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ORIGINAL ARTICLE – COLORECTAL CANCER

Promising Long-Term Outcomes After Pelvic Exenteration

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ABSTRACT

Background. Pelvic exenteration (PE) is a complex and challenging surgical procedure. The reported results of this procedure for primary and recurrent disease are limited and conflicting.

Methods. This study analyzed patient outcomes after all PEs performed in the authors' department between October 2001 and December 2016. Relevant patient data were obtained from a prospective database. Morbidity and mortality were reported for all patients. For patients with malignant disease, differences in perioperative outcomes, prognostic indicators for overall survival, and local and systemic disease recurrence were analyzed using uni- and multivariate analyses.

Results. The study enrolled 187 patients. Of the 183 patients with malignant disease, 63 (38.2%) had primary locally advanced tumors and 115 (62.5%) had recurrent tumors. The 10-year overall survival rate was 63.5% for the patients with primary tumors that were curatively resected and 20.9% for the patients with recurrent disease ($p = 0.02$). The 10-year survival rate for the patients with extrapelvic disease who underwent curative resection was 37%. Multivariable analysis identified margin positivity ($p < 0.01$), surgery lasting longer than 7 h ($p = 0.02$), and recurrent disease ($p < 0.01$) as predictors of poor survival. Multivariate analysis of local and systemic disease recurrence showed recurrent disease ($p < 0.01$) as the only significant prognostic factor.

Conclusions. Pelvic exenteration has good long-term results, even for patients with extrapelvic disease. The oncologic outcome for patients with recurrent disease is worse than for patients with primary disease. However, even for these patients, long-time survival is possible.

Pelvic exenteration (PE) to remove locally advanced primary or recurrent cancer is a complex and challenging procedure with a particularly high morbidity rate. It has a significant impact on the patient's quality of life and is among the most feared operations in general surgery. This holds particularly true when two permanent ostomies need to be constructed. However, in the last two decades, improved surgical techniques and perioperative management have significantly reduced complications and mortality after PEs.[1] Thus, PE has gained attraction as a "salvage" procedure for primary, locally advanced pelvic cancer and recurrent disease.[2]

Recently, we and others formed the PelvEx consortium to pool and analyze the results of pelvic exenterations (PE) used to treat primary rectal cancer.[3] A total of 1291 patients comprised the PelvEx cohort, including 32 patients with colorectal cancer from our center.

Multi-national analysis demonstrated that margin negativity can be achieved in about 80% of cases and that these patients fare relatively well, with a median survival of 43 months. At the same time, the 30-day mortality rate was only 1.5%, demonstrating that this extensive surgical procedure is safe.

In the same collaborative (PelvEx), factors affecting survival after PE were investigated for 47 patients from our institution together with 1184 patients with recurrent rectal cancer. Margin negativity and bone resection were identified as the most important factors affecting survival.[4] However, no long-term outcome data for a large patient

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cohort including primary and recurrent pelvic malignancies after PE have been published to date. To address this, we analyzed all patients who had undergone a PE in our department between October 2001 and December 2016. In our view, the current study is relevant because we assessed the outcomes of all patients who received this procedure, regardless of the underlying disease and whether the cancer was primary or recurrent.

PATIENTS AND METHODS

All patients who underwent PE at our institution between October 2001 and December 2016 were eligible for inclusion in the study. Resections were performed to treat primary and recurrent pelvic malignancies and benign pelvic diseases. Data were collected and maintained prospectively in a dedicated database.

Preoperative Assessment

Patients with malignant indications were subjected to a broad diagnostic workup to evaluate the feasibility of curative resection. A curative resection was defined as a resection with histopathologically confirmed tumor-free margins (> 1 mm) of the operative "pelvic" specimen (R0) and the additional R0 resection of extrapelvic disease, if present.

The local tumor burden was examined preoperatively by clinical examination, endoscopy/endosonography (if feasible), and magnet resonance imaging (MRI) or contrast-enhanced computed tomography (CT) scan of the pelvis. Distant metastases were screened by CT scan of the chest and abdomen. Patients with irresectable extrapelvic disease were excluded from the analysis, and patients with resectable extrapelvic disease detected pre- or intraoperatively were not excluded.

Neoadjuvant treatment (chemoradiotherapy, radiotherapy, or chemotherapy) was offered on a case-by-case basis after discussion by multidisciplinary care teams. Treatment was based on patient history, tumor type, and tumor burden. Preoperative biopsies were taken if histologic confirmation was necessary. The disease stage was determined 6–8 weeks after completion of neoadjuvant treatment and before surgery.

Surgery

Major surgery was performed for all included patients. A total PE (TPE) may include a partial resection of the sacrum or the coccygeum and was defined as an abdominoperineal resection (APR), including resection of the pelvic floor, pelvic side wall, internal genitals, and bladder.

After resection of the bladder, an ileal or colonic conduit was formed. An APR including resection of the internal genitals or sacrum (partial or complete) with the pelvic floor/side wall was defined as a posterior PE (PPE). An anterior PE (APE) was defined as a sphincter-sparing rectal resection with removal of the reproductive organs and bladder.

If preoperative imaging suggested pelvic resectability with close margins, the patients were offered intraoperative radiotherapy (IORT), depending on previous doses. Surgery was performed in a dedicated operating theater with an integrated linear accelerator (Siemens Mobitron, ME, Siemens, Concord, CA, USA). After resection, 10- to 15-Gy single doses were intraoperatively administered to areas with a high risk of residual disease.

Perioperative Morbidity and Mortality

Perioperative adverse effects within 30 days after surgery were classified according to Dindo et al.[5] Grades 1 and 2 were classified as minor complications, and grades 3–5 were classified as major complications. Operative mortality was defined as death within 30 days after the operation.

Adjuvant Therapy

Adjuvant chemotherapy was indicated routinely for patients with node-positive disease according to the postoperative staging and for patients who had received preoperative chemoradiotherapy. Postoperative chemoradiotherapy was not indicated.

Follow-Up Evaluation

Patients were followed up at regular intervals in our outpatient clinics and in the National Center for Tumor Diseases (Heidelberg, Germany). Clinical evaluation included a physical examination every 3 months for 2 years and then annually until 5 years. A CT scan or MRI of the abdomen and pelvis was performed 3 months after surgery and then every 6 months or annually, according to clinical circumstances. Follow-up information on those patients who did not receive postoperative treatment at our institution was obtained periodically from the primary care physicians. All living patients were contacted and followed up until January 2018.

Data Collection and Definitions

Data on patients' demographics, comorbidity, operative details, postoperative mortality, morbidity, and histologic results were obtained from medical charts. The operation time was ascertained from the operation report. All operations were performed or supervised by experienced visceral (including colorectal) surgeons.

Statistical Analyses

The distribution of categorical data was presented as absolute and relative frequencies and compared using the Chi square test. Continuous data were presented as means and standard deviations. Patients with benign disease and those who died within 30 days after surgery were excluded from oncologic outcome analysis.

Overall, local and systemic recurrence-free survival rates were estimated by the Kaplan–Meier method using the log-rank test for statistical comparisons among groups. Time to local recurrence (LR) or systemic recurrence (SR) was measured from the date of surgery to the time of first local or systemic recurrence. Overall survival (OS) was analyzed from the date of surgery until the date of death from any cause or the date of the last follow-up evaluation. The local and systemic recurrence-free survival rates were analyzed for the patients with R0 resection of local disease and no postoperative evidence of extrapelvic disease. These rates were calculated from the date of PE until the date of diagnosis of local or distant disease recurrence, respectively. Patients were censored at the last time point of known contact or death.

Factors potentially related to OS, local recurrence-free survival (LRFS), and systemic recurrence-free survival (SRFS) were assessed using Cox proportional hazard regression models. Variables with a p value lower than 0.10 in the univariate analysis and selected clinical variables were entered into the multifactorial Cox regression models to determine factors independently associated with OS, LRFS, and SRFS. A p value lower than 0.05 was considered statistically significant. For statistical analysis, IBM SPSS software, version 22 (IBM Deutschland GmbH, Ehningen, Germany) was used.

RESULTS

During the study period, PE was performed for 187 patients (4 patients with benign disease and 183 patients with malignant disease). Of the patients with malignant disease, 68 (37.2%) had primary disease and 115 (62.8%) had recurrent disease. Notably, data for 32 patients with primary colorectal cancer (50.8%, 32/63) and 47 patients with recurrent colorectal cancer (40.9%, 47/115) in the current cohort were included in previous multicenter publications. However, both the number of patients and the aim and scope of the current analysis differ considerably from those in these publications.[3,4]

TABLE 1 Indications for 183 pelvic exenterations

	Primary *n* (%)	Recurrent *n* (%)
Total	68 (37.2)	115 (62.8)
Colorectal	40 (58.8)	63 (54.8)
Gynecologic	15 (22.1)	22 (19.1)
Sarcoma	8 (11.8)	7 (6.1)
Anal	0	13 (11.3)
Other	5 (7.4)	10 (8.7)

Patients with colorectal cancer composed the majority of this group, and patients with gynecologic cancer, sarcoma, anal cancer, and rare malignant indications were summarized as "other" for the analysis. The details are depicted in Table 1.

Patient Characteristics

Table 2 summarizes the characteristics of the patients who underwent PE for malignant disease. All the cancer patients (AP, $n = 183$) were analyzed together, and the patients with colorectal cancer (CRC, $n = 103$) also were analyzed separately. In both groups, the patients who had primary disease were compared with the patients who had recurrent disease.

In the AP group and the CRC subgroup, age, gender, American Society of Anesthesiologists class, and presence of extrapelvic disease did not differ between the primary and recurrent patients.

Significantly more patients with primary disease were selected to receive neoadjuvant treatment than patients with recurrent disease (AP: 47.1% [primary] vs. 26.1% [recurrent], $p = 0.004$; CRC: 62.5% [primary] vs. 27% [recurrent], $p < 0.001$). After surgical intervention, 51.5% of all the primary patients and 22.6% of all the recurrent patients received adjuvant chemotherapy ($p < 0.001$). This difference was observed only if the CRC patients were included in the analysis (52.5% vs. 30.2%; $p = 0.023$).

Operative and Perioperative Data

The operative and perioperative results are summarized in Table 3. In this study, TPE was performed for 135

TABLE 2 Characteristics of patients who underwent pelvic exenteration for malignant disease

	All cancer sites				Colorectal cancer			
	Total *n* (%)	Primary *n* (%)	Recurrent *n* (%)	*p* value	Total *n* (%)	Primary *n* (%)	Recurrent *n* (%)	*p* value
n	183	68 (37.2)	115 (62.8)		103	40 (38.8)	63 (61.2)	
Mean age (years)	59 ± 11	59 ± 11	59 ± 12	0.6	60 ± 12	61 ± 12	58 ± 13	0.16
Gender				0.1				0.26
Female	104 (56.8)	44 (64.7)	60 (52.2)		47 (45.6)	21 (52.5)	26 (41.3)	
Male	79 (43.2)	24 (35.3)	55 (47.8)		56 (54.4)	19 (47.5)	37 (58.7)	
ASA stage				0.32				0.18
2	157 (94)	62 (96.9)	95 (92.2)		88 (93.6)	39 (97.5)	49 (90.7)	
3 and 4	10 (6)	2 (3.1)	8 (7.8)		6 (6.4)	1 (2.5)	5 (9.3)	
Neoadjuvant therapy[a]				< 0.01				< 0.01
No	121 (66.1)	36 (52.9)	85 (73.9)		61 (59.2)	15 (37.5)	46 (73)	
Yes	62 (33.9)	32 (47.1)	30 (26.1)		42 (40.8)	25 (62.5)	17 (27)	
Extrapelvic disease				0.65				0.49
No	131 (71.6)	50 (73.5)	81 (70.4)		76 (73.8)	31 (77.5)	45 (59.2)	
Yes	52 (28.4)	18 (26.5)	34 (29.6)		27 (26.2)	9 (22.5)	18 (28.6)	
Adjuvant therapy				< 0.01				0.02
No	122 (66.7)	33 (48.5)	89 (77.4)		63 (61.2)	19 (47.5)	44 (69.8)	
Yes	61 (33.3)	35 (51.5)	26 (22.6)		40 (38.8)	21 (52.5)	19 (30.2)	

ASA American Society of Anesthesiologists

[a]Radiotherapy, chemotherapy, or chemoradiotherapy

(73.8%) of the patients in the entire cohort, whereas APE was performed for 5 (2.7%) and PPE for 43 (23.5%) of the patients. Among the CRC patients, TPE was performed for 79 (76.7%) and PPE for 24 (23.3%) of the patients. The APE procedure was not performed for CRC patients. Overall, 67% of the TPE surgeries were performed for recurrent disease.

In the AP group and the CRC subgroup, the median operative times for the recurrent patients were longer than for the primary patients (AP: 437 ± 139 min [primary] vs. 515 ± 143 min [recurrent], $p < 0.001$; CRC: 454 ± 135 min [primary] vs. 524 ± 138 min [recurrent], $p = 0.013$). In the AP group, the operative times were significantly longer for the patients with bone resection (574 ± 156 min vs. 469 ± 138 min; $p < 0{,}001$) and for the patients who received TPE (509 ± 141 min vs. 420 ± 142 min; $p < 0{,}001$). Furthermore, the duration of surgery also was significantly longer for the patients that received IORT than for the patients without IORT (529 ± 129 min vs. 461 ± 150 min; $p = 0.002$). The longer operative time for the recurrent patients could be explained by the higher rate of TPE, bone resection, and IORT in this group.

A simultaneous bone resection was performed for 26 (25.2%) of 103 CRC patients. In the entire cohort, a simultaneous bone resection was performed for 30 (16.4%) of 183 patients, suggesting that this procedure was predominantly necessary for the CRC patients (recurrent, 30.2% vs. primary, 17.5%).

Bone resection significantly increased the mean intraoperative blood loss (4.3 ± 3.4 l vs. 2.8 ± 1.9 l; $p = 0.02$), and the intraoperative blood loss was significantly higher for the recurrent CRC patients (CRC: 2.6 l; range 0.3–15 l vs. 2 l; range 0.5–15 l; $p < 0.01$; AP: 2.5 l; range 0.3–15 l vs. 2 l; range 0.5–15 l; $p = 0.09$).

Curative R0 resection was achieved for 72% (29/40) of the primary CRC patients, whereas the R0 resection rate for the recurrent CRC patients was 54% (34/63). After PE, curative R0 resection, microscopic positive margins (R1 resection), and gross residual disease (R2 resection) were present respectively in 51.4% (94/183), 61.2% (63/103), and 43.2% (79/183) of the AP patients compared with 35.9% (37/103), 5.5% (10/183), and 2.9% (3/103) of the CRC patients. The two groups did not differ in distribution of primary and recurrent patients.

In the entire cohort, 106 patients (57.9%) had at least one major complication, and 92 patients (50.3%) had at least one minor complication. The major complication rate was higher for the primary patients in the entire cohort and for the CRC subgroup, but this difference was not significant. However, as outlined in Supplementary Table 1, more complications occurred among the recurrent patients than among the primary patients (176 vs. 96 complications). The median hospital stay was similar in the two groups.

TABLE 3 Operative and perioperative data for patients after pelvic exenteration for malignant disease

	All cancer sites				Colorectal cancer			
	Total *n* (%)	Primary *n* (%)	Recurrent *n* (%)	*p* value	Total *n* (%)	Primary *n* (%)	Recurrent *n* (%)	*p* value
n	183	68 (37.2)	115 (62.8)		103	40 (38.8)	63 (61.2)	
	n = 103							
Mean operative time (min)	486 ± 146	437 ± 139	515 ± 143	< 0.01	497 ± 141	454 ± 135	524 ± 138	0.01
Mean blood loss (l)	3.1 ± 0.5	2.7 ± 2.1	3.4 ± 2.9	0.05	3.1 ± 2.4	2.3 ± 1.3	3.6 ± 2.9	0.02
Mean hospital stay (days)	30 ± 23	28 ± 15	30 ± 26	0.56	31 ± 20	31 ± 14	31 ± 24	0.99
Bone resection				0.29				0.3
No	153 (83.6)	61 (89.7)	92 (80)		77 (74.8)	33 (82.5)	44 (69.8)	
Yes	30 (16.4)	7 (10.3)	23 (20)		26 (25.2)	7 (17.5)	19 (30.2)	
Coccygectomy	2 (1.1)	0	2 (1.7)		0	0	0	
Partial sacrectomy	27 (14.8)	7 (10.3)	20 (17.4)		25 (24.3)	7 (17.5)	18 (28.6)	
Complete sacrectomy	1 (0.5)	0	1 (0.9)		1 (1)	0	1 (1.6)	
Pelvic exenteration				0.09				0.2
Complete	135 (73.8)	44 (64.7)	91 (79.1)		79 (76.7)	28 (70)	51 (81)	
Anterior	5 (2.7)	2 (2.9)	3 (2.6)		0	0	0	
Posterior	43 (23.5)	22 (32.4)	21 (18.3)		24 (23.3)	12 (30)	12 (19)	
Perineal reconstruction				0.4				0.69
No	172 (94)	65 (95.6)	107 (93)		97 (94.2)	38 (95)	59 (93.7)	
Yes	11 (6)	3 (4.5)	8 (7)		6 (5.8)	2 (5)	4 (6.4)	
VRAM	4 (2.2)	0	4 (3.5)		2 (1.9)	0	2 (3.2)	
Gluteus flap	4 (2.2)	1 (1.5)	3 (2.6)		2 (1.9)	1 (2.5)	1 (1.6)	
VRAM and gluteus flap	3 (1.6)	2 (3)	1 (0.9)		2 (1.9)	1 (2.5)	1 (1.6)	
IORT				0.04				0.06
No	115 (62.8)	49 (72.1)	66 (57.4)		55 (53.4)	26 (62)	29 (46)	
Yes	68 (37.2)	19 (27.9)	49 (42.6)		48 (46.6)	14 (35)	34 (54)	
Resection margin				0.3				0.17
R0	94 (51.4)	40 (58.8)	54 (47)		63 (61.2)	29 (72.5)	34 (54)	
R1	79 (43.2)	25 (36.8)	54 (47)		37 (35.9)	10 (25)	27 (42.9)	
R2	10 (5.5)	3 (4.4)	7 (6.1)		3 (2.9)	1 (2.5)	2 (3.2)	
Complications[a]								
Major	106 (57.9)	43 (63.2)	63 (59.4)	0.26	68 (66)	29 (72.5)	39 (61.2)	0.27
Minor	92 (50.3)	31 (45.6)	61 (53.0)	0.33	57 (55.3)	21 (52.5)	36 (57.1)	0.64
Mortality (30-day)	3 (1.6)	0	3 (2.6)	0.29	1 (1)	0	1 (1.6)	1

In the entire cohort, three deaths (1.3%) occurred during the perioperative period, and the deceased all were patients with recurrent disease. One patient experienced massive bleeding 3 days after PE and died of hemorrhagic shock. Another patient died of progressive pulmonary insufficiency after pneumonia, and the third patient died of acute respiratory distress syndrome after massive aspiration.

Overall Survival

The 10-year OS (estimated by Kaplan–Meier analysis) for all the primary patients was 53.5% compared with 10.6% for all the recurrent patients ($p < 0.01$). This difference also was seen between the primary and recurrent CRC patients (54.1% vs. 9.2%; $p < 0.01$; Fig. 1a, b). For the curatively resected patients (R0 and M0) with primary disease, the 10-year OS was 65.3% for the AP patients and 63.9% for the CRC patients. Interestingly, the survival rate for the recurrent patients was significantly reduced in both groups, even for the patients with R0 resection of local disease and no distant metastases (AP: 20.9%, $p = 0.02$ [AP primary vs. recurrent disease]; CRC: 18.3%, $p = 0.05$ [CRC primary vs. CRC-recurrent disease]; Fig. 1c, d).

The uni- and multivariate analyses of factors associated with OS are summarized in Table 4. The multivariate analysis (Cox's proportional hazards model) identified

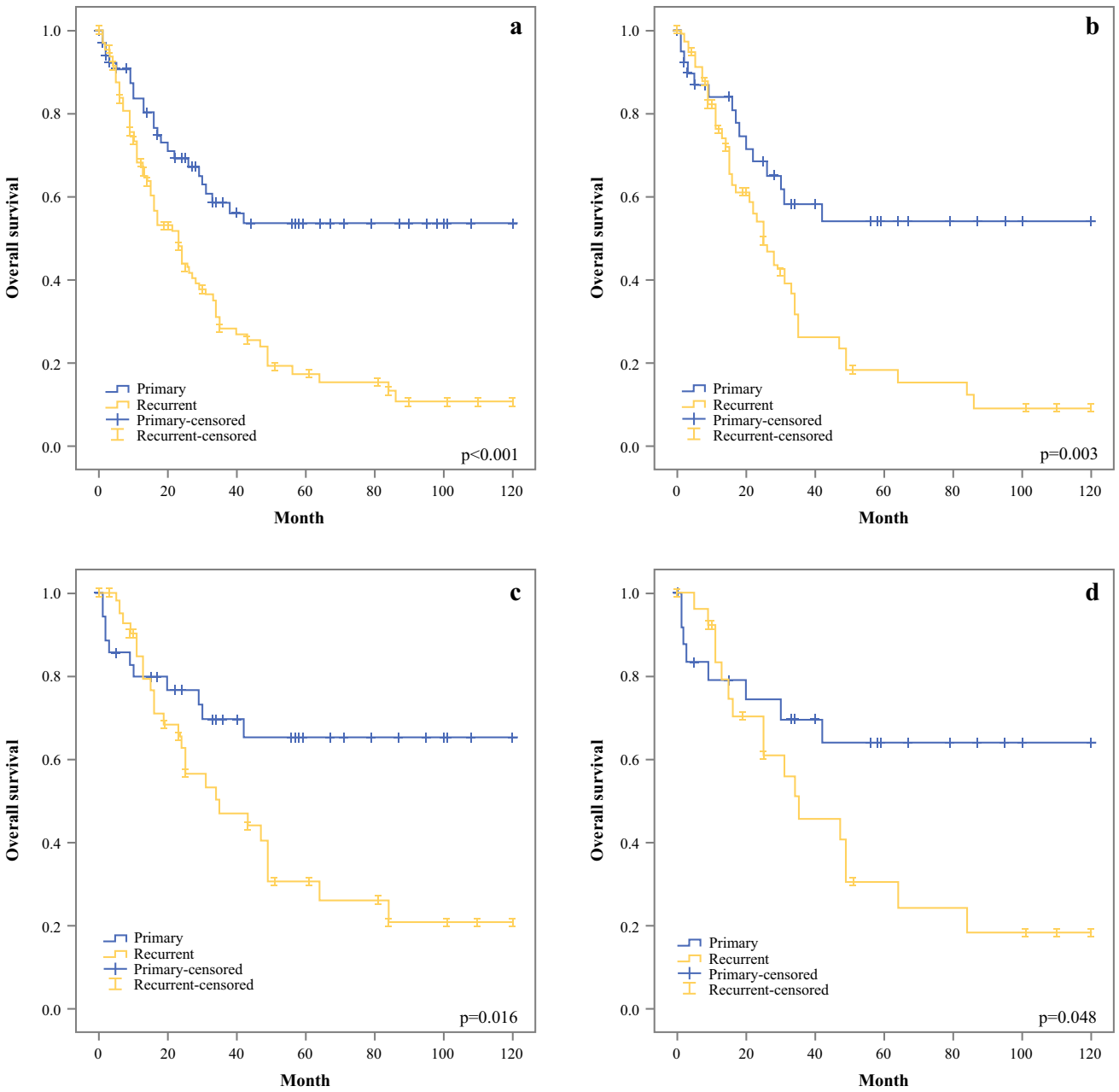

FIG. 1 Overall 10-year survival for **a** all patients, **b** all colorectal cancer patients, **c** all curative resected patients, and **d** all curative resected colorectal cancer patients

recurrent disease [hazard ratio (HR) 2.3; 95% confidence interval (CI) 1.5–3.8; $p < 0.01$], resection margin (HR 1.8; 95% CI 1.2–2.6; $p < 0.01$), and surgery lasting longer than 7 h (HR 1.8; 95% CI 1.1–2.9; $p = 0.02$) as independent predictors of poor OS. In the multivariate analysis of the CRC patients only, surgery time longer than 7 h was not a significant predictor of poor OS. For the CRC patients, recurrent disease (HR 2.1; 95% CI 1.1–3.8; $p = 0.02$), resection margin (HR 2.2; 95% CI 1.2–3.9; $p < 0.01$), and extrapelvic disease at the time of surgery (HR 2.0; 95% CI 1.1–3.6; $p = 0.02$) were independent significant predictors of poor OS.

For the entire cohort, the 10-year OS rates for the R0 resected patients compared with the R1 resected patients were respectively 62.3% and 44.6% (primary) versus 15.6% and 5.9% (recurrent) ($p < 0.01$). These differences also were observed when the CRC patients were analyzed separately (primary, 59.8% vs. 38.1%; recurrent, 14.7% vs. 0.0%; $p < 0.01$).

For the CRC patients, the 10-year OS was 16.4% for those with extrapelvic disease and 39% for those without

TABLE 4 Uni- and multivariate analyses of factors associated with overall survival

	Overall survival							
	All cancer sites (n = 183)				Colorectal cancer (n = 103)			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
	n = 103							
Age > 65 years (yes vs. no)	1.1 (0.7–1.6)	0.8			1.4 (0.8–2.4)	0.23		
Gender (male vs. female)	1.3 (0.9–1.9)	0.24			1.1 (0.6–1.8)	0.8		
ASA (2 vs. 3/4)	0.6 (0.1–2.4)	0.47			1.0 (0.2–4.2)	0.97		
Cancer site	1.1 (0.9–1.2)	0.33						
Recurrent disease (yes vs. no)	2.5 (1.6–4.0)	< 0.01	2.3 (1.5–3.8)	< 0.01	2.4 (1.3–4.4)	< 0.01	2.1 (1.1–3.8)	0.02
Extrapelvic disease (yes vs. no)	1.5 (1.1–2.9)	0.02	1.5 (1.0–2.4)	0.05	2.0 (1.1–3.5)	0.02	2.0 (1.1–3.6)	0.02
IORT (yes vs. no)	1.2 (0.8–1.8)	0.31			1.3 (0.7–2.1)	0.4		
Resection margin (R0 vs. R1/2)	2.0 (1.4–2.8)	< 0.01	1.8 (1.2–2.6)	< 0.01	2.6 (1.6–4.3)	< 0.01	2.2 (1.2–3.9)	< 0.01
Pelvic exenteration (TPE vs. PPE)	1.3 (0.8–2.0)	0.29			1.4 (0.7–2.8)	0.34		
Blood loss > 3 l (yes vs. no)	1.5 (1.0–2.3)	0.05	1.2 (0.7–1.8)	0.47	1.2 (0.7–2.3)	0.51		
Surgery time > 7 h (yes vs. no)	2.1 (1.3–3.4)	< 0.01	1.8 (1.1–2.9)	0.02	2.1 (1.1–4.0)	0.03	1.8 (0.9–3.6)	0.09
Bone resection (yes vs. no)	0.7 (0.4–1.3)	0.26			0.7 (0.4–1.3)	0.3		
Major complication (yes vs. no)	1.1 (0.7–1.7)	0.6			1.5 (0.8–2.5)	0.2		
Adjuvant treatment (yes vs. no)	0.7 (0.4–1.0)	0.08	0.8 (0.5–1.2)	0.25	0.5 (0.3–0.9)	0.02	0.7 (0.4–1.3)	0.27
Neoadjuvant treatment (yes vs. no)	0.9 (0.6–1.5)	0.82			0.7 (0.4–1.2)	0.23		

HR hazard ratio, *CI* confidence interval, *ASA* American Society of Anesthesiologists, *IORT* intraoperative radiation therapy, *TPE* total pelvic exenteration, *PPE* posterior pelvic exenteration

extrapelvic disease (p = 0,016). The 10-year OS rates for the primary CRC patients were 25.0% for those with extrapelvic disease and 61.7% for those without extrapelvic disease (p = 0.25), and the 10-year OS rates for the recurrent patients were 7.3% and 10.5% (p = 0.15).

Disease Recurrence

To identify predictors of disease recurrence (local and systemic), subgroup analyses were performed for the patients with potentially curative resection. These were patients with local R0 resection and no postoperative evidence of systemic disease (79 AP patients; 52 CRC patients). The local and systemic recurrence-free survival rates differed significantly between the two groups (primary vs. recurrent; AP: LRFS, $p < 0.01$ vs. SRFS, p = 0.02 and CRC: LRFS, $p < 0.01$ vs. SRFS, $p < 0.01$) (Figs. 2, 3). The multivariate Cox regression analysis independently predicted recurrent disease for local disease recurrence in the AP and CRC patients (AP: HR 12.3; 95% CI 2.8–54.9; $p < 0.01$; CRC: HR 11.7; 95% CI 2.2–62.9; $p < 0.01$; Table 5). Furthermore, the multivariate analysis showed an independent association between IORT and the development of local recurrence in the CRC patients (HR 0.3; 95% CI 0.1–0.0.9; p = 0.04; Table 6). The multivariate analysis also identified recurrent disease as the only significant prognostic factor of systemic disease recurrence (AP: HR 3.2; 95% CI 1.2–8.9; p = 0.02; CRC: HR 7.1; 95% CI 1.6–32.1; p = 0.01; Table 6).

DISCUSSION

The analysis of our patient cohort demonstrated that the long-term survival rates after PE are excellent for patients with advanced tumors. Furthermore, the analysis provided evidence that patients with primary disease benefit most in the long term. Survival decreases considerably after 3 years for patients with recurrent disease, even for curatively resected patients.

This analysis included 187 PEs during a 15-year period at a single tertiary referral center. We decided to report perioperative and oncologic outcomes for mixed indications (183 patients) because we wanted to analyze the largest number of patients possible to minimize type 2 errors and enhance statistical power. We also reported the outcomes for patients with colorectal malignancies only (103 patients) to enable comparison with previous publications on this topic.

The current study supported existing evidence that PE can be performed safely.[6] Despite a low perioperative mortality of 2.1%, we noted a significant perioperative morbidity of 79.1%. The reported rates for complications

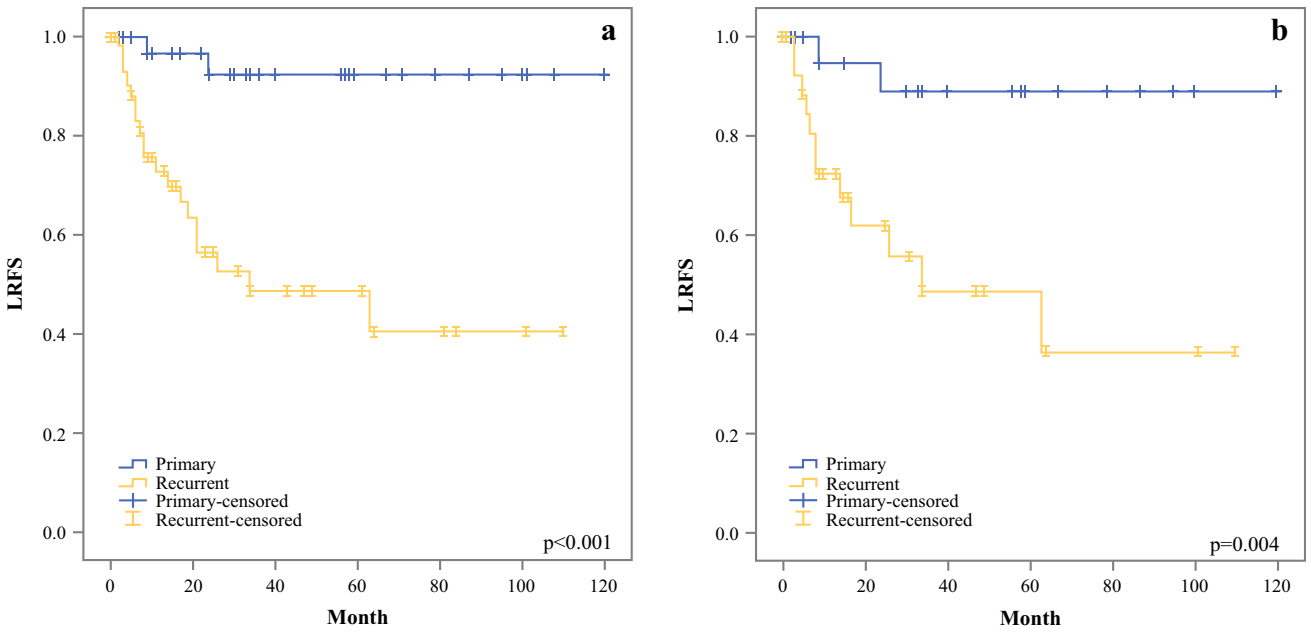

FIG. 2 Local recurrence-free survival for patients who underwent curative resection. **a** All patients, **b** colorectal cancer patients

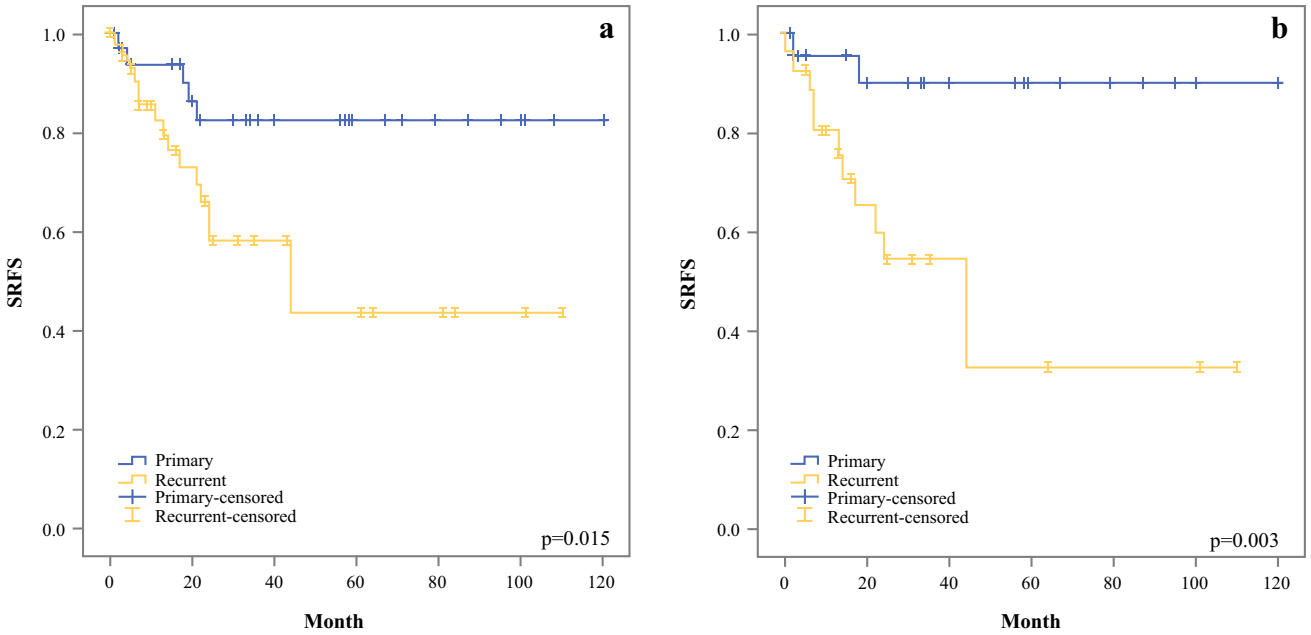

FIG. 3 Systemic recurrence-free survival for patients who underwent curative resection. **a** All patients, **b** colorectal cancer patients

after PE are high (20–100%), depending on the method of reporting.[7,8] Wound infections and abscess formation were the most frequent complications in this cohort, followed by urologic complications. Previous studies have indicated that the complication rates after PE are similar between patients with primary and those with recurrent disease.[9,10] In agreement, we noticed similar rates of major and minor complications between these groups. However, we found that postoperative bleeding was significantly more frequent among the patients with recurrent disease (Supplementary Table 1, 10.4% vs. 1.5%; $p = 0.02$). This may be explained by the significantly higher blood loss and longer operative time for the recurrent patients. In most cases, the surgical conditions are inferior due to previous surgery in the pelvis.

After pelvic exenterative surgery, R0 resection is important for survival.[3,7,11] In the current study, disease stage (primary vs. recurrent), extrapelvic disease, and resection margin were independent prognostic indicators

TABLE 5 Uni- and multivariate analyses of factors associated with local recurrence-free survival after curative plevic exenteration

	Local recurrence-free survival							
	All cancer sites (n = 79)				Colorectal cancer (n = 52)			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
	n = 103							
Cancer site	0.9 (0.6–1.3)	0.58						
Recurrent disease (yes vs. no)	9.9 (2.3–42.8)	< 0.01	12.3 (2.8–54.9)	< 0.01	6.9 (1.5–30.9)	0.01	11.7 (2.2–62.9)	< 0.01
Extrapelvic disease (yes vs. no)	1.6 (0.5–4.8)	0.39			1.7 (0.4–7.7)	0.48		
IORT (yes vs. no)	1.1 (0.5–2.7)	0.79	0.6 (0.2–1.4)	0.2	0.9 (0.3–2.6)	0.89	0.3 (0.1–0.9)	0.04
Pelvic exenteration (TPE vs. PPE)	1.8 (0.6–4.8)	0.27			2.2 (0.5–9.9)	0.3		
Blood loss > 3 l (yes vs. no)	1.9 (0.8–4.8)	0.17			2.8 (0.9–8.5)	0.06	1.7 (0.6–5.4)	0.35
Surgery time > 7 h (yes vs. no)	1.0 (0.4–2.3)	0.94			1.0 (0.3–2.9)	0.99		
Bone resection (yes vs. no)	0.4 (0.1–1.7)	0.21			0.5 (0.1–2.0)	0.45		
Major complication (yes vs. no)	0.7 (0.3–1.6)	0.38			0.7 (0.3–2.1)	0.58		
Adjuvant treatment (yes vs. no)	0.7 (0.3–1.8)	0.5			0.7 (0.5–2.0)	0.52		
Neoadjuvant treatment (yes vs. no)	0.6 (0.2–1.5)	0.24			0.4 (0.1–1.4)	0.15		

HR hazard ratio, *CI* confidence interval, *IORT* intraoperative radiation therapy, *TPE* total pelvic exenteration, *PPE* posterior pelvic exenteration

TABLE 6 Uni- and multivariate analyses of factors associated with systemic recurrence-free survival after curative pelvic exenteration

	Systemic recurrence-free survival							
	All cancer sites (n = 79)				Colorectal cancer (n = 52)			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
	n = 103							
Cancer site	1.1 (0.8–1.6)	0.45						
Recurrent disease (yes vs. no)	3.2 (1.2–8.9)	0.02	3.2 (1.2–8.9)	0.02	7.2 (1.6–32.5)	0.01	7.1 (1.6–32.1)	0.01
Extrapelvic disease (yes vs. no)	2.3 (0.8–6.2)	0.11	2.2 (0.8–6.0)	0.13	1.7 (0.4–7.5)	0.51	1.3 (0.3–5.7)	0.76
Pelvic exenteration (TPE vs. PPE/APE)	1.9 (0.7–5.3)	0.2			2.5 (0.5–11.1)	0.24		
Blood loss > 3 l (yes vs. no)	1.6 (0.6–4.1)	0.37			2.3 (0.7–7.2)	0.16		
Surgery time > 7 h (yes vs. no)	1.8 (0.7–4.5)	0.2			2.9 (0.8–13.3)	0.11		
Bone resection (yes vs. no)	0.7 (0.2–2.2)	0.57			0.9 (0.3–2.8)	0.81		
Major complication (yes vs. no)	0.7 (0.3–1.7)	0.46			0.9 (0.3–2.4)	0.77		
Adjuvant treatment (yes vs. no)	1.2 (0.5–2.9)	0.64			1.1 (0.4–3.2)	0.84		
Neoadjuvant treatment (yes vs. no)	0.6 (0.2–1.5)	0.29			0.5 (0.1–1.4)	0.18		

HR hazard ratio, *CI* confidence interval, *TPE* total pelvic exenteration, *PPE* posterior pelvic exenteration, *APE* anterior pelvic exenteration

for OS according to the multivariable analysis. The reported margin negativity rates differed between patients with primary and recurrent malignancies. These data originate mainly from retrospective analyses of rectal cancer patient cohorts, and higher R0 rates for primary patients were demonstrated in all studies. The R0 rates range from 66 to 98% for primary disease and from 37.5 to 78% for recurrent disease.[6,9,10,12–14]

Nielsen et al.[10] and Bhangu et al.[9] took the different resection margin rates into account and compared primary and recurrent cancer patients after R0 resections. Bhangu et al.[9] reported that curatively resected primary and recurrent patients had similar survival rates after 3 years (3 year OS: 85% [primary] vs. 79% [recurrent]; p = 0.8). Nielsen et al.[10] reported lower 3- and 5-year OS rates for R0 resected recurrent patients than for primary patients after R0 resection. However, due to the small number of patients, these differences were not significant.

In the current study, the R0 resection rate was 72.5% for the primary colorectal patients and 54% for the recurrent colorectal patients. Although we observed similar survival rates after 3 years between the groups (69.6% [primary] vs. 47.2% [recurrent]; $p = 0.2$), the 5- and 10-year survival rates for the curatively resected recurrent patients were significantly lower than for the primary patients (5-year OS: 69.4% [primary] vs. 44.2% [recurrent], $p = 0.04$; 10-year survival: 65.3% [primary] vs. 20.9% [recurrent], $p = 0.02$).

This study included 52 patients with resectable extrapelvic disease. It is not surprising that extrapelvic disease affects OS. Our multivariate analyses showed extrapelvic disease as an independent factor of poor prognosis. However, because studies rarely include patients with distant metastases, the published data on this are scarce. Kusters et al.[15] published their results after PE for patients who had T4 rectal cancer with ($n = 9$) and without ($n = 84$) extrapelvic disease. In this study, patient survival was not dependent on distant metastases. Radwan et al.[16] analyzed 6 patients with distant metastasis among 174 patients with locally advanced rectal cancer. They reported that survival of the patients with distant metastasis was poor and confirmed extrapelvic disease as a prognostic factor for adverse survival. In the current cohort, the overall 5-year survival rate for the patients with extrapelvic disease that could be curatively resected was 37%. Because the 5-year survival rate for the patients with pelvic malignancies is very poor (12%) without surgery,[17] we believe that surgery is justified for a subset of well-selected patients with extrapelvic disease.

In the current study, only recurrent disease was independently associated with local or systemic failure. However, we were able to demonstrate that IORT has a beneficial effect on local recurrence in CRC patients. Usually, IORT is indicated for patients with a high risk for recurrence, which creates a selection bias. This makes comparing recurrence between patients who did and those who did not receive IORT difficult.

The patients who underwent PE for treatment of primary disease received adjuvant or neoadjuvant treatment significantly more often than the patients with recurrent disease. However, we did not find an independent association between adjuvant or neoadjuvant treatment and any oncologic outcome parameter. We assume that the biology of the disease also plays an important role in disease recurrence and survival. Furthermore, surgical treatment of recurrent disease may be less effective than treatment of primary disease because of scar tissue, loss of embryologic layers, and treatment-related fibrosis.

This study was limited by its retrospective nature. The strengths of this study were that it represented a single-center experience and included a reasonable number of patients. The current study supports the growing evidence that PE can have good long-term results at an experienced center. Furthermore, we demonstrated that extrapelvic disease should not always be considered an exclusion criterion for radical resection. Finally, we confirmed the prognostic importance of an R0 resection and underscored the relevance of disease stage for oncologic outcome. The oncologic outcome for recurrent disease is worse than for primary disease. This should be considered during perioperative treatment and follow-up examinations.

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