Biological Mesh Closure of the Pelvic Floor After Extralevator Abdominoperineal Resection for Rectal Cancer A Multicenter Randomized Controlled Trial (the BIOPEX-study)

Biological Mesh Closure of the Pelvic Floor After Extralevator Abdominoperineal Resection for Rectal Cancer

A Multicenter Randomized Controlled Trial (the BIOPEX-study)

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Objective: To determine the effect of biological mesh closure on perineal wound healing after extralevator abdominoperineal resection (eAPR).

Background: Perineal wound complications frequently occur after eAPR with preoperative radiotherapy for rectal cancer. Cohort studies have suggested that biological mesh closure of the pelvic floor improves perineal wound healing.

Methods: Patients were randomly assigned to primary closure (standard arm) or biological mesh closure (intervention arm). A non–cross-linked porcine acellular dermal mesh was sutured to the pelvic floor remnants in the intervention arm, followed by a layered closure of the ischioanal and subcutaneous fat and skin similar to the control intervention. The outcome of the randomization was concealed from the patient and perineal wound assessor. The primary endpoint was the rate of uncomplicated perineal wound healing defined as a Southampton wound score of less than 2 at 30 days postoperatively. Patients were followed for 1 year.

Results: In total, 104 patients were randomly assigned to primary closure (n = 54; 1 dropouts) and biological mesh closure (n = 50; 2 dropouts). Uncomplicated perineal wound healing rate at 30 days was 66% (33/50; 3 not evaluable) after primary closure, which did not significantly differ from 63% (30/48) after biological mesh closure [relative risk 1.056; 95% confidence interval (CI) 0.7854–1.4197; $P = 0.7177$). Freedom from perineal hernia at 1 year was 73% (95% CI 60.93–85.07) versus 87% (95% CI 77.49–96.51), respectively ($P = 0.0316$).

Conclusions: Perineal wound healing after eAPR with preoperative radiotherapy for rectal cancer was not improved when using a biological mesh. A significantly lower 1-year perineal hernia rate after biological mesh closure is a promising secondary finding that needs longer follow-up to determine its clinical relevance.

Keywords: abdominoperineal resection, biological mesh, perineal wound healing, perineal wound infection, primary perineal wound closure

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Perineal wound complications after abdominoperineal resection (APR) for rectal cancer are a frequent source of morbidity.[1] Perineal wound infection, dehiscence, and pelvic abscesses often require prolonged postoperative wound care, which may last for several months and may result in a chronic perineal sinus or fistula. Furthermore, the perineal wound can be associated with prolonged pain, sitting problems, and require daily wound care, all of which can interfere with a patients' quality of life. As rectal cancer is one of the most common cancers in the Western world with up to one third of these patients undergoing an APR, perineal wound complications are an important health care problem.[2]

Treatment-related morbidity has become increasingly important since the oncological outcome of rectal cancer has been optimized with improved surgical techniques. In a standard APR approach, the total mesorectal excision plane is followed down to the pelvic floor. Because of the anatomical narrowing of the distal mesorectum, this results in a typical tapering of the resected specimen at the level of the primary tumor, with a risk of a positive resection margin and perforation. A pooled analysis of 5 European randomized controlled trials showed that standard APR was an independent risk factor for local recurrence and associated with a significantly lower 5-year survival rate compared with low anterior resection.[3] Using an extralevator approach (eAPR), an en bloc resection, which includes the levator muscles, results in a cylindrical specimen. Although there is still controversy about the role of the extralevator approach and the extent of the resection, the surgical quality of APR has improved over time.[4,5] In addition, the increased use of preoperative radiotherapy has contributed to improved locoregional control.[6]

Although both preoperative radiotherapy and wider surgical excision have improved the oncological outcome, it has come at the

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expense of increased perineal wound complications.[7,8] Closure of the perineum after eAPR can either be performed as a primary layered closure of the ischioanal and subcutaneous tissues, or by using a biological mesh or autologous tissue flap. There is currently no consensus as to the best surgical technique for perineal wound closure after eAPR in terms of short- and long-term wound complications and quality of life. Available data from cohort studies are for the most part of low quality. Despite the lack of evidence, biological meshes are increasingly being used for pelvic floor closure after eAPR. Several recent reviews concluded that there is a need for a properly designed prospective study to address this important question.[9,10] This a multicenter randomized controlled trial aimed to determine the effectiveness of pelvic floor reconstruction using a biological mesh in improving perineal wound healing compared to primary perineal wound closure after eAPR in patients with low rectal cancer who have undergone preoperative radiotherapy.

METHODS

Study Design

The BIOPEX-study is a multicenter, parallel-group, single blinded, superiority, randomized controlled trial, performed in 1 nonteaching hospital, 6 teaching hospitals, and 4 university hospitals in the Netherlands, and 1 university hospital in the United Kingdom. In this investigator-initiated study, eligible patients were randomized between primary closure of the perineal defect (standard arm) and pelvic floor reconstruction using a biological mesh followed by primary perineal closure (intervention arm) (Fig. 1). An independent observer, unaware of the intervention to which the patient was allocated, evaluated perineal wound healing using the Southampton wound scoring system (Supplemental Digital Content 1, http://links.lww.com/SLA/B118) and perineal herniation after 7 and 30 days, and 3, 6, 9, and 12 months postoperatively.[11] An independent observer also took photographs of the perineal wound on clinical follow-up, which were evaluated by the trial coordinators (G.M, C.K.) in relation to the Southampton wound score assigned by the independent observer. When a discrepancy arose, the trial coordinator contacted the local independent observer to reach consensus. At twelve months postoperatively, computed tomography (CT-scan) of the pelvis was performed, to assess for the presence of a presacral sinus, perineal sinus, and perineal herniation. Quality of Life questionnaires were taken at each follow-up interval. In addition during follow-up, the nature and severity of any wound event, all medical or surgical interventions, re-operations and oncological outcome were

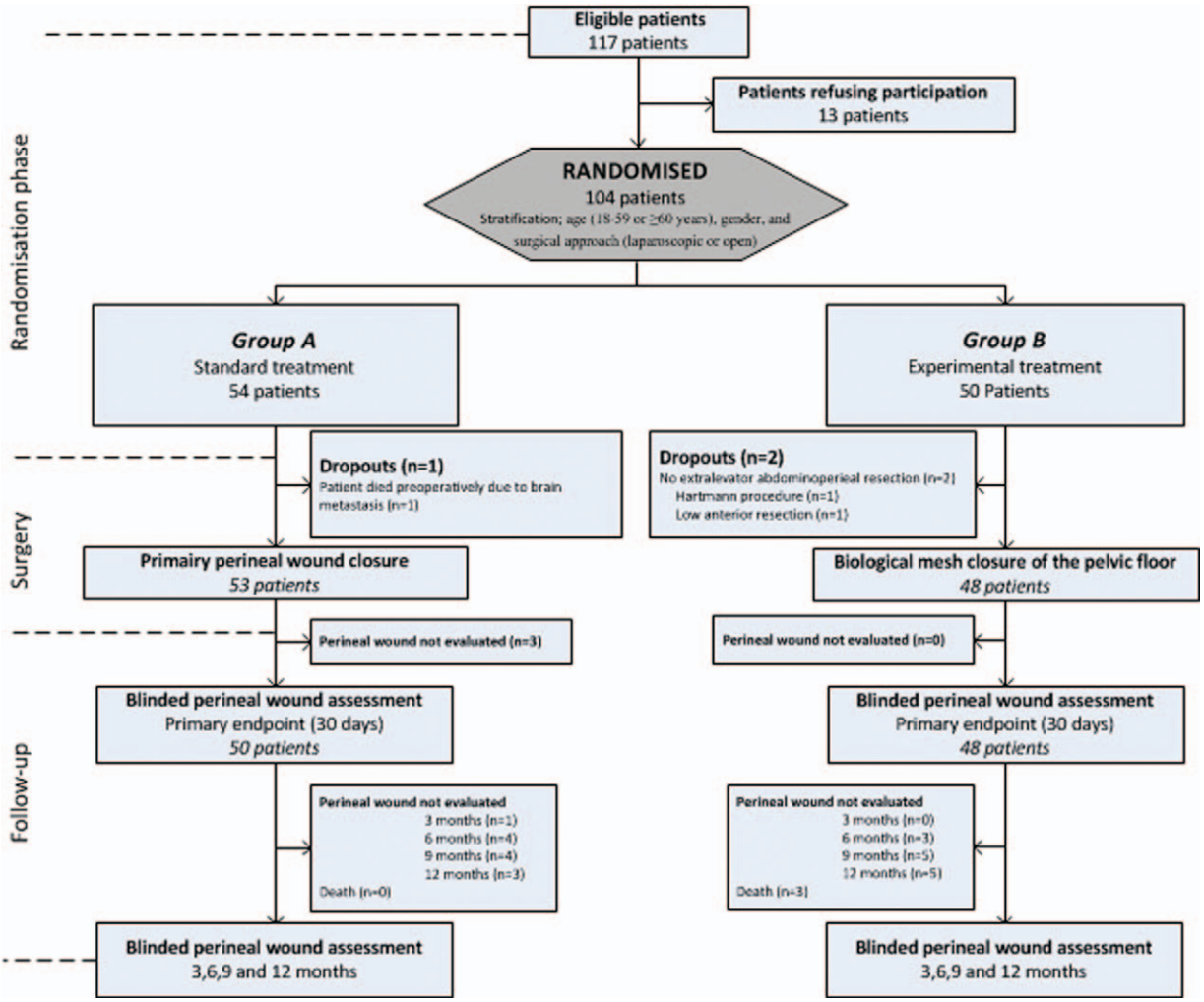

FIGURE 1. Flow diagram of the BIOPEX study.

recorded. The study protocol was approved by the ethical review board of the Academic Medical Center, Amsterdam, the Netherlands. The study protocol has been previously published and was available online at the start of the trial.[12]

Patients

Eligible patients were preoperatively approached for participation into the BIOPEX-study at the surgical outpatient clinics. A patient was classified as eligible when the following criteria were fulfilled; age older than 18 years, primary rectal cancer, life expectancy of more than 2 years, preoperative radiotherapy for rectal cancer, planned for an eAPR, and able to return for outpatient follow-up visits. Preoperative radiotherapy could consist of either short-course radiotherapy (5×5 Gy) or long-course chemoradiotherapy. Exclusion criteria were the need for a total exenteration, sacral resection above the level of S4/5, previous pelvic irradiation, severe systemic or collagen disorders which could affect wound healing (ie, renal failure requiring dialysis, liver cirrhosis, immunocompromised status, and Marfan syndrome), sensitivity to porcine-derived products or polysorbate, and enrolment in other trials that could influence wound healing. Written informed consent was obtained for all participating patients before randomization.

Randomization and Masking

After written informed consent, patients were randomly assigned by the local physician to primary perineal wound closure (standard arm) or pelvic floor reconstruction using a biological mesh followed by primary perineal closure (intervention arm) in a 1:1 ratio. Randomization was performed by a central automated randomization Web site preoperatively, with random concealed block sizes (2, 4, and 6) and stratification for age (18−59 or 60 years or older), sex, and surgical approach (laparoscopic or open). The allocation of the treatment was blinded to the patient and perineal wound assessor.

Procedures

All patients received preoperative antibiotics, according to the local trial site protocol. Patient positioning for the perineal phase of the eAPR (supine or prone), the surgical approach (laparoscopic or open), and the use of omentoplasty were left to the discretion of the operating surgeon. In all patients, the principles of an extralevator approach were adhered to, in which the levator muscles were laterally transected to leave a muscular cuff around the resected tumor. The coccyx was not routinely resected, except for surgical exposure or oncological reasons. Excision of the perineal skin and ischioanal fat was limited if oncologically justified. The quality of the resected specimen was evaluated by the local trial site pathologists and photographs were sent to the trial coordinator (G.M.).

In the standard arm, the perineal wound was closed in layers by stitching together the ischioanal and subcutaneous fat using interrupted Vicryl (Ethicon Inc, Johnson & Johnson, New Brunswick, New Jersey) sutures. The skin was closed using interrupted sutures according to the preference of the surgeons. Placement of an abdominal drain and/or perineal drain was left to the discretion of the local surgeon. For pelvic floor reconstruction in the experimental arm, an acellular non−cross-linked biological mesh derived from porcine dermis (6×10 cm, Strattice, LifeCell, Acelity Company, Branchburg, NJ), was fixed using interrupted Prolene (Ethicon Inc, Johnson and Johnson) or polydioxanone sutures. The mesh was sutured posteriorly either side of the coccyx or sacrum. Laterally, the biological mesh was attached to the remnant of the levator muscle and anteriorly to the transverse perineal muscles. A suction drain was placed on top of the mesh and the ischioanal and subcutaneous fat and skin were closed, similar to the control arm. To ensure a standardized technique of biological mesh closure, a course on fresh frozen cadavers was undertaken before the start of the trial and a refreshment course was delivered after 52 patients had been included in the study. In addition, in centers with limited experience in biological mesh closure at the start of the trial, the technique for pelvic floor reconstruction was proctored by an experienced principle investigator (P.T.) at their trial site hospital.

Outcome

The primary endpoint was the percentage of uncomplicated perineal wound healing defined as a Southampton wound score of less than 2 at 30 days postoperatively. Secondary endpoints were perineal wound healing according to the Southampton wound score, symptomatic and asymptomatic perineal hernia, postoperative pain according to the visual analogue scale at 3, 6, 9, and 12 months. Other secondary outcomes were the presence of persistent perineal or presacral sinus, need for readmission or reinterventions related to presacral abscesses or perineal wound problems, and length of hospital stay during 1 year of follow-up. Generic quality of life was assessed using the Short Form-36 version 2 and a 5-level version of the 5-dimensional EuroQol (EQ-5D-5L) preoperatively, and at 3 and 12 months after surgery. Health utilities were derived from patients' scoring profiles on the EQ-5D-5L based on available crosswalk value sets. Also the gastrointestinal quality of life was assessed using the EORTC (QLQ-C30/CR29) preoperatively and at 3, 6, 9, and 12 months postoperatively.

All serious adverse events defined as death, a life-threatening event, need for hospitalization, prolongation of hospitalization, significant disability, or incapacity were reported to the trial coordinators (G.M., C.K.) and the ethical review board. Although this was considered to be a low-risk trial because of the use of biological meshes for pelvic floor reconstruction in routine clinical practice outside a trial setting, an interim analysis on safety was nevertheless performed after 52 included patients. This analysis showed a non-skewed distribution in serious adverse events between both groups.

Statistical Analyses

Given the lack of high-quality data in the current literature, we defined a clinically relevant difference in primary uncomplicated perineal wound healing as a difference of 25%, which would justify the routine use of a costly biological mesh in addition to primary perineal closure. Applying a chi-square test with a 2-sided 0.05 significance level and a power of 80% with an estimated drop-out of 5%, a total number of 104 patients (52 per group) was needed to detect an increase in uncomplicated wound healing from 60% to 85%. According to distribution, descriptive data were reported as median with interquartile range (IQR) or mean with standard deviation (SD). Categorical data were analyzed with the chi-square test or Fisher exact test and continuous variables were analyzed using the Mann-Whitney-Wilcoxon test. The primary endpoint was assessed using chi-square test and presented with absolute incidences and relative risk (RR) with 95% confidence interval (95% CI). A post-hoc multivariable Cox regression (without a time variable) on the primary endpoint was performed to assess the effect of wound closure, corrected for the way in which the operation started (abdominal phase or perineal phase), omentoplasty and perineal drain (excluding the 3 stratification parameters age, sex, and type of surgery associated with randomization); results are presented as RR and 95% CIs. A P value of 0.05 was considered significant. Perineal hernia rate was assessed with a Kaplan-Meier curve, and study arms were compared using a log rank test. Pain scores over time were analyzed using a generalized linear mixed model with log link, assuming Poisson distributed pain scores and a first-order autoregressive covariance structure. Treatment and the repeating times of measurement were modeled as fixed effects. Perineal wound scores over time were

analyzed using a generalized estimating equations model with logit link, assuming a multinomial ordinal distribution of the perineal wound score and a first-order autoregressive repeated covariance structure. Treatment and time (as the within-subject factor) were modeled as fixed effects. All questionnaires were analyzed according to the manuals and presented as domain and summarized scores. Questionnaire outcome comparisons were analyzed using linear mixed models with treatment and time modeled as fixed effects. Diagonal covariance structures were assumed. The Bonferroni method was applied to correct for multiple comparisons of different points in time. All the data were analyzed in accordance to the intention-to-treat principle. No data monitoring committee was installed. The trial was registered on a trial registration Web site under the registration code NCT01927497 (clinicaltrials.gov).

RESULTS

Recruitment

Between the first of February 2013 and the first of September 2014, 117 eligible patients were approached to participate in the BIOPEX study. Of those 117 patients, 104 patients consented to the trial (Supplemental Digital Content 2, http://links.lww.com/SLA/B118) of which 54 patients were randomly assigned to primary perineal wound closure (standard arm) and 50 patients to biological mesh closure of the pelvic floor (intervention arm). After randomization, 1 patient in the primary perineal closure group died preoperatively, and 2 patients in the biological mesh closure group did not undergo eAPR, but a sphincter preserving procedure. Because these 3 patients could not be evaluated for the primary endpoint, these patients were excluded from further analysis, resulting in 53 patients in the standard arm and 48 patients in the intervention arm (Fig. 1). A protocol violation occurred in 2 additional patients (no preoperative radiotherapy in the control group, VRAM flap closure in the experimental group), but these patients were analyzed in the assigned groups according to intention to treat.

Baseline Characteristics

The baseline characteristics of the included patients are described in Table 1. The mean age of the whole group was 64 years (SD 12), and 74% (75/101) of the patients were male. Surgery

TABLE 1. Baseline Characteristics

		Group A Primary Wound Closure (n = 53)	Group B Biological Mesh Closure (n = 48)	*P*
Hospital	Nonteaching hospital (n, %)	4 (8)	7 (15)	0.6868
	Teaching hospital (n, %)	29 (55)	21 (44)	
	University hospital (n, %)	20 (38)	20 (42)	
Sex	Male (n, %)	39 (74)	36 (75)	0.9200
	Female (n, %)	14 (26)	12 (25)	
Age	Years ± SD	64 (12)	65 (12)	0.9972
Body mass index	kg/m^2 ± SD	26 (3)	26 (5)	0.8885
ASA-classification	ASA-1 (n, %)	37 (70)	29 (60)	0.5533
	ASA-2 (n, %)	15 (28)	17 (35)	
	ASA-3 (n, %)	1 (2)	2 (4)	
Previous surgery	Abdominal surgery (n, %)	11 (21)	6 (13)	0.2681
	Pelvic surgery (n, %)	2 (4)	3 (6)	0.6664
	Anorectal surgery (n, %)	5 (9)	4 (8)	1.0000
Comorbidity	Diabetes (n, %)	4 (8)	5 (10)	0.7326
	Respiratory (n, %)	5 (9)	4 (8)	1.0000
	Cardiac (n, %)	6 (11)	10 (21)	0.5868
	Vascular (n, %)	1 (2)	2 (4)	0.6030
	Smoking (n, %)	6 (11)	3 (6)	0.4803
Medication	Immunosuppressants (n, %)	2 (4)	0	0.4962
Weight loss before surgery	>10% of total body weight (n, %)	5 (9)	3 (6)	0.7811
Obstruction	For which diverting stoma (n, %)	4 (8)	4 (8)	1.0000
Tumor location	Distance between lower border tumor and anal verge in cm on MRI (IQR)	1 (0–3)	2 (0–3)	
Preoperative radiotherapy*	Short course (5 × 5 Gy) (n, %)	10 (19)	10 (21)	0.8414
	Long course chemoradiotherapy (n, %)	42 (79)	38 (79)	
Quality of resected specimen	High quality (n, %)	31 (58)	30 (62)	0.9320
	Moderate quality (n, %)	4 (8)	3 (6)	
	Poor quality (n, %)	3 (5)	4 (8)	
	Not reported (n, %)	15 (28)	11 (23)	
Radical surgical resection	Circumferential resection margin >1 mm (n, %)	49 (92)	44 (92)	1.0000
γpTNM stage	Stage 1 (n, %)	19 (36)	24 (50)	0.4848
	Stage 2 (n, %)	16 (30)	11 (23)	
	Stage 3 (n, %)	12 (23)	10 (21)	
	Stage 4 (n, %)	6 (11)	3 (6)	

Data are presented according to distribution in means with standard deviation (SD) or in medians with interquartile range (IQR).

*A protocol violation occurred in 2 additional patients, of which 1 patient, in the primary closure group, did not receive preoperative radiotherapy.

ASA classification indicates American Society of Anesthesiologists classification; high-quality specimen, mesorectum intact and cylindrical specimen; moderate-quality specimen, small defects in mesorectum or conical specimen; MRI, magnetic resonance imaging; N, number of patients; poor quality, dissection of the rectal wall or perforation; γpTNM, pathological tumor staging after neoadjuvant (chemo)radiotherapy.

started with the abdominal phase first in 32 (60%) of the 53 patients in the primary closure group, which was significantly less than 42 (88%) of the 48 patients in the biological mesh group ($P = 0.0030$). Laparoscopic surgery for the abdominal phase was performed in 60% (32/53) of the patients who underwent primary closure, and in 62% (30/48) of the patients who underwent biological mesh closure ($P = 0.8409$). An omentoplasty was placed in the pelvis in 70% (37/53) of the patients undergoing primary closure, which was significantly higher compared to 50% (24/48) in the biological mesh group ($P = 0.0420$). The coccyx was resected in 19% (10/53) of the patients in the primary closure group, which did not significantly differ from 17% (8/48) in the biological mesh group ($P = 0.8008$). The additional resections performed during eAPR are displayed in the Supplemental Digital Content 3, http://links.lww.com/SLA/B118. Tumor or rectal perforation occurred in 6% (3/53) of the patients in the primary closure group, and in 8% (4/48) of the patients in the biological mesh group ($P = 0.7055$). A perineal drain was placed in 30% (16/53) of the patients in the primary closure group, which is significantly lower than 79% (38/48) in the biological mesh group ($P < 0.0001$). The mean duration of the surgery after primary closure was 222 minutes (SD 67), which is significantly less than 275 minutes (SD 81) for the biological mesh group ($P = 0.0005$).

The number of patients in whom the perineal wound was not assessed at the different follow-up intervals is shown in Figure 1.

Primary Outcome

At 30 days postoperatively, the percentage of patients with uncomplicated perineal wound healing (Southampton wound score <2) was 66% (33/50, 3 patients could not be evaluated) after primary perineal closure, which did not significantly differ from 63% (30/48) after biological mesh closure (RR 1.056; 95% CI 0.7854–1.4197; $P = 0.7177$). Also the severity of the perineal wound infection according to the Southampton wound score was not significantly different between primary closure and biological mesh closure at postoperative day 30 ($P = 0.1599$–0.5916; Table 2). Correcting for the differences in baseline characteristics between the randomization groups in a post-hoc multivariable regression analysis, did not reveal any significant association between uncomplicated perineal wound healing at 30 days and primary perineal closure (RR 1.035; 95% CI 0.582–1.840; $P = 0.9067$), perineal phase first (RR 1.127; 95% CI 0.611–2.078; $P = 0.7019$), no omentoplasty (RR 1.111; 95% CI 0.651–1.897; $P = 0.6986$), and no perineal drain (RR 1.017; 95% CI 0.566–1.825; $P = 0.9562$). The post-hoc power for the primary endpoint, with an increase in uncomplicated perineal wound healing from 60% to 85%, applying a chi-square test with a 2-sided 0.05 significance level with 50 and 48 patients in the randomized groups, respectively, was 80%.

Secondary Outcomes

During 1 year of follow-up, perineal wound healing was uncomplicated at any postoperative time interval in 52% (27/52, missing 1 patient) of the patients after primary closure, and in 54% (26/48) of the patients after biological mesh closure (RR 1.028; 95% CI 0.952–1.110; $P = 0.4706$). During the complete follow-up period, there was no significant difference between randomization groups for the severity of the perineal wound infection according to the Southampton wound score ($P = 0.7461$; Supplemental Digital Content 4, http://links.lww.com/SLA/B118).

Freedom from perineal hernia at 1 year was 73% (95% CI 60.93–85.07) of the patients after primary closure, which was significantly less than 87% (95% CI 77.49–96.51) in the biological mesh group [$P = 0.0316$ (log-rank test); Table 2]. The median duration between surgery and a perineal hernia was nine months (IQR 5–12). As assessed by clinical examination and/or CT scan, perineal hernias occurred throughout the follow-up period in the primary closure group, but mainly at the end of the 12-month follow-up in the biological mesh group (Fig. 2). Of the 17 patients with a perineal hernia, 6 patients were asymptomatic, 3 patients were operated for their perineal hernia, and the remaining 8 patients were symptomatic but conservatively treated.

TABLE 2. Perineal Wound Healing

		Group A Primary Closure (n = 53)*	Group B Biological Mesh Closure (n = 48)*	P
Normal perineal wound healing (Southampton wound score <2)	7 Days postoperative (n, %)	35/50 (70)	34/47 (72)	0.7993
	30 Days postoperative (n, %)	33/50 (66)	30/48 (63)	0.7177
	3 Months postoperative (n, %)	42/52 (81)	39/48 (81)	0.9511
	6 Months postoperative (n, %)	43/49 (88)	39/45 (87)	0.8643
	9 Months postoperative (n, %)	44/49 (90)	41/43 (95)	0.4419
	12 Months postoperative (n, %)	49/50 (98)	41/43 (95)	0.5940
Severity of infection (at 30 days)	Erythema and other signs of inflammation (n, %)	0	2/48 (4)	0.2373
	Clear or hemoserous discharge (n, %)	7/50 (14)	9/48 (19)	0.5916
	Pus discharge (n, %)	7/50 (14)	2/48 (4)	0.1599
	Deep or severe wound infection (n, %)	3/50 (6)	5/48 (10)	0.4823
Surgical complications (within 90 days)	Overall (n, %)	20 (38)	20 (42)	0.8964
Nonsurgical complications (within 90 days)	Overall (n, %)	2 (6)	3 (6)	0.6689
Perineal hernia	Freedom from perineal hernia (%, 95% CI)	73 (61–85)	87 (77–97)	0.0316
Within 12 months	Asymptomatic perineal hernia (n, %)	4 (8)	2 (4)	
Surgical reinterventions	Total (n, %)	5 (10)	3 (6)	0.7169
For perineal wound problems	Perineal hernia correction (n, %)	2 (4)	1 (2)	
within 12 months	Abscess drainage (n, %)	1 (2)	2 (4)	
	Gluteus flap (n, %)	2 (4)	0	
Percutaneous reintervention For perineal wound problems within 12 months	Abscess drainage (n, %)	1 (2)	3 (6)	0.3480

Surgical complications are urinary retention, ileus, trocar hernia, postoperative bleeding, presacral fistula, stoma dysfunction, pneumonia, perineal hernia <90 days, (appendix). Nonsurgical complications are; atrial fibrillation, heart decompensation, urinary tract infection, cholecystitis, the flu (appendix).

*Number of evaluable patients for each group differs for different time intervals postoperatively (Fig. 1).

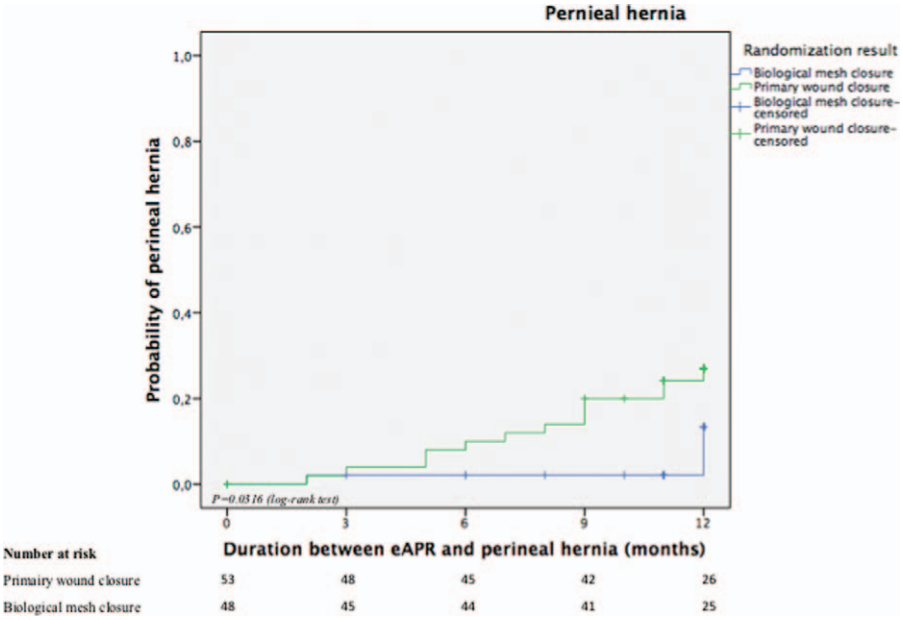

FIGURE 2. Kaplan-Meier curve of developing a perineal hernia over time.

The median postoperative stay was 7 days (IQR 6–11) after primary closure and 8 days (IQR 7–13) after biological mesh closure ($P = 0.2080$). Postoperative complications (within 90 days) were not significantly different between the randomization groups for surgical complications ($P = 0.8964$) and nonsurgical complications ($P = 0.6689$; Table 2, Supplemental Digital Content 6, http://links.lww.com/SLA/B118). There was also no significant difference between both groups for surgical ($P = 0.7169$) and percutaneous reinterventions ($P = 0.3480$) within 12 months (Table 2). None of the biological meshes had to be explanted. Postoperative pain did not significantly differ between the randomization groups at all follow-up visits ($P = 0.764$; Supplemental Digital Content 5, http://links.lww.com/SLA/B118).

Quality of Life

The response rates of the quality of life questionnaires (Short Form-36 version 2, EQ 5D-5L, EORTC QLQ C30, and EORTC QLQ CR29) varied between 74% (75/101) at 9 months postoperatively to 91% (92/101) for the preoperative questionnaires. The quality of life questionnaires showed no significant differences in the main outcome scores. In addition, the subscales also did not show any statistically significant differences after correction for multiple testing. The responses and subscales are shown in the Supplemental Digital Content 7, http://links.lww.com/SLA/B118.

Oncological Follow-up

During follow-up, adjuvant chemotherapy was given to 6 patients in the primary closure group and in 8 patients in the biological mesh group ($P = 0.5680$). A local recurrence occurred in three patients after primary closure and in 1 patient after biological mesh closure ($P = 0.3621$; log-rank test). Metastasis to liver or lung occurred in 14 patients. In total, 3 patients died, all in the biological mesh group, but unrelated to the intervention. One patient died after a Bricker procedure for a bladder fistula 11 months after eAPR, 1 patient died due to septic shock of unknown origin 3 months after eAPR during adjuvant chemotherapy, and 1 patient died due to an intracerebral bleeding 10 months after eAPR.

DISCUSSION

Biological mesh closure of the pelvic floor following eAPR in patients who have undergone preoperative radiotherapy resulted in an uncomplicated perineal wound healing rate of 63% at 30 days postoperatively, which did not significantly differ from 66% in the primary perineal wound closure group. No other significant differences in perineal wound healing or quality of life were observed at other time intervals postoperatively between both randomization groups up to 1 year after surgery. Freedom of perineal hernia at 1 year was significantly higher in the biological mesh group compared with the control group, namely 87% versus 73%, respectively.

The strength of the present study is the randomized design. Furthermore, this was a multicenter trial in which university hospitals, teaching, and nonteaching hospitals in the Netherlands and United Kingdom participated, thereby reflecting routine daily practice and increases the external validity of the trial. All participating surgeons are experienced rectal cancer specialists. Regarding surgical quality assurance in biological mesh placement, hands-on workshops, and onsite proctoring was provided.

Limitations of the present study could be that some participating centers did not assess all patients for participation in the BIOPEX study, or did not report all eligible nonparticipating patients to the trial coordinators. In addition, eligible nonparticipating patients who were reported to the trial coordinators did not gave informed consent to assess their medical records and comparability with the included patients. Furthermore, this trial was designed to look for a significant difference of at least 25% in perineal wound healing. One might argue that the study was underpowered to detect smaller differences, but the observed percentages of wound healing (63% vs 66%) do not indicate any difference at all in favor of the biological mesh. Finally, to objectively assess perineal wounds with limited inter- and intraobserver variability is challenging, especially when wound scoring systems are limited and not validated for every type of wound. The Southampton wound score was, however, the best available method for this purpose.

The increasing use of biological meshes to close the defect in the pelvic floor in routine practice may be a result of a number of

publications suggesting a positive effect on perineal wound healing. We performed an update of our previously published systematic review with meta-analysis.[8] The pooled perineal wound complication rate after eAPR with preoperative radiotherapy was 38% (95% CI 24–54; I^2 72%; 3 studies, n = 188)[13–15] after primary closure, and 11% (95% CI 6–19; I^2 0%; 3 studies, n = 104)[14,16,17] after biological mesh closure (Supplemental Digital Content 8, http://links.lww.com/SLA/B118). These were, however, all nonrandomized cohort studies with almost exclusively retrospective data. Furthermore, surgical and patient characteristics greatly differed among the primary closure studies, which may explain the considerable statistical heterogeneity (I^2).

The considerable difference in perineal wound complication rates between the systematic review of the literature and the present randomized controlled trial is most likely related to several methodological shortcomings of the previously published cohort studies. Besides potential confounding by indication, perineal wound complications were not prospectively evaluated using a standardized wound scoring in the cohort studies, but mostly by retrospective chart review. In addition, patients and wound assessors were not blinded. All these factors may have resulted in underreporting of perineal wound complications in the biological mesh studies.

One explanation for not finding a significant effect on perineal wound healing might be that any positive effect of biological mesh reconstruction of the pelvic floor is nullified by creating a dead space between the biological mesh and the closed perineum. In this dead space, fluid may accumulate and develop into an abscess within a contaminated field. A perineal drain was most often placed in the biological mesh group but did not show a significant effect in the post-hoc analysis on perineal wound healing. Therefore, a perineal drain might be insufficient to collapse the dead space between the biological mesh and skin. The filling of this dead space with a muscle or fasciocutaneous transposition flap might, therefore, increase wound healing. The downside of a tissue flap is, however, donor side morbidity and the risk of flap necrosis.

The updated pooled perineal hernia rate of the literature was 4% (95% CI 1–11; I^2 67%; 6 studies, n = 411)[13,14,18–20] after primary wound closure, and 7% (95% CI 4.5–11; I^2 0%; 8 studies, n = 287)[14,16,21–26] after biological mesh closure. In contrast, the 1-year perineal hernia rate of 27% after primary wound closure in the present RCT was significantly higher than 13% after biological mesh closure. The remarkably low rate of perineal hernia after primary wound closure in the updated systematic review is likely related to the primary oncological design of these cohort studies, without a focus on perineal wound complications, and retrospective data collection. Biological mesh studies are often primarily concerned with perineal wound outcome, which explains the similar hernia rate compared to our RCT (7% vs 9%). Follow-up of cohort series in literature often exceeds the 12 months follow-up in the present study. Degradation of the non–cross-linked biological mesh starts at around 6 months, whereas full degradation may take up to 1 year.[27] As a result, the perineal hernia rate is expected to increase over time. Perineal hernia repair is considered a noncontaminated procedure and can be performed with a less expensive synthetic mesh. Although promising, it seems to be too early to conclude on the cost-effectiveness of biological mesh closure after eAPR at 12 months follow-up considering the reduced perineal hernia rate.

Newer techniques need to be investigated to resolve the increasing clinical problem of perineal wound complications. Currently, only 1 single-center, open-label randomized controlled trial is being conducted in which patients are randomized between a porcine biological mesh and gluteus maximus myocutaneous flap closure of the perineal wound after eAPR (NEAPE; clinicaltrial.gov identifier: NCT01347697). The present study does not include a primary closure group. In a systematic review of cohort studies, pelvic floor closure after eAPR with tissue flaps was found to be equally effective as a biological mesh closure, but results of the NEAPE trial are awaited.[9]

We conclude that biological mesh closure of the pelvic floor is not superior in perineal wound healing after eAPR in patients with rectal cancer who have undergone preoperative radiotherapy when compared to primary perineal wound closure. Furthermore, biological mesh closure did not improve the quality of life, but did increase the duration of surgery. Biological mesh closure resulted in a significantly lower perineal hernia rate after 1 year, but to determine whether a perineal hernia is really prevented in a number of patients or only delayed by biological mesh closure needs longer follow-up.

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REFERENCES

1. Asplund D, Prytz M, Bock D, et al. Persistent perineal morbidity is common following abdominoperineal excision for rectal cancer. *Int J Colorectal Dis*. 2015;30:1563–1570.
2. Weitz J, Koch M, Debus J, et al. Colorectal cancer. *Lancet*. 2005;365:153–165.
3. Den Dulk M, Putter H, Collette L, et al. The abdominoperineal resection itself is associated with an adverse outcome: the European experience based on a pooled analysis of five European randomized clinical trials on rectal cancer. *Eur J Cancer*. 2009;45:1175–1183.
4. Zhou X, Sun T, Xie H, et al. Extralevator abdominoperineal excision for low rectal cancer: a systematic review and meta-analysis of the short-term outcome. *Colorectal Dis*. 2015;17:474–481.
5. Van Leersum N, Martijnse I, Den Dulk M, et al. Differences in circumferential resection margin involvement after abdominoperineal excision and low anterior resection no longer significant. *Ann Surg*. 2014;259:1150–1155.
6. McCarthy K, Pearson K, Fulton R, et al. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. *Cochrane Database Syst Rev*. 2012;12:CD008368.
7. Prytz M, Angenete E, Bock D, et al. Extralevator abdominoperineal excision for low rectal cancer-extensive surgery to be used with discretion based on 3-year local recurrence results: a registry-based, observational national cohort study. *Ann Surg*. 2016;263:516–521.
8. Musters GD, Buskens CJ, Bemelman WA, et al. Perineal wound healing after abdominoperineal resection for rectal cancer: a systematic review and meta-analysis. *Dis Colon Rectum*. 2014;57:1129–1139.
9. Foster JD, Pathak S, Smart NJ, et al. Reconstruction of the perineum following extralevator abdominoperineal excision for carcinoma of the lower rectum: a systematic review. *Colorectal Dis*. 2012;14:1052–1059.
10. Butt HZ, Salem MK, Vijaynagar B, et al. Perineal reconstruction after extralevator abdominoperineal excision (eLAPE): a systematic review. *Int J Colorectal Dis*. 2013;28:1459–1468.
11. Bailey IS, Karran SE, Toyn K, et al. Community surveillance of complications after hernia surgery. *BMJ*. 1992;304:469–471.
12. Musters GD, Bemelman WA, Bosker RJ, et al. Randomized controlled multicenter study comparing biological mesh closure of the pelvic floor with primary perineal wound closure after extralevator abdominoperineal resection for rectal cancer (BIOPEX-study). *BMC Surg*. 2014;14:1458.
13. De Broux E, Parc Y, Rondelli F, et al. Sutured perineal omentoplasty after abdominoperineal resection for adenocarcinoma of the lower rectum. *Dis Colon Rectum*. 2005;48:476–481.
14. Han JG, Wang ZJ, Qian Q, et al. A prospective multicenter clinical study of extralevator abdominoperineal resection for locally advanced low rectal cancer. *Dis Colon Rectum*. 2014;57:1333–1340.
15. Nissan A, Guillem JG, Paty PB, et al. Abdominoperineal resection for rectal cancer at a specialty center. *Dis Colon Rectum*. 2001;44:27–35.
16. Han JG, Wang ZJ, Gao ZG, et al. Pelvic floor reconstruction using human acellular dermal matrix after cylindrical abdominoperineal resection. *Dis Colon Rectum*. 2010;53:219–223.

17. Vaughan-Shaw PG, King AT, Cheung T, et al. Early experience with laparoscopic extralevator abdominoperineal excision within an enhanced recovery setting: analysis of short-term outcomes and quality of life. *Ann R Coll Surg Engl*. 2011;93:451–459.
18. Bebenek M. Abdominosacral amputation of the rectum for low rectal cancers: ten years of experience. *Ann Surg Oncol*. 2009;16:2211–2217.
19. Musters GD, Sloothaak DA, Roodbeen S, et al. Perineal wound healing after abdominoperineal resection for rectal cancer: a two-center experience in the era of intensified oncological treatment. *Int J Colorectal Dis*. 2014;29:1151–1157.
20. Toshniwal S, Perera M, Lloyd D, et al. A 12-year experience of the Trendelenburg perineal approach for abdominoperineal resection. *ANZ J Surg*. 2013;83:853–858.
21. Christensen HK, Nerstrom P, Tei T, et al. Perineal repair after extralevator abdominoperineal excision for low rectal cancer. *Dis Colon Rectum*. 2011;54:711–717.
22. Dalton RS, Smart NJ, Edwards TJ, et al. Short-term outcomes of the prone perineal approach for extra-levator abdomino-perineal excision (elAPE). *Surgeon*. 2012;10:342–346.
23. Dinnewitzer A, Meissnitzer M, Meissnitzer T, et al. Dynamic magnetic resonance imaging evaluation of pelvic reconstruction with porcine dermal collagen mesh following extra-levator abdominoperineal excision for primary rectal cancer. *Int J Colorectal Dis*. 2015;30:491–496.
24. Han JG, Wang ZJ, Wei GH, et al. Randomized clinical trial of conventional versus cylindrical abdominoperineal resection for locally advanced lower rectal cancer. *Am J Surg*. 2012;204:274–282.
25. Jensen KK, Rashid L, Pilsgaard B, et al. Pelvic floor reconstruction with a biological mesh after extralevator abdominoperineal excision leads to few perineal hernias and acceptable wound complication rates with minor movement limitations: single-center experience including clinical examination and interview. *Colorectal Dis*. 2014;16:192–197.
26. Peacock O, Simpson JA, Tou SI, et al. Outcomes after biological mesh reconstruction of the pelvic floor following extra-levator abdominoperineal excision of rectum (APER). *Tech Coloproctol*. 2014;18:571–577.
27. Pascual G, Sotomayor S, Perez-Lopez P, et al. Long term behavior of biological prostheses used as abdominal wall substitutes. *Histol Histopathol*. 2014;29:139–149.