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Original Article

Perineal wound complications after total neoadjuvant therapy or chemoradiotherapy followed by abdominoperineal excision in patients with high-risk locally advanced rectal cancer in the RAPIDO trial

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Abstract

Background: Perineal wound complications (PWCs) occur in 15–30% of patients after abdominoperineal excision (APE) and are associated with adverse events, such as delayed wound healing, prolonged hospitalization, a delay in initiating postoperative chemotherapy, and decreased quality of life. Preoperative radiotherapy and chemotherapy are risk factors for wound complications. It is unknown whether total neoadjuvant treatment (TNT) affects the risk of PWCs compared with chemoradiotherapy (CRT).

Methods: This study compared patients from the experimental (EXP; short-course radiotherapy, chemotherapy, and surgery as TNT) and standard-of-care (STD; CRT, surgery, and postoperative chemotherapy depending on hospital policy) treatment arms of the RAPIDO trial who underwent APE within 6 months after preoperative treatment. The primary outcome was the incidence of PWCs (infection, abscess, dehiscence, wound discharge, presacral abscess affecting the perineum) of any grade ≤ 30 days after APE. Secondary outcomes were the incidence of PWCs >30 days after APE, length of hospital stay, characteristics associated with PWCs, and oncological outcomes in patients with *versus* without PWC.

Results: Of the 901 patients who started treatment (460 in EXP arm, 441 in STD arm), 153 (33%) and 160 (36%) underwent APE after TNT and CRT, respectively. After TNT and CRT, the incidence of PWCs ≤30 days after APE, readmission, and reoperation was 54 of 153 (35%) *versus* 53 of 160 (33%) ($P = 0.69$), 9% *versus* 12% ($P = 0.54$), and 7% *versus* 8% ($P = 0.75$), respectively. The median length of hospital stay was 2–3 days longer for patients with PWC. Univariable analysis revealed that pretreatment albumin <35 g/l, hypertension, and haemoglobin ≤ 8.0 mmol/l were associated with PWC. Oncological outcomes were similar between patients with and without PWCs.

Conclusion: In the RAPIDO trial, TNT and CRT resulted in a similar incidence of PWCs among patients with high-risk locally advanced rectal cancer who underwent APE.

Introduction

In recent decades, preoperative radiotherapy (RT) or chemoradiotherapy (CRT) and total mesorectal excision have improved the outcomes of patients with locally advanced rectal cancer. Compared with CRT, total neoadjuvant therapy (TNT) regimens result in superior disease-free survival (DFS) or disease-related treatment failure rates, fewer distant metastases (DMs), and a higher number of patients achieving a complete response[1–4]. Although these superior outcomes may justify the use of TNT, the treatment intensification could affect wound healing.

Wound healing after an abdominoperineal excision (APE) is of concern because perineal wound complications (PWCs) occur in at least 15–30% of patients, depending on preoperative treatment with or without RT[5]. PWCs can result in problems such as delayed wound healing, a prolonged hospital stay, and

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decreased quality of life, in addition to preventing the prompt initiation of postoperative chemotherapy and requiring expensive treatment[6–8]. Moreover, PWCs may potentially indicate worse oncological outcomes[9], similar to increased locoregional recurrence (LRR) rates in patients with anastomotic leakage after a low anterior resection[10–12].

RT is among the most important risk factors for impaired wound healing. Studies[5,13,14] have reported an increased risk of PWCs in patients who underwent preoperative CRT or RT, with odds ratios ranging between 1.9 and 5.2. Preoperative chemotherapy may also be associated with an increased risk of PWCs[15], but the evidence in rectal cancer is more limited because chemotherapy has mostly been provided after surgery. Several studies[16–18] have reported an approximate 20% incidence of any postoperative wound complications after preoperative chemotherapy, which was lower than the rate after CRT reported in two phase III randomized trials[16,17], but does not indicate a positive or negative effect of preoperative chemotherapy on wound healing. Given the well known adverse effects of RT and the unknown effects of chemotherapy, it is important to study the side-effects of TNT, because TNT will most probably be extensively used in the future.

The side-effects of TNT on perineal wound healing can be explored using data from the RAPIDO trial. In the RAPIDO trial[1], patients were treated before surgery with 5 × 5 Gy of short-course radiotherapy (scRT) and 18 weeks of chemotherapy (as TNT) or 50 Gy CRT in 5 weeks. The characteristics of these regimens that may influence the occurrence of side-effects are RT fractionation, overall treatment time, and the application of chemotherapy. Side-effects such as radiation-induced fibrosis can develop as early as 4 months and progress over months, similar to endothelial damage[19,20]. In the RAPIDO trial, the longer interval between scRT and surgery compared with CRT and surgery (22–26 *versus* 6–10 weeks) may increase the risk of developing these adverse effects[19,21,22]. Conversely, delaying surgery by several weeks after scRT results in a similar or even lower incidence of postoperative surgical complications after any type of resection compared with CRT or scRT with surgery in < 1 week[23,24]. In addition to RT, chemotherapy is provided during the long interval between RT and surgery; because the effects of chemotherapy on wound healing are unknown, the potential beneficial or unfavourable effects of TNT on wound healing are even more unclear.

Because the effects of different characteristics of treatment regimens on wound healing are uncertain, the aim of this substudy of the RAPIDO trial was to compare the incidence of PWCs after APE between patients who underwent TNT and those who underwent CRT before surgery. In addition, the potential impact of PWCs on oncological outcomes was investigated.

Methods

Study design and patient selection

The RAPIDO trial was an investigator-initiated international multicentre phase III randomized trial. Details of the RAPIDO trial have been published elsewhere[1]. Briefly, patients with a biopsy-proven rectal cancer < 16 cm from the anal verge on rigid endoscopy and who had at least one high-risk feature on magnetic resonance imaging, namely cT4a/b, cN2, extramural vascular invasion, involvement of the mesorectal fascia, or enlarged (>10 mm) lateral lymph nodes, were included in the RAPIDO trial. All surgical reports were reviewed and patients who underwent APE with curative intent within 6 months after completion of preoperative treatment, including intersphincteric APE, extralevator abdominoperineal excision (ELAPE), and pelvic exenteration combined with perineal excision, were included in the present study. Patients with DM before or during APE were included in analyses of PWCs because the presence of DM was not expected to affect the occurrence of PWCs (*Fig. 1*).

Procedures

Patients in the experimental (EXP) treatment group received 5 × 5 Gy radiotherapy in 5–7 days, followed by 6 cycles of CAPOX (capecitabine and oxaliplatin) or 9 cycles of FOLFOX4 (5-fluorouracil, leucovorin, and oxaliplatin) for 18 weeks and surgery within 2–4 weeks. In the standard-of-care (STD) treatment group, patients received long-course radiotherapy (25 × 2 or 28 × 1.8 Gy) with concurrent capecitabine followed by surgery after 6–10 weeks. According to prespecified hospital policy before trial initiation, patients in the STD treatment group either did or did not receive 8 cycles of CAPOX or 12 cycles of FOLFOX4 after surgery.

The radiotherapy protocol stated that the clinical target volume should include the entire mesorectum down to the pelvic floor for low tumours, and that the perineum, ischiorectal fossa, and anal canal should be included only if the tumour grew into the levator muscles or anal canal. Although surgery according to the principles of total mesorectal excision with *en bloc* resection of invaded adjacent organs was mandatory, choices regarding intersphincteric, standard or extralevator resection, the surgical approach, the extent of the surgery, and the technique by which the perineum was closed were left to the discretion of the attending surgeon. The protocol allowed the use of omentoplasty, perineal mesh, drains, flap reconstruction, or combinations of these. The immediate postoperative follow-up was left to the expertise of the surgeon and the first study follow-up was protocolized at 6 months, but more intense follow-up was allowed.

Outcomes and data collection

The primary outcome was the incidence of PWCs of any grade, defined as perineal infection, abscess, dehiscence, or wound discharge, during the first 30 days after surgery and scored according to the Clavien–Dindo (CD) classification[25]. A presacral abscess was considered a PWC when it affected the perineal wound (spontaneous or surgical drainage through the perineum). Problems removing perineal drains, perineal bleeding, or partial flap necrosis were classified as other complications. In patients with multiple PWCs, only the most severe (that with the highest CD grade) was recorded, but the date of the first occurring PWC was recorded as the start date, regardless of severity. Vacuum-assisted closure therapy was classified as CD grade III when administered for an infection or abscess and as grade I for wound discharge.

Secondary outcomes were the incidence of PWCs beyond the first 30 days after surgery, readmission and reoperation due to a PWC, wound status at discharge, characteristics associated with a PWC, length of hospital stay (LOS) after surgery, and survival. As exploratory analyses, oncological outcomes were compared between patients with and without PWCs, in the treatment groups combined, and stratified by treatment. All oncological outcomes were evaluated in patients who underwent curative surgery within 6 months after ending preoperative treatment. Finally, patients in the EXP and STD treatment groups were jointly analysed to identify characteristics associated with PWCs. Subsequently, multivariable analysis was used to investigate

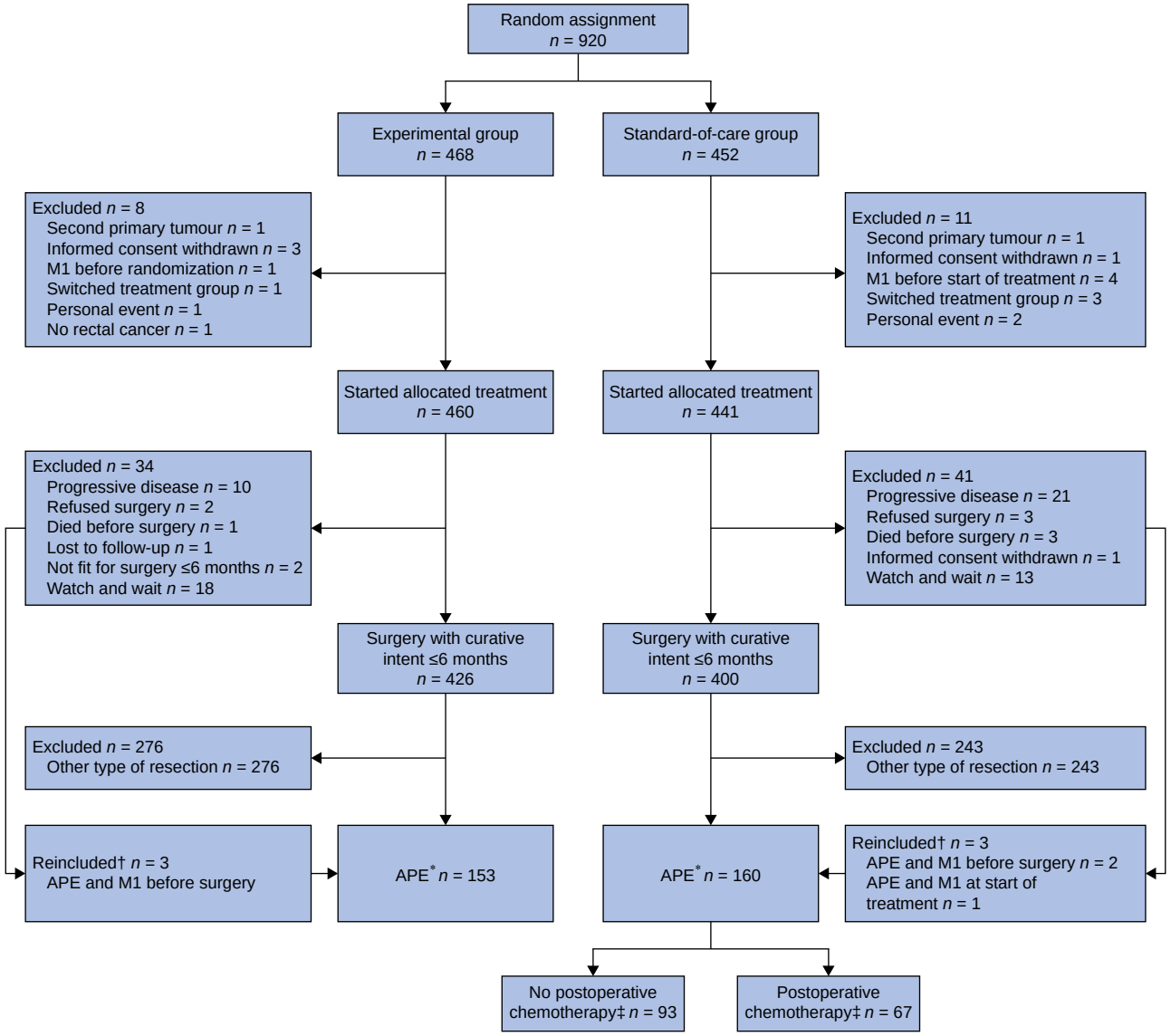

Fig. 1 Flow chart for the present study

Oncological outcomes were compared between the 149 patients in the experimental treatment group and 156 patients in the standard-of-care group. *Distant metastatic disease (M1) was found in one patient in both arms during abdominoperineal excision (APE); both patients were excluded from analyses on oncological outcomes. †A further three patients each in both groups were excluded from analyses of oncological outcomes. ‡As predefined by hospital policy before initiation of the trial.

interactions between the treatment group and characteristics to identify possible differences associated with PWCs.

Data regarding postoperative complications, hospital discharge, and readmission were collected prospectively using case report forms. Perioperative and additional data regarding the PWC were extracted from prospectively collected surgical reports and discharge letters, respectively. Queries were sent to local principal investigators, who gathered data retrospectively from patient records regarding medical history, medication, factors associated with perineal healing, the status of the perineal wound at discharge, or missing data on PWCs.

Statistical analysis

Categorical variables were compared using χ^2 tests and continuous variables, depending on their distribution, were compared using unpaired *t* tests or Mann–Whitney *U* tests. Normally distributed continuous variables are presented as the mean (standard deviation), whereas skewed continuous variables are presented as the median with interquartile range (i.q.r.). Two-sided $P \leq 0.050$ was considered statistically significant. Univariate logistic regression was used to investigate variables associated with PWCs, and those with $P \leq 0.150$ in univariate analysis were included in the multivariate logistic regression analysis. Subsequently, a forward stepwise selection method was used to test whether there were statistically significant differences between the EXP and STD treatment groups in variables associated with PWCs. The cumulative probability of DFS, LRR, DM, and overall survival (OS) since surgery was calculated by Cox regression analysis and expressed as hazard ratios with 95% confidence intervals. For DM and LRR, all causes of death were included as competing risks. A DFS event was defined as LRR, DM, any cause of death, or other second primary cancer. Median follow-up was calculated using the reverse Kaplan–Meier method. Statistical analyses were performed using SPSS® for Windows® version 28.0 (IBM, Armonk, NY, USA).

Results

Of the 920 patients included in the RAPIDO trial, 460 and 441 started treatment in the EXP and STD groups, respectively. In all, 426 (93%) and 400 (91%) patients in the EXP and STD groups, respectively, underwent resection with curative intent within 6 months after the end of preoperative treatment. Of these patients, 149 in the EXP group (35%) and 156 in the STD group (39%) underwent a curative APE after TNT and CRT, respectively, and were included in the survival analyses in this study (*Fig. 1*). Eight patients underwent APE, although a DM was detected, resulting in 153 of 460 patients in the EXP group (33%) and 160 of 441 patients in the STD group (36%) being analysed for PWCs.

The baseline and treatment characteristics of the patients included in this study are presented in *Tables S1* and *S2*. The baseline characteristics were similar between the EXP and STD treatment groups, with the exception of more frequent corticosteroid use ($P = 0.030$) and lower median serum albumin concentrations before surgery ($P < 0.001$) in the EXP treatment group. There were no significant differences in treatment characteristics between the EXP and STD treatment groups (*Table S2*).

One patient in the STD treatment group, without PWCs, died within 30 days after surgery and one patient who had liver cirrhosis, undetected before the start of EXP treatment, died within 60 days after developing perineal infection, grade IV sacral decubitus, sepsis, and pneumonia requiring mechanical ventilation. Of the 67 patients in whom postoperative chemotherapy was planned, 6 (9%) did not receive the chemotherapy owing to postoperative complications; 4 of these patients (6%) had a PWC.

Incidence of PWCs, LOS, readmission, and reoperation

A PWC occurred within 30 days after surgery in 54 of 153 patients (35%) in the EXP treatment group and in 53 of 160 patients (33%) in the STD treatment group ($P = 0.69$). Only 6 of all 60 PWCs (10%) in the EXP treatment group and 4 of 57 (7%) in the STD treatment group occurred after 30 days (*Table 1*). The type of PWC did not differ between the two treatment groups ($P = 0.86$), with perineal infection the most common PWC in both groups. In 12 and 10% of patients in the EXP and STD groups, respectively, the PWC required surgical or radiological intervention (CD grade ≥ III).

Table 1 Incidence of PWCs according to treatment group

	Experimental treatment group ($n = 153$)	Standard-of-care group ($n = 160$)	P*
Incidence of PWCs			0.51
Yes	60 (39%)	57 (36%)	
No	93 (61%)	103 (64%)	
Timing of PWCs (days)			
≤ 30	54 (35%)	53 (33%)	0.69
> 30	6 (4%)	4 (3%)	0.48
Types of PWC			0.87
Perineal infection	24 (16%)	28 (18%)	
Perineal abscess	9 (6%)	10 (6%)	
Wound dehiscence	13 (9%)	9 (6%)	
Wound discharge	8 (5%)	7 (4%)	
Presacral abscess	4 (3%)	2 (1%)	
Other	2 (1%)	1 (1%)	
Clavien–Dindo grade			0.74
Grade I–II	41 (27%)	41 (26%)	
Grade ≥III	19 (12%)	16 (10%)	

*P-values were generated using chi-square tests for categorical variables and unpaired *t*-test or Mann–Whitney *U* test for continuous variables. PWC, perineal wound complication.

In both the EXP and the STD treatment groups, median LOS was 2–3 days longer in patients with than without a PWC (*Table 2*). A PWC led to readmission in 9 and 12% of patients in the EXP and STD groups, respectively ($P = 0.54$), with 7 and 8%, respectively, requiring reoperation because of a PWC ($P = 0.75$) (*Table 2*). The most frequent reasons for readmission owing to a PWC in the EXP and STD groups were perineal infection (3 *versus* 6%, respectively) and perineal abscess (5 *versus* 4%, respectively). Reoperation because of a PWC was most often necessary because of a perineal abscess (4 *versus* 5% in the EXP and STD groups, respectively). Specific treatment details for CD grade I–II and grade ≥ III PWCs are presented in *Tables S3* and *S4*, respectively. The median time from first hospital discharge to readmission for PWCs appeared to be longer in the EXP than STD treatment group (18 (i.q.r. 11–34) *versus* 9 (5–14) days), although the number of patients analysed was small (12 *versus* 18, respectively).

Perineal wound healing

In the EXP and STD treatment groups, at the time of first discharge from hospital, 73 and 79%, respectively, of perineal wounds had

Table 2 Length of hospital stay, readmissions, and reoperations according to treatment group and the presence of PWCs

	Groups		P*
	EXP	STD	
LOS (days), median (i.q.r.)			
PWC+ and PWC– combined (EXP, 153; STD, 160)	9 (7–13)	8 (6–13)	0.11
PWC+ (EXP, 60; STD, 57)	11 (7–14)	10 (7–17)	0.71
PWC– (EXP, 93; STD, 103)	9 (6–13)	7 (6–11)	**0.029**
	PWC+	**PWC–**	
LOS (days), median (i.q.r.)			
STD and EXP combined (PWC+, 117; PWC–, 195)	10 (7–15)	8 (6–11)	**< 0.001**
STD (PWC+, 57; PWC–, 103)	10 (7–17)	7 (6–11)	**< 0.001**
EXP (PWC+, 60; PWC–, 93)	11 (7–14)	9 (6–13)	0.08
	EXP ($n = 153$)	**STD ($n = 160$)**	
Readmission for PWC			0.54†
Yes	14 (9%)	19 (12%)	
No	25 (16%)	21 (13%)	
Not yet discharged	21 (14%)	16 (10%)	
Unknown		1 (1%)	
Reason for readmission			0.59†
Perineal infection	4 (3%)	9 (6%)	
Perineal abscess	8 (5%)	7 (4%)	
Presacral abscess	1 (1%)	2 (1%)	
Other PWCs	1 (1%)	1 (1%)	
Other than for PWC	12 (8%)	9 (6%)	
Unknown		1 (1%)	
Reoperation for PWCs			0.75
Yes	11 (7%)	12 (8%)	
No	49 (32%)	45 (28%)	
Reason for reoperation			0.68
Perineal infection	2 (1%)	2 (1%)	
Perineal abscess	6 (4%)	8 (5%)	
Wound rupture	1 (1%)		
Presacral abscess		1 (1%)	
Perineal bleeding	1 (1%)		
Infected perineal seroma		1 (1%)	
Adhesive perineal drain	1 (1%)		
Other than for PWC	8 (5%)	8 (5%)	

*P-values were generated using chi-square tests for categorical variables and unpaired *t*-test or Mann–Whitney *U* test for continuous variables. †Calculated over patients with known values. PWC, perineal wound complication; EXP, experimental treatment group; STD, standard-of-care treatment group; LOS, length of hospital stay; i.q.r., interquartile range. Bold values indicate statistical significance.

healed without complication, 11 and 8% of patients, respectively, had a perineal infection, 10 and 8% of patients, respectively, had wound discharge, and 5 and 4% of patients, respectively, had a dehiscent wound ($P = 0.82$).

Characteristics associated with PWCs

There were no significant differences between the EXP and STD treatment groups in associations between PWCs and patient, tumour, and treatment characteristics ($P_{interaction} > 0.050$). In the univariate analyses, preoperative albumin < 35 g/l, hypertension, and haemoglobin ≤ 8.0 mmol/l were associated with PWCs (*Table 3*).

No associations were found between treatment characteristics and PWCs (*Table S5*). In multivariate analysis, none of the characteristics was statistically significantly associated with PWCs.

Oncological outcomes

Baseline and treatment characteristics of the EXP and STD groups according to the presence of PWCs are presented in *Tables S6–S9*. The median follow-up time since surgery was 7.4 (i.q.r. 5.1–7.8) years. Over the course of the 7.5-year follow-up, there were no significant differences between patients with and without a PWC in the cumulative probability of DFS, LRR, DM, and OS (*Table 4*).

Table 3 Associations between baseline characteristics and perineal wound complications

	Univariate analysis			Multivariate analysis		
	No. at risk	Odds ratio	P	No. at risk	Odds ratio	P
Treatment			0.512			
Standard care	160	1.00 (reference)				
Experimental	153	1.17 (0.74, 1.84)				
Age at randomization (years)			0.829			
< 65	171	1.00 (reference)				
≥ 65	142	1.05 (0.66, 1.67)				
Sex			0.279			
Male	220	1.00 (reference)				
Female	93	1.32 (0.80, 2.16)				
ECOG score			0.433			
0	258	1.00 (reference)				
1	55	0.78 (0.42, 1.45)				
BMI (kg/m^2)*			0.157			
< 25.0	141	1.00 (reference)				
25.0–30.0	110	0.70 (0.41, 1.19)				
≥ 30	62	1.29 (0.70, 2.36)				
Smoker†			0.157			
No	150	1.00 (reference)				
Yes	58	1.71 (0.92, 3.16)				
Former	61	0.89 (0.48, 1.68)				
Corticosteroid use‡			0.119			0.416
No	170	1.00 (reference)		94	1.00 (reference)	
Yes	32	1.83 (0.86, 3.92)		23	1.53 (0.55, 4.23)	
Type 2 diabetes			0.951			
No	276	1.00 (reference)				
Yes	37	1.02 (0.50, 2.08)				
Hypertension§			0.057			0.155
No	195	1.00 (reference)		72	1.00 (reference)	
Yes	107	0.61 (0.37, 1.01)		45	0.57 (0.26, 1.24)	
Albumin level (g/l)¶			0.033			0.368
≥ 35	151	1.00 (reference)		90	1.00 (reference)	
< 35	51	2.01 (1.06, 3.82)		27	1.55 (0.60, 4.03)	
Haemoglobin (mmol/l)#			0.053			0.465
>8.0	214	1.00 (reference)		86	1.00 (reference)	
≤8.0	81	0.58 (0.33, 1.01)		31	0.73 (0.31, 1.72)	
Leucocyte number	311	0.99 (0.90, 1.08)	0.757			
Clinical tumour category			0.900			
cT2	10	1.00 (reference)				
cT3	171	0.85 (0.23, 3.14)				
cT4	132	0.94 (0.25, 3.51)				
Clinical node category			0.832			
cN0	35	1.00 (reference)				
cN1	96	1.26 (0.56, 2.82)				
cN2	182	1.12 (0.52, 2.39)				
ELLN status			0.896			
ELLN–	250	1.00 (reference)				
ELLN+	63	1.04 (0.59, 1.84)				
MRF status			0.486			
MRF–	57	1.00 (reference)				
MRF+	256	1.24 (0.68, 2.27)				
EMVI status			0.205			
EMVI–	227	1.00 (reference)				
EMVI+	86	1.39 (0.84, 2.30)				

Values in parentheses are 95% confidence intervals. Unknown value for *2, †37, ‡106, §7, ¶104, and #18 patients. OR, odds ratio; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; ; ELLN, enlarged lateral lymph nodes; MRF, mesorectal fascia; EMVI, extramural vascular invasion.

Table 4 Oncological outcomes comparing patients with and without perineal wound complications

	Hazard ratio	P
EXP and STD groups combined (*n* = 190 PWC– *versus* *n* = 115 PWC+)		
Disease-free survival	0.87 (0.59, 1.25)	0.45
Locoregional recurrence	0.85 (0.34, 2.10)	0.72
Distant metastases	0.79 (0.49, 1.28)	0.34
Overall survival	0.95 (0.60, 1.50)	0.83
EXP(*n* PWC– = 90 *versus* *n* = 59 PWC+) and STD (*n* PWC– = 100 *versus* *n* = 56 PWC+) groups separately		
Disease-free survival		
STD	1.29 (0.79, 2.11)	0.31
EXP	0.59 (0.34, 1.04)	0.07
Locoregional recurrence		
STD	1.56 (0.42, 5.80)	0.51
EXP	0.50 (0.14, 1.85)	0.30
Distant metastases		
STD	1.10 (0.58, 2.06)	0.78
EXP	0.56 (0.27, 1.16)	0.12
Overall survival		
STD	1.04 (0.55, 1.98)	0.90
EXP	0.87 (0.45, 1.67)	0.67

Values in parentheses are 95% confidence intervals. Oncological outcomes are shown for the standard-of-care (STD) and experimental (EXP) treatment groups combined and separately over a 7.5-year follow-up. PWC, perineal wound complication.

Discussion

This substudy of the RAPIDO trial showed that the incidence of PWCs in patients with high-risk locally advanced rectal cancer is similar after CRT *versus* TNT using scRT followed by APE. Despite the greater intensity of preoperative TNT compared with CRT, which results in both superior DFS and doubled pathological complete response rates, enabling organ preservation for more patients[1–4], patients who undergo APE after TNT do not have an increased risk of postoperative PWCs.

The 35% incidence of PWCs of any grade ≤ 30 days after APE in this study is within the range of 25–50% reported in literature after scRT and CRT among patients who underwent either APE or ELAPE, although definitions of PWC vary among studies[5,14,15,26–31]. The CAO/ARO/AIO-12 trial[32] reported a 13% incidence of sacral wound problems in a *post hoc* analysis when the groups that received CRT with induction or consolidation chemotherapy were combined. However, in that study, all types of resection were analysed jointly, and sacral wound problems were not defined. In patients subjected to intersphincteric or standard APE, 30 of 86 patients (35%) experienced sacral wound problems[32], similar to the present findings (35%), although patients who underwent ELAPE were also included here.

It has been reported that between 7 and 14% of patients who have undergone APE or ELAPE need surgical or radiological intervention owing to a PWC after scRT and CRT[13–15,30,33], which is comparable to the rates of 10% (CRT) and 12% (TNT) in the present study; however, one previous study[26] reported a rate of only 3%. In the CAO/ARO/AIO-12 trial[32], the only study on TNT, grade III–IV PWCs was reported in 8 of 86 patients (9%) who underwent APE, similar to the 12% found in the present study.

In the present study, LOS was approximately 2 days longer in those with than those without PWCs in the EXP, STD, and both treatment groups combined. This implies that LOS depends more on whether a PWC occurs rather than on the type of preoperative treatment. However, in the absence of PWCs, the median LOS was shorter after CRT than TNT (7 *versus* 9 days; $P = 0.029$), indicating that CRT may be slightly less burdensome. However, the authors cannot provide a precise explanation for this difference because data on important confounding factors were no available. In general, the LOS for patients who underwent APE in the RAPIDO trial appears to be slightly shorter than the 9–13 days reported previously after scRT or CRT[6,13–15].

In the EXP and STD treatment groups, 14 of 60 (23%) and 19 of 53 (33%) patients, respectively, were readmitted, and 11 of 60 (18%) and 12 of 53 (23%) patients, respectively, underwent reoperation because of PWCs. This illustrates the patient burden of PWCs and emphasizes the importance of providing a proper back-up system for discharged patients.

The present study did not identify any characteristics that were strongly associated with the occurrence of a PWC. Hypoalbuminaemia was associated with PWCs in the univariate analysis and is the only characteristic consistently associated with PWCs in the literature[6,15]. A haemoglobin level of ≤ 8.0 mmol/l was associated with PWCs in the present study, but this association has not been confirmed in the literature[13,33]. In both the present study and in previous studies[13–15,33,34], there were no clear associations between PWCs and corticosteroid use, diabetes, and smoking. Although there was no association between PWCs and obesity in the present study, two previous studies[13,34] have reported an association.

Although preoperative RT and chemotherapy increase the risk of PWCs[5,15], the combined effect of scRT followed by chemotherapy did not increase the occurrence of PWCs compared with CRT. A possible explanation for this could be that the interval between the end of scRT and surgery (22–26 weeks), used to provide chemotherapy, is sufficient to recover from the acute effects of RT. Further research is needed to determine whether long-term adverse effects become relevant, such as radiation-induced fibrosis, as suggested by a previous study[35], possibly hampering pelvic surgery in the case of LRR or another malignancy.

The three studies that compared survival between patients with and without PWCs after preoperative RT are hampered by methodology, such that firm conclusions cannot be drawn. Specifically, these limitations include: a small size (129 patients)[36]; including patients without preoperative treatment (78%)[37] and with recurrent (14%) or metastatic disease (13%)[38]; and a retrospective study design without reporting of baseline characteristics[36–38]. In addition, these studies hypothesized that PWCs affect survival because they prevent administration of postoperative chemotherapy, but this was the case in only 6% of patients planned for postoperative chemotherapy in the present study. In the present study, subgroup analyses were undertaken, and, although data from a randomized trial were used with similar baseline characteristics between the groups analysed, the possibility of confounding or chance findings owing to patient selection cannot be ruled out.

This study has some limitations. First, it is a substudy of the randomized RAPIDO trial, which was not powered for these analyses, but the primary and most important secondary outcomes were analysed with data gathered prospectively from a reasonable number of patients. In addition, in analyses of oncological outcomes, the potential value of postoperative chemotherapy was not considered because analyses with even smaller absolute numbers are of limited value[39]. Nonetheless, the exploratory analyses are relevant because studies have shown that LRR rates are higher in patients with anastomotic leakage after a low anterior resection[10–12].

Overall, although based on analyses with limited statistical power, this study indicates that PWCs are not associated with inferior oncological outcomes.

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Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

A data-sharing statement is provided in the supplementary appendix of the research protocol, published previously[1].

Author contributions

Wouter H. Zwart (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft, Writing—review & editing), Esmée A. Dijkstra (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft, Writing—review & editing), Geke A. P. Hospers (Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing—original draft, Writing—review & editing), Corrie A. M. Marijnen (Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing—original draft, Writing—review & editing), Hein Putter (Formal analysis, Investigation, Methodology, Supervision), Joakim Folkesson (Data curation), Cornelis J. H. Van de Velde (Conceptualization, Funding acquisition, Supervision), Annet G. H. Roodvoets (Data curation, Project administration, Resources), Elma Meershoek-Klein Kranenbarg (Data curation, Project administration, Resources), Bengt Glimelius (Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing—original draft, Writing—review & editing), Boudewijn van Etten (Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing—original draft, Writing—review & editing), and Per J. Nilsson (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing—original draft, Writing—review & editing)

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