analyses. For all patients, follow-up was standardized at 6-, 12-, 24-, 36- and 60-months post-surgery.

2.3. Outcomes

For this report, time to recurrence (TTR) after a pCR was the primary outcome measure, defined as time from surgery until the first LRR or distant recurrence. Secondary endpoints encompassed overall survival (OS) since surgery, and the influence of OTT on achieving pCR within each treatment group. In addition, exploratory analyses on characteristics associated with pCR (EXP and STD group combined), characteristics associated with the doubled pCR rate after TNT *vs.* CRT, and the respective analyses on the CR cohort (pCR + sustained cCR group) were performed.

2.4. Statistical analyses

The primary and secondary outcomes were compared between patients from the EXP and STD groups who had a resection within six months after finishing treatment and achieved a pCR (group 4 in Figure 1). Associations with CR were identified in patients who started treatment (group 1 in Figure 1). Analyses were performed with data after 7.7 years median follow-up (IQR 7.6–7.8). We compared categorical variables by chi-square test and continuous variables by Mann-Whitney U or unpaired t-test, depending on distribution. Missing values were excluded from calculations. The median follow-up time was analysed using the reverse Kaplan-Meier method. The cumulative probability of TTR, LRR and DM was calculated accounting for all causes of death as competing risk, using Cox regression, reporting cause-specific hazard ratio (HR) with 95% confidence interval (CI). Cox regression with Firth correction was used in case of zero events. OS was analysed using the Kaplan-Meier method, calculating HR and 95% CI using Cox regression.

Univariate logistic regressions were performed to investigate associations of baseline and tumour characteristics on achieving pCR and CR (pCR + sustained cCR group). Variables with a p-value < 0.15 in either the pCR or CR model were included in the multivariate analyses. In the second step, a forward stepwise selection method was employed to test whether the EXP and STD treatment had statistically significant differences in associations between characteristics and pCR or CR. Lastly, to visualize the differential effect of both treatments on separate baseline characteristics, odds ratios (OR) were calculated and presented in a forest plot.

Statistical significance was defined as p-values ≤ 0.050 and all tests were two-tailed. The analyses were performed using SPSS® version 27 (IBM, Armonk, USA) and R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1
Baseline characteristics of patients in whom treatment resulted in pCR comparing the STD with EXP treatment.

	Experimental (n = 120)		Standard-care (n = 57)		p-value
Gender					0.569
Male	81	(68%)	36	(63%)	
Female	39	(33%)	21	(37%)	
Age at randomisation					0.501
Median (range)	62	(32-78)	61	(31-78)	
ECOG performance status					0.470
0	102	(85%)	46	(81%)	
1	18	(15%)	11	(19%)	
Pre-treatment CEA					0.322 *
< 5	81	(68%)	34	(60%)	
≥ 5	30	(25%)	18	(32%)	
Unknown	9	(8%)	5	(9%)	
Tumour size					0.583 *
< 40 mm	24	(20%)	12	(21%)	
40-70 mm	73	(61%)	32	(56%)	
≥ 70 mm	22	(18%)	10	(18%)	
Unknown	1	(1%)	3	(5%)	
Clinical T-stage					0.028
cT2	6	(5%)	5	(9%)	
cT3	77	(64%)	43	(75%)	
cT4	37	(31%)	9	(16%)	
Clinical N-stage					0.962
cN0	13	(11%)	7	(12%)	
cN1	26	(22%)	11	(19%)	
cN2	81	(68%)	39	(68%)	
mrMRF status					0.542
MRF+	69	(58%)	30	(53%)	
MRF-	51	(43%)	27	(47%)	
mrEMVI status					0.437
EMVI+	34	(28%)	13	(23%)	
EMVI-	86	(72%)	44	(77%)	
Enlarged lateral lymph nodes on MRI					0.139
ELLN+	15	(13%)	12	(21%)	
ELLN-	105	(88%)	45	(79%)	
Distance from anal verge‡					0.167 *
< 5 cm	42	(35%)	13	(23%)	
5-10 cm	43	(36%)	21	(37%)	
≥ 10 cm	34	(29%)	23	(40%)	
Unknown	1	(1%)	0	(0%)	
Number of high-risk criteria					0.303
1 criterion	42	(35%)	25	(44%)	
2 criteria	45	(38%)	22	(39%)	
3 or more criteria	33	(28%)	10	(18%)	

Data is presented as n (%), unless otherwise indicated. Percentages might not equal 100 % due to rounding. *ECOG* Eastern Cooperative Oncology Group. *CEA* carcinoembryonic antigen. *T-stage* tumour stage. *N-stage* nodal stage. *MRF* mesorectal fascia. *EMVI* extramural vascular invasion. *ELLN* enlarged lateral lymph node.
‡ Unknown values on endoscopy were complemented with MRI and subsequently digital rectal examination.
* Calculated over the known values.

3. Results

3.1. Study population

Figure 1 displays the consort diagram, including reasons for protocol deviations. Between June 2011 and June 2016, 920 patients were enrolled in the RAPIDO trial, of whom 901 started allocated treatment

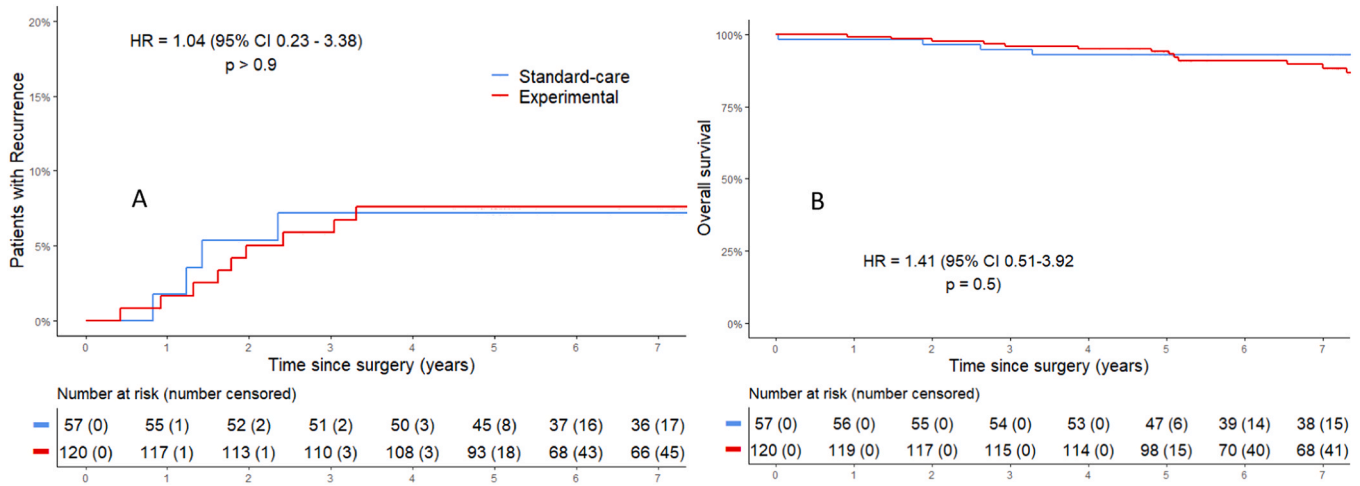

Fig. 2. Cumulative probability of recurrence (locoregional or distant) [A] and overall survival [B] of patients who achieved a pCR, stratified by treatment.

(group 1). From those patients, 18/460 (4%) in the EXP and 13/441 (3%) in the STD group did not undergo planned surgery, *i.e.*, they were considered to follow a W&W programme, aiming for organ preservation, of which 17 in the EXP and 9 in the STD group sustained a cCR longer than a year (Fig. S1). Of the patients who started allocated treatment, 423/460 (92%) patients in the EXP and 398/441 (90%) in the STD group underwent resection within 6 months (group 3). In the EXP group 120/423 (28%) patients achieved a pCR, whereas 57/398 patients (14%) achieved a pCR in the STD group ($p < 0.001$). The CR rate was 137/460 (30%) and 66/441 (15%) in the EXP and STD groups, respectively ($p < 0.001$).

Table 1 presents baseline characteristics of patients in whom treatment resulted in a pCR. A higher proportion of patients with pCR in the EXP group had a cT4 (31% EXP *vs.* 16% STD). Other characteristics were seen in similar proportions between the treatments. Treatment and baseline characteristics of patients who achieved a pCR, non-pCR and sustained cCR are provided in Table S1, S2 and S3 in the *Online Appendix,* respectively.

3.2. Oncological outcomes

The 5-year cumulative TTR rates after a pCR were 8% (95%CI 3–12) in the EXP and 7% (95%CI 2–14) in the STD group (HR 1.04, 95%CI 0.32–3.38; $p > 0.9$) (Figure 2). The first occurring events were 7 DM and 2 LRR (EXP) and 4 DM (STD), respectively. The 5-year cumulative LRR and DM rates between the EXP and STD treatment were 3% (95%CI 0–5.5) *vs.* 0% (95%CI 0–0) (HR 3.31, 95%CI 0.32–444.54; $p = 0.36$) and 7% (95%CI 2.10–11.20) *vs.* 7% (95%CI 1.50–13.70) (HR 0.92, 95%CI 0.28–3.06; $p = 0.90$), respectively. The 5-year OS rate was 94% (95%CI 90–98) in the EXP group and 93% (95%CI 87–100) in the STD group (HR 1.41, 95%CI 0.51–3.92; $p = 0.50$).

3.3. Associations with a pCR

The EXP treatment, a pretreatment CEA value < 5 μg/L, tumour size < 40 mm, cT2-stage, absence of both mrEMVI and mrMRF involvement were associated with achieving a pCR (Table 2). In the multivariate analysis, the EXP treatment, CEA, cT2-stage, and tumour size were independently associated with pCR. A statistically significant difference was only found between treatment arms and tumour height ($P_{interaction}$=0.042). Figure 3 shows the effect of patient and tumour characteristics on achieving a pCR in the EXP *vs.* STD arms. The pCR rates in patients with tumour height < 5 cm in the EXP and STD arm were 41% *vs.* 11% (OR 5.72, 95%CI 2.85–11.48), respectively. Characteristics independently associated with CR (Table S4) were similar as for pCR, and in addition, mrEMVI- and mrMRF- demonstrated statistical significance in the multivariate analysis.

3.4. Influence of the OTT on achieving pCR

Fig. 4 shows proportions of patients who achieved a pCR of those who were operated ≤ 6 months, stratified by 2-week OTT intervals. OTT intervals with less than ten patients are not shown. pCR rates were similar within the EXP and STD treatment during the 22–28- and 12–18-week intervals, with 27–34% and 12–15% of the patients achieving pCR, respectively. Few patients had a longer or shorter OTT since this was not protocolised.

4. Discussion

This substudy of the RAPIDO trial is the first report that compared oncological outcomes following a pCR after receiving TNT or CRT in a randomised setting. As in other recent trials, TNT in the RAPIDO trial resulted in doubled pCR rates compared to CRT and this report reveals that patients with high-risk LARC who achieved pCR have similar, favourable oncological outcomes, irrespective of the type of neo-adjuvant treatment.

The 5-year survival outcomes in our study are similar to literature. This study found cumulative TTR rates of 8% (EXP) and 7% (STD), comparable to patients who achieved pCR after scRT in the Stockholm III trial [4]. The LRR, DM and OS rates were 0%, 7% and 93% after CRT, compared to approximately 0–5%, 7–11% and 85–93% in literature after CRT or scRT, respectively [2–4,14]. Moreover, the CR rates of 30% *vs.* 15% enable a doubling of patients who potentially can follow a W&W approach aimed at rectal preservation, when receiving the EXP treatment compared to the STD treatment CRT.

This substudy did not find statistically significant differences in LRR and DM in contrast to previous reports on the entire RAPIDO cohort after 5 years follow-up [15,16]. Thus, differences in 5-year oncological outcomes appear to occur in non-pCR patients.

Regarding our secondary aims, tumour height had a statistically significantly different association between treatment arms, indicating that distal tumours were associated with pCR, mainly after TNT. However, this result is difficult to explain either by differences in radiation techniques or underlying tumour biology. Additionally, both proximal and distal tumours have been associated with a pCR, and a lack of association has also been reported [17–20]. Patients with a cT4 tumour may have higher odds of achieving a pCR with the EXP treatment (27% *vs.* 8%), although differences were not statistically significant. Altogether, our findings indicate that patient and tumour characteristics do

Table 2
Univariate and multivariate logistic regression on characteristics associated with pCR.

		Univariate				Multivariate				
				Standard-care				Experimental		$P_{interaction}$‡
Variable	**Number of patients at risk**	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)*	*P*-value*	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)*	*P*-value*	
Treatment			< 0.001				< 0.001			
Standard-care	423	1				1				
Experimental	398	2.37 (1.67-3.37)				2.70 (1.83-3.97)				
Gender			0.837							
Female	273	1				-				
Male	548	0.96 (0.68-1.37)				-				
Age	821	0.99 (0.97-1.00)	0.100			0.99 (0.97-1.01)	0.173			
ECOG performance status			0.034				0.121			
0	638	1				1				
1	183	0.62 (0.40-0.66)				0.69 (0.42-1.11)				
Pre-treatment CEA			< 0.001				0.001			
≥ 5	328	1				1				
< 5	444	2.04 (1.41-2.96)				1.95 (1.30-2.91)				
Tumour size at baseline			0.002				0.044			
≥ 70 mm	193	1				1				
40-70 mm	512	1.30 (0.84-2.01)				1.12 (0.69-1.81)				
< 40 mm	105	2.63 (1.51-4.57)				1.99 (1.09-3.65)				
Clinical T-stage			0.007				0.124			
cT4	259	1				1				
cT3	537	1.33 (0.91-1.94)				1.10 (0.71-1.70)				
cT2	24	3.92 (1.65-9.30)				2.78 (1.03-7.50)				
Clinical N-stage			0.567							
cN2	529	1				-				
cN1	217	0.89 (0.60-1.32)				-				
cN0	74	1.24 (0.71-2.18)				-				
Enlarged lateral lymph nodes (MRI)			0.725							
ELLN+	123	1				-				
ELLN-	698	0.92 (0.58-1.46)				-				
mrEMVI status			0.009				0.089			
EMVI+	286	1				1				
EMVI-	535	1.63 (1.13-2.36)				1.44 (0.95-2.18)				
mrMRF status			0.019				0.084			
MRF+	561	1				1				
MRF-	260	1.52 (1.07-2.14)				1.43 (0.95-2.16)				
Distance from anal verge			0.438		0.536				0.019	0.042
≥ 10 cm	280	1		1				1		
5-10 cm	313	1.01 (0.67-1.50)		1.15 (0.56-2.36)				1.17 (0.67-2.05)		
< 5 cm	224	1.27 (0.84-1.94)		0.74 (0.33-1.65)				2.27 (1.23-4.20)		

CI confidence interval. *ECOG* Eastern Cooperative Oncology Group. *CEA* carcinoembryonic antigen. *T-stage* tumour stage. *N-stage* nodal stage. *ELLN* enlarged lateral lymph node. *EMVI* extramural vascular invasion. *MRF* mesorectal fascia. *MRI* magnetic resonance image.
* The odds ratio (95% CI) and p-value within the EXP and STD treatment were presented when the $P_{interaction}$ was ≤ 0.05.
‡ Comparison of all variables in the multivariate analysis between the EXP *vs.* STD treatment; only a $P_{interaction} \leq 0.05$ was presented.

not explain the doubled pCR rate, whereas type of treatment might. Recently, population-based register data indicated that increased adoption of TNT over time may have increased CR rates [21].

Although TNT resulted in a doubled pCR rate compared to CRT, it is difficult to define a certain explicatory treatment component because of differences in radiotherapy dose and fractionation, use of radiosensitizer, preoperative chemotherapy and OTT. Moreover, a doubled pCR rate has been reported from other TNT trials with differences in type of TNT and patient selection [6,7].

Regarding the OTT, literature suggests that the protocolised OTT in both arms of the RAPIDO trial, 22–26 (EXP) and 12–16 weeks (STD), are optimal for achieving pCR. A large meta-analysis of uncontrolled studies showed that pCR rates were higher after an interval of ≥ 8 weeks between CRT and surgery (13 weeks OTT) [22], but did not increase beyond 10 weeks (16 weeks OTT) [23], similar to our results. A phase II trial compared pCR rates after CRT followed by no, two, four or six

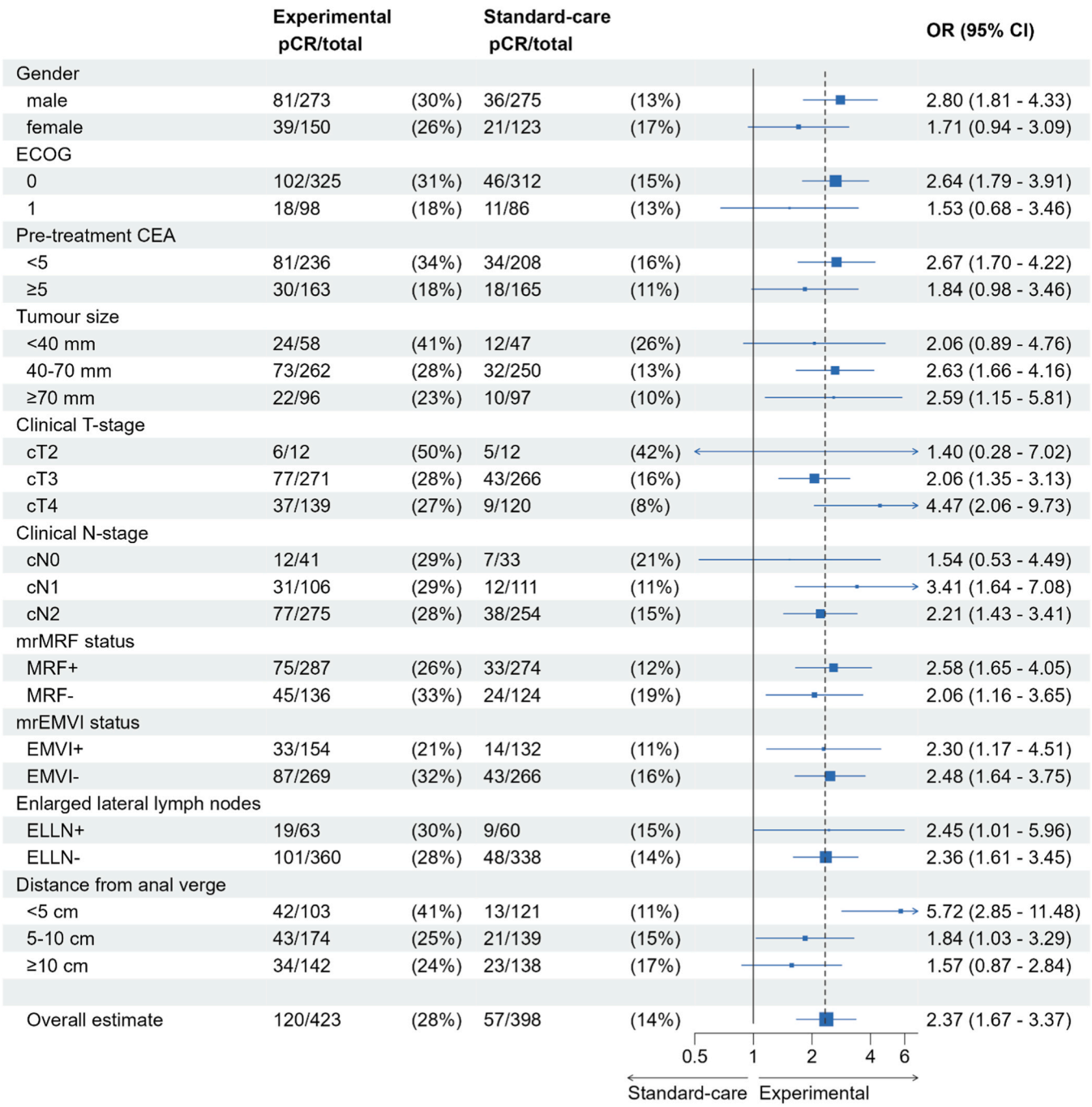

Fig. 3. Forest plot of the effect of patient and tumour characteristics on achieving a pCR in the EXP *vs.* STD treatment. The number of patients who achieved a pCR per variable are shown, relative to those who were operated ≤ 6 months with the variable (group 3). The dashed vertical line indicates the overall association between the EXP and STD treatment on achieving a pCR, favouring the experimental treatment with an OR of 2.37. *OR* odds ratio. *CI* confidence interval. *ECOG* Eastern Cooperative Oncology Group. *CEA* carcinoembryonic antigen. *T-stage* tumour stage. *N-stage* nodal stage. *ELLN* enlarged lateral lymph node. *EMVI* extramural vascular invasion. *MRF* mesorectal fascia.

cycles of chemotherapy before TME. pCR rates increased with increasing number of chemotherapy cycles, to 38% after six cycles (25 weeks OTT). This indicates that prolonging the OTT or adding chemotherapy increases pCR rates. However, within the limits of the protocolised intervals for both treatment arms, our results did not suggest an increase in pCR rates when prolonging OTT. Thus, it is our belief that adding preoperative chemotherapy is most relevant for the doubled pCR rate.

The pretreatment characteristics associated with pCR in our study show that less advanced tumours are more likely to achieve pCR, irrespective of type of treatment, consistent with literature [24,25]. In this substudy and in literature, patients with a CEA < 5 *vs.* ≥ 5 at baseline had a 2-times higher odds of achieving pCR [12,26]. We found smaller tumours to be independently associated with achieving pCR, which is reflected in higher odds for (p)CR in cT2-stage and negative MRF-status [12]. The association between mrEMVI and pCR has been investigated in a few retrospective studies, with conflicting results [11–13].

Our study is accompanied by a few limitations. Firstly, it is a substudy on patients from a randomised trial, underpowered for these analyses. Furthermore, we did not take the potential value of postoperative chemotherapy in the STD group on survival after a pCR into account,

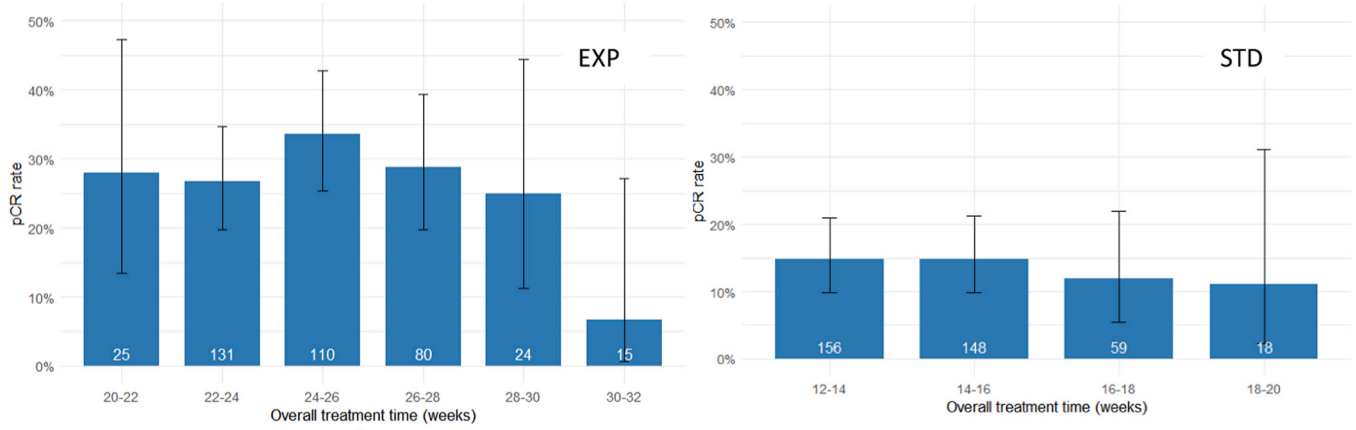

Fig. 4. pCR rate with corresponding 95% CI in patients in whom surgery was performed ≤ 6 months (group 3), stratified by 2-week OTT intervals, within the experimental and standard-care group. Total number of patients who underwent surgery are shown in white. OTT intervals with less than 10 patients are not shown. The protocolised OTT was 22–26 and 12–16 weeks for the EXP and STD treatment, respectively. *OTT* overall treatment time. *EXP* experimental. *STD* standard-care. *CI* confidence interval.

because of conflicting results on the effects of postoperative chemotherapy after pCR [27–29]. Moreover, the limited number of recurrences after pCR, renders subgroup analyses irrelevant. Additionally, the time limit of one year without regrowth in cCR patients is arbitrary, but this can be considered as a similar response to the treatment as patients with pCR. Lastly, the effect of OTT on pCR was not tested statistically and patients were not randomised to different OTT-intervals.

In conclusion, to our knowledge, this is the first randomised study showing that patients with high-risk LARC have similar oncological outcomes, irrespective of whether TNT or CRT precedes pCR. Moreover, a prolonged OTT did not appear to affect pCR rates. Besides the EXP treatment, tumour size, cT-stage and pre-treatment CEA were associated with pCR. The treatment intensification by TNT, yielding a 28% pCR rate in resected patients, appears to be the result of a higher tumour cell killing effect for more patients compared to CRT.

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Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114044.

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