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Pelvic Floor Rehabilitation After Rectal Cancer Surgery

A Multicenter Randomized Clinical Trial (FORCE Trial)

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Objective: To investigate the effects of PFR after LAR compared to usual care without PFR.

Summary of background data: Functional complaints, including fecal incontinence, often occur after LAR for rectal cancer. Controversy exists about the effectiveness of PFR in improving such postoperative functional outcomes.

Methods: This was a multicenter, randomized controlled trial involving 17 Dutch centers. Patients after LAR for rectal cancer were randomly assigned (1:1) to usual care or PFR and stratified by sex and administration of neoadjuvant therapy. Selection was not based on severity of complaints at baseline. Baseline measurements were taken 3 months after surgery without temporary stoma construction or 6 weeks after stoma closure. The primary outcome measure was the change in Wexner incontinence scores 3 months after randomization. Secondary outcomes were fecal incontinence-related quality of life, colorectal-specific quality of life, and the LARS scores.

Results: Between October 2017 and March 2020, 128 patients were enrolled and 106 randomly assigned (PFR n = 51, control n = 55); 95 patients (PFR n = 44, control n = 51) were assessable for final analysis. PFR did not lead to larger changes in Wexner incontinence scores in nonselected patients after LAR compared to usual care [PFR: −2.3, 95% confidence interval (CI) −3.3 to −1.4, control: −1.3, 95% CI −2.2 to −0.4, $P = 0.13$]. However, PFR was associated with less urgency at follow-up (odds ratio 0.22, 95% CI 0.06–0.86). Patients without near-complete incontinence reported larger Wexner score improvements after PFR (PFR: −2.1, 95% CI −3.1 to −1.1, control: −0.7, 95% CI −1.6 to 0.2, $P = 0.045$). For patients with at least moderate incontinence PFR resulted in relevant improvements in all fecal incontinence-related quality of life domains, while the control group deteriorated. These improvements were even larger when patients with near-complete incontinence were excluded. No serious adverse PFR-related events occurred.

Conclusion: No benefit was found of PFR in all patients but several subgroups were identified that did benefit from PFR, such as patients with urgency or with at least moderate incontinence and no near-complete incontinence. A selective referral policy (65%–85% of all patients) is suggested to improve postoperative functional outcomes for patients after LAR for rectal cancer.

Trial Registration: Netherlands Trial Registration, NTR5469, registered on 3 September 2015.

Keywords: functional outcomes, low anterior resection syndrome, quality of life, rectal cancer

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One of the historical milestones in rectal cancer surgery is the improvement of oncological outcomes while sphincter-preservation rates have also increased.[1,2] Given the current developments in organ-preserving treatment, a further increase in sphincter-preservation treatment is expected. This will lead to a larger group of patients with restored continuity who have to live with the aftermath of their disease. Up to 90% of all patients experience some form of anorectal dysfunction, the so called low anterior resection syndrome (LARS).[3,4] The symptoms associated with this syndrome, which include fecal incontinence, fragmentation, and clustering,[5–7] have a significant impact on patients' quality of life (QoL).[4,8]

An existing therapy for fecal incontinence in nonsurgical patients is pelvic floor rehabilitation (PFR), with reported success rates between 50% and 80%.[9–11] Because management for LARS is mainly symptom-based, it is suggested that PFR might also be effective in patients after rectal cancer surgery. Previously conducted nonrandomized studies with elements of PFR such as biofeedback

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Approval by the Ethics Committee in Arnhem/Nijmegen, the Netherlands, reference number NL59799.091.16.

All authors provide consent for publication.

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Authors and contributors: JvdH was the coordinating investigator, performed data management and analysis, and drafted the manuscript. JK was the former coordinating investigator and PFR expert. BK, JK, PB, EvW, and JP helped to draft this manuscript. BK serves as first contact person and BK and JK checked the analysis. All authors had full access to all the data and approved the final manuscript.

Data collected for the study, including individual participant data and a data dictionary will be made available to others within 12 months after at the end of the long-term follow-up. This includes individual participant data that underlie the results reported in this article, after de-identification. Additional related documents are already open-access available in the study protocol publication. Data will be shared with researchers who provide a methodologically sound proposal, with to goal of achieve aims in the approved proposal or for individual participant data meta-analysis. Proposals should be directed to the corresponding author (Dr. B.R. Klarenbeek) to gain access. Data requestors will need to sign a data access agreement.

The authors report no conflicts of interest.

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after rectal cancer surgery, showed encouraging results. Nevertheless, the scope of these studies was often limited by the lack of a control group or by the outcome measures selected.[12–17] The randomized trial presented here aims to investigate the effects of PFR after LAR compared to usual care without PFR, focusing primarily on fecal incontinence and QoL. It, therefore, addresses a great gap in current available knowledge on aftercare for patients after LAR who suffer from functional complaints.

METHODS

A multicenter, 2-armed, randomized controlled trial (RCT) was conducted in 17 Dutch hospitals between October 2017 and March 2020. Eligible patients had undergone LAR for rectal cancer, were 18 years or older, and were capable of participating in PFR. Patients with inflammatory bowel disease, a short life expectancy (<1 year as estimated by the attending physician), locally advanced tumors that required extensive resections and could possibly experience worse functional outcomes (ie, in the obturator region or extended procedures such as multivisceral resections), and patients who had participated in biofeedback therapy during the past 6 months were excluded. All patients provided written informed consent. The study was approved by the Medical Ethics Committee Arnhem/Nijmegen (NL59799.091.16).[18] Due to the COVID-19 related national lockdown, a temporary protocol adjustment was made to protect study data (Supplementary File 1, http://links.lww.com/SLA/D602). The trial was reported in accordance with the CONSORT guidelines (Supplementary File 2a, http://links.lww.com/SLA/D603) and was preregistered in the Dutch Trial Register (NTR5469).[19]

Patients were randomly assigned (1:1) to usual care or PFR. Randomization was done by a computerized sequence generator (CastorEDC, Amsterdam) with stratification in blocks for sex and radiotherapy. Surgeons, physiotherapists, and all other study personnel were blinded to the questionnaires and study outcomes. Complete blinding of patients and participating physiotherapists was impossible.

Procedures and Course of the Study

Patients were counseled for participation either within 3 months after LAR or within 6 weeks after stoma closure. Baseline outcomes (M2) were measured 3 months after LAR without stoma construction, or 6 weeks after stoma closure. A preoperative measurement (M1) with the same questionnaires as used continuously through the study administered before surgery reduced inclusion rates to such an extent that it had to be removed from the study protocol.[18] Randomization took place after completion of M2. Subsequently, patients either continued with usual care without PFR or participated in a standardized PFR program for 3 months, after which the primary endpoint (M3) analysis was done (Fig. 1). A substantial improvement in Wexner scores after PFR was hypothesized.

Pelvic Floor Rehabilitation

A detailed description of PFR was published previously.[18] In brief, patients participated individually in weekly treatment sessions for 3 months led by a certified pelvic floor physiotherapist who had received trial-related training in advance. A network of on average 3 PFR centers around every participating hospital was created. Four PFR modalities were included: (1) Pelvic floor muscle training, to increase maximum strength, to extend duration of contractions, and to improve coordination of the pelvic floor muscles. (2) Biofeedback, a behaviouristic and coordination therapy with a feedback loop. It allows patients to directly visualize the effects of muscle contraction/relaxation. and helps to produce high-quality pelvic floor movements. (3) Functional electrostimulation, causing the pelvic floor to contract and, by sensory feedback of this artificial contraction, the patient is able to relearn and optimize muscle contractions. (4) Rectal balloon training, training, and simulating to resist the urge to defecate. Patients were also instructed to do exercises at home. A MAPLe probe (Novuqare, Rosmalen, the Netherlands) or a Anuform probe for biofeedback or functional electrostimulation, and the Rivium Training Balloon Catheter (Pelvitec, Delft, the Netherlands) for rectal balloon training was used.

Usual Care

Patients in the control group did not participate in PFR. Usual care included all regular postoperative care that was routinely provided in the participating centers, such as the use of bulking agents and advice on lifestyle, fluid intake, use of fibers, diet, and toilet posture. This trial did not add new elements of supportive care.

Outcomes

The primary outcome was the Wexner incontinence score. Wexner scores $\geq$1 were considered to be symptomatic (1–4: mild, 5–8: moderate, 9–20: severe incontinence).[20] A clinically relevant improvement was defined as an improvement of at least 2 points.[21]

Secondary outcomes were the scores obtained on the Fecal Incontinence Quality of Life Scale (FIQL)[22] (score 1–4, poor-good QoL, minimal clinically important difference 0.4), the LARS-score (score 0–42, no/minor/major LARS), and the European Organization for Research and Treatment for Cancer (EORTC) colorectal-specific QoL questionnaire (EORTC-QLQ-CR29, various function, and symptom scales, score 0 to 100, a higher function scores resembles a better outcome, a higher symptom score represents more complaints). Also the LARS score was evaluated.[23]

Statistical Analysis

The sample size calculation was based on previously published studies that were able to reduce Wexnerincontinence scores in patients treated with PFR after LAR with 5 points [standard deviation (SD) = 8].[12–17] Assuming an alpha error of 0.05 and a beta error of 0.20, a total number of 64 patients were needed to detect a difference between the 2 groups.[24] Seeing that a withdrawal/replacement rate of 50% was anticipated,[12–17] 128 patients were included.[18] Primary analysis was done in the intention-to-treat population, supplemented by a per-protocol analysis, including patients who participated in PFR without serious protocol deviations and controls who did not participate in any form of PFR during follow-up. The mean change in Wexner scores was compared between groups by analysis of covariance. Because of the large difference in baseline scores, univariable and multivariable linear regression was first used to identify factors as predictors for baseline Wexner scores to include them in the analysis as covariates. The factors identified were age, preoperative tumor height, and neoadjuvant treatment (borderline significant, included as covariate given its status as risk factor and its role in the stratification process). Because not all of the differences at baseline could be explained by these factors, the baseline Wexner score was included as covariate too.

Subgroup analyses based on severity of complaints at baseline were performed to identify the groups who might benefit most. Secondary outcome measures were also analyzed by analysis of covariance, with their baseline score as covariate only. Categorical variables were compared using the chi-square test or Fisher exact test. The effect of PFR on specific LARS domain scores was evaluated by binary logistic regression analysis. Potentially associated factors were tested in univariable analysis and taken into multivariable analysis if $P < 0.1$. Outcomes were presented as odds ratios with 95% confidence intervals (CIs). All outcomes were scored according to their scoring manuals.[25–29] A difference from baseline

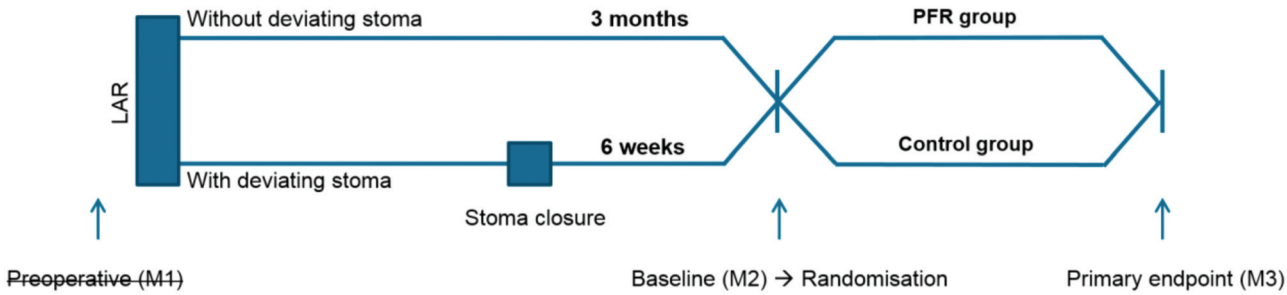

FIGURE 1. Study overview. LAR indicates low anterior resection;M1, preoperative measurement (crossed out because of it has been removed from the study protocol);M2, baseline measurement;M3, primary endpoint; PFR, pelvic floor rehabilitation.

of ≥5 points on the EORTC-QLQ questionnaire was considered as clinically relevant.[30] This difference also needed to be ≥5 points better than the competing study arm. Statistically significant differences in EORTC-QLQ scores without clinical relevance were not reported. Missing data were treated as missing. A safety analysis with all subjects who received at least 1 session of PFR was done to evaluate adverse events or potential harms. Two-sided *P* values or 95% CIs were reported and *P* values < 0.05 were considered statistically significant. The data were analyzed with IBM SPSS, Version 25.0 (IBM, Armonk, New York, USA).

Role of the Funding Source

The authors acknowledge the Netherlands Organisation for Health Research and Development (ZonMw) for funding this study. In addition, the rectal balloons and Anuform probes (Pelvitec) and the MAPLe rectal probes and biofeedback equipment (Novuqare) were provided by way of in-kind sponsorship to enable the PFR program.

The funding parties had no role in data collection, management, analysis, interpretation of data, writing the report, or in the decision to submit the report for publication. They had no authority over these activities whatsoever.

RESULTS

Between October 2017 and March 2020, 128 patients were enrolled. Twenty-two were excluded before randomization because of medical reasons (n = 2), no bowel continuity (n = 9) or no questionnaire follow-up (n = 11). The remaining 106 patients were randomly assigned (51 to PFR, 55 to usual care). Eleven patients dropped out of the study (7 in the PFR group, 4 in the control group) either for medical reasons, psychological distress, or other personal reasons. Ninety-five patients were assessable for analysis, 44 in the PFR group and 51 in the control group (Supplementary File 2b, http://links.lww.com/SLA/D604). Ten patients were excluded from the per-protocol population, 8 from the PFR group (3 of whom did not start PFR, while 5 started PFR, but were excluded on account of serious breaches of protocol) and 2 from the control group (both had started with PFR outside the context of the trial).

Patient characteristics are provided in Table 1. Of the patients 59.1% in the PFR group and 64.7% in the control group were men, with a median age at inclusion of 63.0 years for both groups [interquartile range (IQR) 12 and 17 for PFR and control group]. The mean preoperative tumor height was 7.8 cm (SD 3.6) in the PFR group and 9.2 cm (SD 3.6) in the control group. Administration of neo-adjuvant therapy was distributed equally among the groups, with 18.2% radiotherapy and 31.8% chemoradiation in the PFR group and 19.6% radiotherapy and 27.5% chemoradiation in the control group. In approximately 46% of both groups, a temporary stoma had been constructed with a median time to closure of 3 months. Except for (y)pT-stage ($P = 0.02$), no statistically significant differences were found in patient characteristics (Supplementary File 3, http://link-s.lww.com/SLA/D605).

There were relevant differences in Wexner scores between the groups at baseline (PFR: 10.5, IQR 8.0, control: 5.0, IQR 12.0). Inclusion of the baseline scores as reported by the patients who dropped-out would have led to a smaller, but still relevant, baseline difference (PFR 10.0, IQR 9.0, control 6.0, IQR 12.0).

Summary of Significant Outcome Measures

An improvement in incontinence scores after PFR was found for patients with a baseline Wexner score lower than 16 (PFR: −2.1, n = 36, control: −0.7, n = 45, $P = 0.045$). Furthermore, multivariable logistic regression analysis showed a benefit of PFR for complaints of urgency after correction for presence of urgency at baseline and preoperative tumor height [odds ratio (OR) 0.220, 95% CI 0.056–0.859, $P = 0.03$]. Regarding fecal incontinence related quality of life, patients who reported at least moderate incontinence reported clinically relevant improvements after PFR on all 4 FIQL domains. Even more substantial improvements in QoL were found in patients with at least moderate incontinence but with a baseline Wexner score lower than 16.

Primary Outcome Measure

The observed improvement in Wexner scores was −2.8 (95% CI −4.0 to −1.7) in the PFR group and −0.8 (95% CI −1.8 to 0.1) in the control group. After correction for age, preoperative tumor height, neoadjuvant treatment, and baseline Wexner scores no difference in improvement scores remained (PFR: −2.3, 95% CI −3.3 to −1.4, control: −1.3, 95% CI −2.2 to −0.4, $P = 0.13$). In the perprotocol population, the adjusted improvement score in the PFR group was −2.6 (95% CI −3.7 to −1.5, n = 36) and in the control group it was −1.2 (95% CI −2.2 to −0.3, n = 49, $P = 0.08$) (Table 2).

Subgroup Analyses

An improvement after PFR was found for patients with a baseline Wexner score lower than 16 (PFR: −2.1, n = 36, control: −0.7, n = 45, $P = 0.045$). Other subgroup analyses did not reach statistical significance: symptomatic patients only (Wexner >1, score change/improvement, PFR: −2.5, n = 44, control: −1.6, n = 44, $P = 0.18$), at least moderate incontinence (Wexner >5, PFR: −3.6, n = 35, control: −2.6, n = 28, $P = 0.27$) and patients with severe incontinence only (Wexner >9, PFR: −3.8, n = 28, control: −3.3, n = 19, $P = 0.72$) (Fig. 2 and Supplementary File 4, http://links.lww.com/SLA/D606).

TABLE 1. Patient Characteristics

	Intention to Treat	
	Intervention Group n = 44	**Control Group n = 51**
Demographics		
Age, yr, median (IQR)	63.0 (12)	63.0 (17)
Males, n (%)	26 (59.1)	33 (64.7)
Body mass index, kg/m^2, median (IQR)	25.5 (6.5)	25.8 (5.2)
Medical history		
Diabetes mellitus, n (%)	5 (11.4)	4 (7.8)
History of anal surgery, n (%)*	5 (11.4)	7 (13.7)
ASA classification, n (%), - ASA 1–2	36 (81.8)	46 (90.2)
ASA 3–4–5	8 (18.2)	4 (7.8)
Not reported adequately	0 (0.0)	1 (2.0)
Tumor characteristics		
Tumor height in cm assessed by MRI, mean (SD)	7.2 (3.0)	8.6 (3.4)
MRI data missing, n (%)	3 (6.8)	6 (11.8)
Tumor height in cm assessed by MRI, if unavailable completed by scopy, mean (SD)	7.8 (3.6)	9.2 (3.6)
Anastomosis height in cm from anal verge, mean (SD)	5.7 (2.5)	5.4 (2.3)
Data missing, n (%)	11 (25.0)	12 (23.5)
(y-) Pathological TNM stage, - T0	0 (0.0)	2 (3.9)
-T1	3 (6.8)	8 (15.7)
-T2	23 (52.3)	13 (25.5)
-T3	18 (40.9)	25 (49.0)
-T4	0 (0.0)	3 (5.9)
-N0	34 (77.3)	28 (54.9)
-N1	9 (20.5)	21 (41.2)
-N2	1 (2.3)	2 (3.9)
-M0	44 (100.0)	48 (94.1)
-M1†	0 (0.0)	3 (5.9)
Additional therapy		
Neoadjuvant therapy, n (%)		
-None	22 (50.0)	27 (52.9)
-Radiotherapy	8 (18.2)	10 (19.6)
-Short course (5 x 5 gy)	7 (15.9)	10 (19.6)
-Long course	1 (2.3)	0 (0.0)
-Chemoradiation	14 (31.8)	14 (27.5)
Adjuvant chemotherapy, n (%)	1 (2.3)	3 (5.9)
Surgery related factors		
Type of surgery, n (%), - Laparoscopic	34 (77.3)	42 (82.4)
-Robot	9 (20.5)	7 (13.7)
-Conversion to open	1 (2.3)	2 (3.9)
Construction of a stoma, n (%)‡, - No stoma construction	23 (52.3)	28 (54.9)
-Yes, stoma construction	21 (47.7)	23 (45.1)
-Ileostomy	21 (100.0)	21 (91.3)
-Colostomy	0 (0.0)	2 (8.7)
Time to stoma closure, months, median (IQR)	3.0 (2.0)	3.0 (4.0)
Stoma closure within 3 months, n (%), - Yes, within 3 mo	8 (38.1)	8 (34.8)
-No, after 3 mo	13 (61.9)	15 (65.2)
Complications, n (%), - Peri-operative complications§	2 (4.5)	6 (11.8)
-Postoperative complications, n (%)	13 (29.5)	14 (27.5)
-Of which anastomotic leakage with stoma construction	3	1
-Others (gastroparesis/ileus/pneumonia/wound infection)	15	18
Type of anastomosis, n (%), - Side-to-end	32 (72.7)	40 (78.4)
-End-to-end	11 (25.0)	10 (19.6)
-Side-to-side	0 (0.0)	1 (2.0)
-Not reported adequately	1 (2.3)	0 (0.0)
Obstetric history, n = females	n = 18	n = 18
Number of women who delivered a child, n (%)	14 (77.8)	16 (88.9)
Parity among women, median (range)	2.0 (1.0)	2.0 (1.0)
Women with only vaginal deliveries, n (%)	18 (100.0)	17 (94.4)
Presence of vaginal tears or episiotomy procedures, n (%)	6 (33.3)	10 (55.6)

Except for (y)pT-stage ($P = 0.02$), no statistically significant differences were found.

*Control group: a history of surgery for fistula (1X), perianal abscess (1X), endoscopic mucosal resection (EMR, 1 X), endoscopic submucosal dissection (ESD, 1 X), Transanal Endoscopic Microsurgery (TEM)/wait and see (3X). Intervention group: a history of surgery for fistula (1 X), ESD (1 X), TEM (2x), unknown type of surgery 20yr ago (1 X).

†All synchronic metastasis that were treated by primary resection (1 X, control group), ablation (1 X, control group) or complete response after neoadjuvant treatment (1 X, control group), all before LAR.

‡At index surgery or constructed in the first postoperative period (ie, due to complications).

§Control group: Started as TEM but converted to LAR due to perforation (1 x), iatrogenic bladder perforation, repaired by sutures (1 X), conversion to open surgery due to the patients' anatomy and limited space (2x), perioperative fecal spill, continuation of antibiotics postoperative (1X), iatrogenic injury to the vas deferens due to adhesions caused by radiotherapy (1X). Intervention group: conversion to open surgery due to the patients' anatomy and limited space (1X), iatrogenic bladder perforation, repaired by sutures (1X).

ASA classification indicates the American Society of Anaesthesiologists (ASA) physical status classification system; IQR, interquartile range; TNM, tumor-node-metastasis classification system.

TABLE 2. Wexner Incontinence Score

Outcomes	Timing of Measurement	Intention to Treat		
Intention to Treat Population		**Control Group n = 51**	**Intervention Group n = 44**	***P* Value**
Total Wexner score, median (IQR)	M2 (baseline)	5.0 (12.0)	10.5 (8.0)	0.01
	M3	5.0 (7.0)	6.0 (8.0)	0.17
Change scores (M3-M2)	Objected mean difference	−0.8	−2.8	0.01
		95% CI −1.8 till 0.1	95% CI −4.0 till −1.7	
	Adjusted mean difference*	−1.3	—2.3	0.13
		95% CI −2.2 till —0.4	95% CI −3.3 till −1.4	
Per Protocol Population		**Control Group n = 49**	**Intervention Group n = 36**	***P* Value**
Total Wexner score, median (IQR)	M2 (baseline)	5.0 (12.0)	10.5 (7.0)	0.01
	M3	5.0 (4.0)	5.5 (8.0)	0.21
Change scores (M3-M2)	Objected mean difference	−0.8	−3.2	<0.01
		95% CI −1.7 till 0.2	− 4.5 till −1.8	
	Adjusted mean difference*	−1.2	−2.6	0.08
		95% CI −2.2 till −0.3	95% CI −3.7 till −1.5	
Intention to Treat Population Baseline Wexner Score <16 (No Near-complete Incontinence)		**Control Group n = 45**	**Intervention Group n = 36**	***P* Value**
Total Wexner score, median (IQR)	M2 (baseline)	4.0 (9.0)	9.0 (8.0)	0.01
	M3	5.0 (4.0)	5.0 (5.0)	0.21
Change scores (M3-M2)	Objected mean difference	−0.3	−2.6	<0.01
		95% CI −1.2 till 0.6	95% CI −3.8 till −1.4	
	Adjusted mean difference*	−0.7	−2.1	0.045
		95% CI −1.6 till 0.2	95% CI −3.1 till −1.1	

*ANC0VA with mean change in Wexner incontinence score (M3-M2) adjusted for age, preoperatively assessed tumor height, neoadjuvant treatment and Wexner baseline score. ANCOVA indicates analysis of covariance; IQR, interquartile range; M2, baseline measurement; M3, primary endpoint.

Secondary Outcomes

At baseline, urgency was reported in 29.4% (n = 15) and 61.4% (n = 27) of the patients in the control and PFR groups, respectively. After 3 months, 25.5% (n = 13) of the patients in the control group and 25.0% (n = 11) in the PFR group reported urgency. Multivariable logistic regression analysis showed a benefit of PFR after correction for presence of urgency at baseline and preoperative tumor height (OR 0.220, 95% CI 0.056–0.859, $P = 0.03$). No associations between PFR and the presence of stool frequency, flatus, clustering, and liquid stool were found.

The changed scores on the 4 domains of FIQL scale were not different after PFR in nonselected patients. In the per-protocol population, an improvement in depression and self-perception scores was found (PFR: 0.36, n = 36, control: −0.15, n = 49, $P = 0.03$). Patients who reported at least moderate incontinence reported clinically relevant improvements after PFR on all 4 FIQL domains. Even more substantial improvements in QoL were found in patients with at least moderate incontinence but with a baseline Wexner score lower than 16: lifestyle (PFR: 0.66, control: −0.19, $P = 0.01$), coping and behaviour (PFR: 0.57, control: −0.17, $P = 0.01$), depression and self-perception (PFR: 0.44, control: −0.32, $P = 0.01$), and embarrassment (PFR: 0.34, control: −0.44, $P = 0.03$) (Table 3 and Supplementary File 5, http://links.lww.com/SLA/D607).

The EORTC QLQ-CR29 data showed no significant differences after correction for baseline scores in nonselected patients (Supplementary File 5, http://links.lww.com/SLA/D607). Relevant domains that reached clinical significance in favor of PFR were anxiety (PFR: −6.8, control: 0.0, $P = 0.13$) and urinary frequency (PFR: −9.7, control: −4.1, $P = 0.35$). Questions related to sexual activity were frequently left open and are therefore not reported in this manuscript.

After adjustments for baseline scores, no difference in LARS score improvements were found (PFR: −2.4, 95% CI −4.5 to −3.1, control: −2.3, 95% CI −4.3 to −0.3, $P = 0.93$) (Supplementary File 5, http://links.lww.com/SLA/D607). Multivariable logistic regression analysis with major LARS at follow-up as dependent variable, showed no benefit for PFR after correction for baseline and preoperative tumor height (OR 0.499, 95% CI 0.17–1.5, $P = 0.22$).

Safety Analysis

No serious adverse events related to PFR were reported. Two PFR patients were referred to the outpatient clinic (anastomotic stricture and suboptimal laxative use). No participants were withdrawn from the study on account of PFR-related harm.

DISCUSSION

This RCT evaluated the effects of PFR on postoperative bowel-related functional outcomes after LAR for rectal cancer in comparison to usual care without PFR. No improvements in incontinence scores or QoL were found after PFR in the group as a whole, while better functional outcomes were found in several subgroups, such as patients with urgency or those with at least moderate incontinence.

This is the first RCT to investigate PFR in a multicenter setting in patients after rectal cancer surgery. Few studies have investigated the role of PFR in comparison with usual care. A previously published, matched case-control study suggested that anal sphincter training after rectal cancer surgery could improve fecal incontinence specific QoL.[12] The present study found similar results in selected patients but not in the group as a whole. Most studies that found improvements in incontinence scores after pelvic floor muscle training and biofeedback lacked a control group.[15,31,32] This hampers clinical interpretation, because spontaneous recovery of bowel function is expected to occur.[33] Other studies that compared PFR to usual care investigated an intervention that was not provided by a registered physiotherapist.[13,34,35] Nevertheless, they reported that pelvic

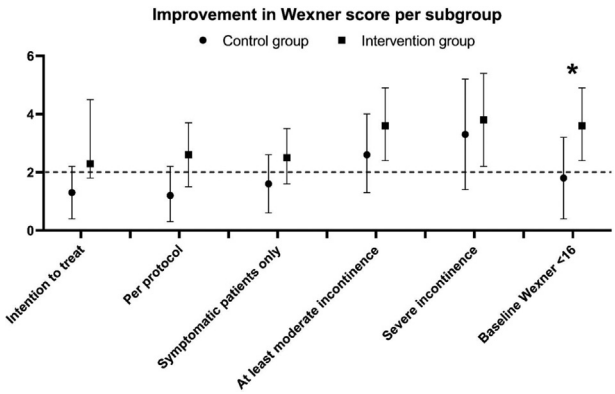

FIGURE 2. Improvement in mean Wexner incontinence score per subgroup. 95% confidence intervals are shown. Symptomatic incontinence only (baseline Wexner score >0), at least moderate incontinence (baseline Wexner score ≥5), severe incontinence (baseline Wexner score ≥9). The dashed line represents the border for clinically relevant improvements. *Statistical significance.

floor muscle training affects QoL positively[16,35] or leads to lower Wexner scores.[34]

Although this trial did not find an improvement in incontinence scores after PFR in all patients, specific groups were identified that did benefit from PFR. First, PFR led to less urgency at follow-up. Urgency is considered to be one of the most distressing symptoms from a patient's perspective.[36,37] Patients who have no control over urgency of defecation and as a consequence hardly ever leave their homes, might in actual fact rarely be incontinent, but their QoL will be detrimentally affected.[38] In case of urgency problems it, therefore, seems justified to refer patients for PFR. Because it was not the goal of this study to investigate the effect of urgency of QoL, no direct comparison on QoL-items comparing patients who did or did not improve regarding urgency was made. This might explain why overall QoL in the entire group was not significantly different between the control and intervention group. Nevertheless, reduced urgency in the multivariate analysis might still have important impact on QoL, as we know from previous literature. Second, an improvement in incontinence scores after PFR was found when only patients with a baseline Wexner score below 16 were included. This would suggest that patients who suffer from near-complete incontinence are unlikely to respond to rehabilitation. The impact of severe damage to

TABLE 3. Fecal Incontinence Related Quality of Life (FIQL)

		Intention to Treat Population		
FIQL Change Scores	**Timing of Measurement**	**Control Group**	**Intervention Group**	***P* Value**
Nonselected patients		n = 51	n = 44	—
Lifestyle	Adjusted mean difference*	0.04 95% CI −0.34 to 0.42	0.36 95% CI −0.05 to 0.77	0.26
Coping and behaviour	Adjusted mean difference*	0.01 95% CI −0.29 to 0.31	0.23 95% CI −0.10 to 0.55	0.34
Depression and self-perception	Adjusted mean difference*	−0.15 95% CI −0.45 to 0.14	0.28 95% CI −0.04 to 0.59	0.05
Embarrassment	Adjusted mean difference*	−0.33 95% CI −0.72 to 0.06	0.16 95% CI −0.26 to 0.58	0.09
At least moderate incontinence at baseline		n = 28	n = 35	—
Lifestyle	Adjusted mean difference*	−0.06 95% CI −0.49 to 0.37	0.58 95% CI 0.20 to 0.97	0.03
Coping and behaviour	Adjusted mean difference*	−0.09 95% CI −0.44 to 0.27	0.44 95% CI −0.12 to 0.75	0.03
Depression and self-perception	Adjusted mean difference*	−0.31 95% CI −0.64 to 0.02	0.36 95% CI 0.06 to 0.65	<0.01
Embarrassment	Adjusted mean difference*	−0.41 95% CI −0.85 to 0.03	0.21 95% CI −0.19 to 0.60	0.04
Baseline Wexner <16 (no near-complete incontinence)		n = 45	n = 36	—
Lifestyle	Adjusted mean difference*	−0.02 95% CI −0.44 to 0.40	0.38 95% CI −0.08 to 0.85	0.20
Coping and behaviour	Adjusted mean difference*	−0.03 95% CI −0.37 to 0.30	0.29 95% CI −0.08 to 0.67	0.20
Depression and self-perception	Adjusted mean difference*	−0.14 95% CI −0.46 to 0.19	0.32 95% CI −0.05 to 0.68	0.07
Embarrassment	Adjusted mean difference*	−0.34 95% CI −0.77 to 0.10	0.26 95% CI −0.22 to −0.75	0.07
At least moderate incontinence at baseline and baseline Wexner <16 (no near-complete incontinence)		n = 22	n = 27	—
Lifestyle	Adjusted mean difference*	−0.19 95% CI −0.68 to 0.30	0.66 95% CI 0.22 to 1.1	0.01
Coping and behaviour	Adjusted mean difference*	−0.17 95% CI −0.57 to 0.23	0.57 95% CI 0.21 to 0.93	<0.01
Depression and self-perception	Adjusted mean difference*	−0.32 95% CI −0.70 to 0.06	0.44 95% CI 0.09 to 0.78	<0.01
Embarrassment	Adjusted mean difference*	−0.44 95% CI −0.95 to 0.07	0.34 95% CI −0.12 to 0.81	0.03

*ANCOVA with mean change score (M3-M2) adjusted for baseline score. ANCOVA indicates analysis of covariance.

the fecal continence system, including both afferent and efferent nerves, may be the reason. Without some remaining control over the continence system, PFR cannot achieve any effects.[39]

Third, patients with at least moderate incontinence reported relevant improvements in all FIQL domains after PFR, while controls showed deterioration. This group was represented by approximately 65% of all included patients. It seems obvious that patients with perfect continence cannot improve with PFR. QoL improved even more when patients who reported near-complete incontinence were excluded. This finding supports our hypothesis that only patients without complete loss of function will benefit from PFR. These findings are in line with previous reports stating that better scores in all 4 FIQL domains after pelvic floor muscle treatment and biofeedback were found after including patients with bowel dysfunction after LAR.[32] This all argues in favor of selective use of PFR after LAR to improve QoL. It should be noted that, in comparison with similar studies, a relatively high percentage of patients suffered from severe incontinence. This may be explained by the possibility that those with few symptoms did not want to participate in this trial, while those with lots of complaints did.

Besides PFR being a physical training, it is also considered a form of general counseling with attention for patients' lifestyle, coping mechanisms, and psychosocial status.[12] The improved QoL of patients who suffer from incontinence may therefore be subject to a placebo effect.[40] However, the reduction of incontinence in specific groups makes it unlikely that improvements are due to such an effect. Nevertheless, we cannot exclude any placebo effect, especially because it was theoretically impossible to blind patients for PFR.

One of the strengths of this RCT was that it succeeded in creating a network of dedicated pelvic floor physiotherapists serving the participating hospitals. They were all trained to work with the same uniform PFR protocol. This assured us that every patient received a well-defined intervention in contrast to previous studies. Furthermore, the combination of all 4 relevant training modalities in the PFR protocol and the selection of the questionnaires, is a strength of this study.[17,41] Lastly, broad inclusion criteria were used to design a trial that evaluates the effectiveness of an intervention in real-life routine clinical practice. This greatly benefits the external validity of this study. It should be noted that patients were included before the introduction of the new definition of rectal cancer (below the sigmoid take-off) which could have consequences on the patient selection.

The main limitation of this study is a difference in incontinence scores at baseline. These differences are considered to be coincidental seeing that baseline questionnaires were completed before randomization and all patients were correctly allocated to their study arm. An investigator driven selection bias is unlikely because an randomization was done by a computerized sequence generator without the use of input from the baseline measurements.

It complicates the process of making a statement about the efficacy of PFR after LAR for nonselected rectal cancer patients because of the need for statistical corrections with linear regression. Possibly, a larger sample size would have been necessary in retrospect.

Furthermore, selection bias could have been introduced by patients with severe functional complaints who therefore were not willing to participate in this trial given the possibility of being allocated to the non-PFR group. This also applies to patients who experienced postoperative complications such as anastomotic leakage. Finally, patients in the control group received usual care. This implies that variations in daily practice between hospitals introduces heterogeneity. However, it may also be seen as a strength because it improves the external validity.

Future research will evaluate costs and sustainability of results. We emphasize the importance of future research regarding the identification of factors that might predict therapeutic success of PFR (Supplementary File 6, http://links.lww.com/SLA/D608). In addition, further studies can select patients based on this trial for robust evidence on secondary outcomes as well given that subgroup analyses should be interpreted with a certain amount of caution because of potential bias due to reduced statistical power.

In conclusion, no benefit was found of PFR in all patients after LAR for rectal cancer. Several subgroups were identified that did benefit from PFR, such as patients with urgency or with at least moderate incontinence and no near-complete incontinence. A selective referral policy to PFR for these patients promises better postoperative functional outcomes.

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