BMC Cancer

RESEARCH

Open Access

Postoperative venous thromboembolism after surgery for locally recurrent rectal cancer

Chikako Kusunoki[1], Mamoru Uemura[1*], Mao Osaki[1], Nobuo Takiguchi[1], Masatoshi Kitakaze[1], Masakatsu Paku[1], Yuki Sekido[1], Mitsunobu Takeda[1], Tsuyoshi Hata[1], Atsushi Hamabe[1], Takayuki Ogino[1], Norikatsu Miyoshi[1], Mitsuyoshi Tei[2], Yoshinori Kagawa[3], Takeshi Kato[4], Hidetoshi Eguchi[1] and Yuichiro Doki[1]

Abstract

Background Local recurrence is common after curative resections of rectal cancer. Surgical resection is considered a primary curative treatment option for patients with locally recurrent rectal cancer (LRRC). LRRC often requires a combined resection of other organs, especially in the case of posterior recurrence, which requires a combined resection of the sacrum, making the surgery highly invasive. Venous thromboembolism (VTE) is one of the lethal complications in the postoperative period, particularly in the field of pelvic surgery. We found no reports regarding the risks of postoperative VTE in surgery for LRRC, a typical highly invasive procedure in the field of colorectal surgery. This study aims to evaluate the risk of postoperative VTE in surgery for LRRC patients.

Methods From April 2010 to March 2022, a total of 166 patients underwent surgery for LRRC in the pelvic region at our institutions. Clinicopathological background and VTE incidence were compared retrospectively.

Results Among the 166 patients included in the study, 55 patients (33.1%) needed sacral resection. Pharmacological prophylaxis for prevention of VTE was performed in 121 patients (73.3%), and the incidence of VTE was 9.09% (5/55 patients) among those who underwent surgery for LRRC with sacral resection, while it was 1.8% (2/111 patients) in those without sacral resection. In univariate analysis, the combination with sacral resection was identified as a risk factor for VTE in surgery for LRRC ($p = 0.047$).

Conclusions This study demonstrates that surgery for LRRC combined with sacral resection could be a significant risk factor for VTE.

Keywords Locally recurrent rectal cancer, Total pelvic exenteration, Sacral resection, Venous thromboembolism, Pharmacological prophylaxis

Background

Colorectal cancer (CRC) is the third most common cancer, with 1.9 million new cases in 2020, contributing to 10.7% of new cases. Locally recurrent rectal cancer (LRRC) is a common form of recurrence after a curative resection of rectal cancer, and it occurs at rates of 5.6 to 11% [1–4].

R0 resection with pathologically negative margin is considered important in surgery for LRRC, and in order to achieve R0 resection, highly invasive surgical procedures, such as total pelvic exenteration (TPE) and/

*Correspondence:
Mamoru Uemura
uemura7777@hotmail.com
[1] Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, 2-2 Yamada-oka, Suita City, Osaka 565-0871, Japan
[2] Department of Surgery, Osaka Rosai Hospital, Sakai, Japan
[3] Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan
[4] Department of Surgery, NHO Osaka National Hospital, Osaka, Japan

or sacral resection are often required [5, 6]. For these reasons, in cases of LRRC surgery, which often involve highly invasive procedures, the high frequency of postoperative complications becomes a significant issue.

Generally, the frequency of postoperative complications associated with surgery for LRRC has been reported to be high, ranging from 24 to 68%, and includes complications such as pelvic collections, perineal and abdominal wound infections, bowel obstruction or ileus, urologic problems, postoperative bleeding, and pelvic abscess [4, 5, 7, 8]. This high rate of postoperative complications has been consistent with our previous reports [4, 9]. In particular, the frequency of severe complications that can be fatal was about 38% in our prior report, underscoring that the management of these complications is an extremely important factor in improving the treatment outcomes of LRRC surgery.

Venous thromboembolism (VTE) is one of the lethal complications in the postoperative period, particularly in the field of pelvic surgery. It is essential to accurately assess the occurrence of VTE and manage it effectively. The incidence of postoperative VTE after colorectal cancer surgery is reported to be about 1.1–2.5% [10]. We found no reports regarding the risks of postoperative VTE in surgery for LRRC, a typical highly invasive procedure in the field of colorectal surgery. This study aims to evaluate the risk of postoperative VTE in surgery for LRRC patients.

Methods

Patients

We retrospectively reviewed the medical data obtained from the surgical records and the charts of 166 patients who underwent surgery for LRRC in the pelvic region at our department (Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, and Department of Surgery, National Hospital Organization Osaka National Hospital) between April 2010 and March 2022. The information reviewed included factors such as age, sex, body mass index (BMI), American Society of Anesthesiologists physical status (ASA-PS) classification, preoperative therapy, comorbidities, and medical history. We reviewed short-term surgical outcomes including approach (Laparotomy, Laparoscopy, with/ without laparoscopic transanal or transperineal approach), multivisceral resection, sacral resection, TPE, lateral lymph node dissection (LLND), blood loss, operating time, postoperative complications, postoperative hospital stay, pharmacological prophylaxis of VTE, and incidence of VTE. Postoperative complications were classified according to the Clavien-Dindo (C-D) classification, and Clavien- Dindo grade IIIa or higher was defined as a severe complication [11]. If the preoperative D-dimer level exceeded the threshold, a lower limb ultrasound or contrast-enhanced computed tomography (CT) was performed. The D-dimer threshold was set at 500 μg/L for patients aged 50 years or younger, and age x 10 μg/L for those older than 50 years [12]. Since 2019, contrast-enhanced CT from the chest to the lower limbs has been routinely performed on all cases preoperatively, enabling the evaluation of VTE before surgery. In this study, none of the 166 patients had a preoperative diagnosis of VTE.

If postoperative D-dimer levels were elevated, or if there was clinical suspicion of VTE due to symptoms such as swelling of the lower limbs, asymmetry in lower limb circumference, or lower limb pain, a lower limb ultrasound was performed. When elevated D-dimer levels were accompanied by other clinical symptoms or elevated inflammatory markers, a contrast-enhanced CT scan from the chest to the lower limbs was performed at the discretion of the attending physician to evaluate both the presence of VTE and other potential complications. For patients undergoing surgery for LRRC, a highly invasive procedure with a high incidence of postoperative complications, contrast-enhanced CT scans from the chest to the lower limbs were also performed periodically, generally one week and four weeks after surgery, to evaluate postoperative complications. Therefore, asymptomatic VTE can also be evaluated. The follow-up period was calculated from the date of surgery. This study was approved by the clinical research institutional review board of the National Hospital Organization Osaka National Hospital, and Osaka university.

Statistical analysis

Numerical data are expressed as the median (IQR, Interquartile range). Differences between the variables were compared using Fisher's exact test. Differences in quantitative parameters were compared using Wilcoxon signed-rank test. Risk factors for preoperative VTE were analyzed by univariate logistic regression. The odds ratio was presented with 95% confidence interval (CI). A p-value < 0.05 was considered to indicate statistical significance. All statistical analyses were carried out using JMP Pro software version 17.0.0 for Mac (SAS Institute Inc., Cary, NC, USA).

Results

Patients characteristics

Patient characteristics are presented in Table 1. A total of 166 patients underwent surgery for LRRC in the pelvic region at our department from April 2010 to March 2022. The median age of patients was 62.5 years (IQR, 53.8–71 years), with 113 males (68.1%) and 53 females (31.9%). The median body mass index (BMI) was 22.1 kg/m^2 (IQR, 20–24.1 kg/m^2), and 4 patients were classified

Table 1 Clinical characteristics of the patients with locally recurrent rectal cancer in the pelvic region

	n **= 166**
Age (year-old), median (IQR)	62.5 (53.8–71)
Sex, [male / female], n (%)	113 (68.1%)/ 53 (31.9%)
Body Mass Index, median (IQR)	22.1 (20-24.1)
ASA-PS ≧ 3, n (%)	4 (3.2%)
Preoperative treatment +/-, n (%)	132 (79.5%)/ 34 (20.5%)
Chemotherapy/RT/CRT	33/ 5/ 94
Comorbidity/Past history	
HT, n	31
HL, n	8
DM, n	22
Af, n	3
IBD, n	3
Paralysis/ Stroke, n	5
VTE, n	1

IQR Interquartile range, *BMI* Body Mass Index, *ASA-PS* American Society of Anesthesiologists physical status, *RT* Radiotherapy, *CRT* Chemoradiotherapy, *HT* High blood pressure, *HL* Hyperlipemia, *DM* Diabetes mellitus, *Af* Atrial fibrillation, *IBD* Inflammatory bowel disease, *VTE* Venous thromboembolism

Table 2 Surgical procedures for treating locally recurrent rectal cancer

	n **= 166**
Approach, n (%)	
Laparotomy Laparoscopy[a]	110 (66.3%) 56 (33.7%)
Combined with laparoscopic anal/ perineal approach, n (%)	21 (12.7%)
Multivisceral resection, n (%)	120 (72.3%)
Sacral resection, n (%) S2/ S3/ S4	55 (33.1%) 18/ 23/ 14
TPE, n (%)	52 (31.3%)
LLND, n (%)	102 (61.4%)
Blood loss, median, ml (IQR)	455 (121.3–1470)
Blood transfusion, n (%)	61 (36.7%)
Operating time, median, min (IQR)	619 (399-766.5)
Postoperative complication, Clavien Dindo ≧ 3a, n (%)	53 (31.9%)
Hospital stay, median, days (range)	33.5 (22-51.5)
Pharmacologic Prophylaxis of VTE, n (%) Fondaparinux sodium (FPX)/ Enoxaparin sodium (ENP)	121 (73.3%) 36/ 85
VTE, n (%)	7 (4.2%)

TPE Total pelvic exenteration, *LLND* Lateral lymph node dissection, *IQR* Interquartile range, *VTE* Venous thromboembolism

[a] In 3 cases, the procedure was converted from laparoscopy to laparotomy; 1 case was performed with robotic assistance

as ASA-PS class III or higher. Of the 132 patients who received preoperative treatment, 33 underwent chemotherapy, 5 underwent radiotherapy (RT), and 94 underwent chemoradiotherapy (CRT). Regarding comorbidity and past history, 31 patients had high blood pressure (HT), 8 had hyperlipemia (HL), 22 had diabetes mellitus (DM), 3 had atrial fibrillation (Af), 3 had inflammatory bowel disease (IBD), 5 had paralysis or stroke, and 1 had a past history of VTE.

Surgical outcomes

Table 2 presents the short-term outcomes according to surgical procedures. Of the 166 patients, 110 patients underwent open abdominal surgery (66.3%) and 56 underwent laparoscopic surgery (33.7%). Among those who underwent laparoscopic surgery, 3 cases were converted from laparoscopic surgery to open abdominal surgery, and 1 case was performed with robot-assisted endoscopic surgery. Out of the 56 patients who underwent laparoscopic surgery, a total of 21 (37.5%) were treated with an additional laparoscopic transanal or transperineal approach. Of the 166 patients, 120 (72.3%) needed multivisceral resection. In terms of sacral resection, 55 patients (33.1%) required it, with 18 having the resection level located above the lower edge of the S2 vertebra, 23 above the lower edge of the S3 vertebra, 14 above the lower edge of the S4 vertebra.

Additionally, 102 patients (61.4%) needed lateral lymph node dissection. The median blood loss volume was 455 ml (IQR, 121.3–1470 ml), and 61 patients (36.7%) needed a blood transfusion. The median operative time was 619 min (IQR, 399–766.5 min). Postoperative severe complications, graded IIIa or higher according to the Clavien-Dindo classification, occurred in 53 patients (31.9%). The median duration of hospital stay was 33.5 days (IQR, 22-51.5 days). Pharmacologic prophylaxis for the prevention of VTE was administered to 121 patients (73.3%) using Fondaparinux sodium (FPX) and Enoxaparin sodium (ENP). The VTE incidence was 4.2% (7 patients) among patients who underwent surgery for LRRC.

The details of the patient characteristics are shown in Table 3. Patient characteristics revealed no significant difference between the VTE group and the no-VTE group. Short-term outcomes according to surgical procedures are summarized in Table 4. Sacral resection was performed more often in the VTE group than in the no-VTE group (71.4% vs. 31.5%, $p = 0.041$). Operating time was longer in the VTE group than in the no-VTE group (median, 915 min vs. 606 min, $p = 0.006$) and the hospital stay period was longer in the VTE group than in the no-VTE group (median, 68 days vs. 33 days, $p = 0.013$). The other parameters showed no significant difference between the two groups.

Postoperative VTE incidence was evaluated for each factor using univariate analysis (Table 5). Univariate

Table 3 Clinical characteristics of the patient with locally recurrent rectal cancer in the pelvic region, comparing the VTE group and no-VTE group

	VTE(+) ***n*** **= 7**	**VTE(-)** ***n*** **= 159**	***p*** **value**
Age (year-old), median (IQR)	51 (46–68)	63 (54–71)	0.169
Sex, [male/ female], n (%)	1 (14.3%)/ 6(85.7%)	52 (32.7%)/ 107(67.3%)	0.432
BMI, median (IQR)	23.1 (10.4–26.6)	22.0 (10.0- 24.1)	0.472
ASA-PS ≧ 3, n (%)	0 (0%)	4 (3.4%)	1.000
Comorbidity/ Past history, n (%)	3 (42.9%)	85 (53.5%)	0.707
HT, n (%)	2 (28.6%)	29 (18.2%)	0.616
HL, n (%)	1 (14.3%)	7 (4.4%)	0.297
DM, n (%)	1 (14.3%)	21 (13.2%)	1.000
Af, n (%)	0 (0%)	3 (1.9%)	1.000
IBD, n (%)	0 (0%)	3 (1.9%)	1.000
Paralysis/ Stroke, n (%)	1 (14.3%)	4 (2.5%)	0.196
VTE, n (%)	0 (0%)	1 (0.6%)	1.000
Preoperative treatment, n (%)	5 (71.4%)	127 (79.9%)	0.517
Chemotherapy, n (%)	1 (14.3%)	32 (20.1%)	0.694
RT, n (%)	1 (14.3%)	4 (2.5%)	0.183
CRT, n (%)	3 (42.9%)	91 (57.2%)	0.455
Preoperative D-dimer, median (IQR)	0.49 (0.32–1.79)	0.52 (0.29–1.01)	0.988

IQR Interquartile range, *BMI* Body Mass Index, *ASA-PS* American Society of Anesthesiologists physical status, *HT* High blood pressure, *HL* Hyperlipemia, *DM* Diabetes mellitus, *Af* Atrial fibrillation, *IBD* Inflammatory bowel disease, *VTE* Venous thromboembolism, *RT* Radiotherapy, *CRT* Chemoradiotherapy

Table 4 Surgical procedures for treating locally recurrent rectal cancer, comparing the VTE group and no-VTE group

	VTE(+) ***n*** **= 7**	**VTE(-)** ***n*** **= 159**	***p*** **value**
Approach, n (%)	3 (42.9%)	53 (33.3%)	0.689
Laparoscopy	4 (57.1%)	106 (66.7%)	
Laparotomy			
Combined with laparoscopic anal/perineal approach, n (%)	0 (0%)	21 (13.2%)	0.5973
Multivisceral resection, n (%)	6 (85.7%)	114 (71.7%)	0.675
Sacral resection, n (%)	5 (71.4%)	50 (31.5%)	*0.041*
S2/ S3/ S4	2/ 2/ 1	16/ 21/ 13	
TPE, n (%)	2 (28.6%)	50 (31.5%)	1.000
LLND, n (%)	6 (85.7%)	96 (60.4%)	0.251
Blood loss, median (ml, IQR)	1200 (530–4820)	400 (110–1320)	0.052
Blood transfusion, n (%)	4 (57.1%)	57 (35.9%)	0.263
Operating time, median (min, IQR)	915 (804–956)	606 (390–760)	*0.006*
Hospital stay (days, IQR)	68 (48–139)	33 (22–50)	*0.013*
Pharmacologic Prophylaxis of VTE, n (%)	5 (71.4%)	116 (73.4%)	1.000
Fondaparinux sodium (FPX)/ Enoxaparin sodium (ENP)	3/ 2	82/ 34	0.633

LLND Lateral lymph node dissection, *IQR* Interquartile range, *VTE* Venous thromboembolism

analysis showed that VTE incidence was significantly higher in the patients who required sacral resection (OR = 5.45, 95% CI: 1.02–29.06, $p = 0.047$). In this study, univariate analysis showed statistical significance for only one factor, with other factors not demonstrating significance. Additionally, there was a clear correlation among these factors, suggesting the potential for multicollinearity. Therefore, to avoid the complexities of interpretation associated with multicollinearity, multivariate analysis was not conducted in this study. The cutoff value for age, a known risk factor for VTE, was set at 50 years. Additionally, the cutoff value for BMI, following the standards for obesity in Japan, was set at 25 kg/m^2. The cutoff values for blood loss and operating time were determined based on median values.

Table 6 presents the results regarding postoperative VTE. The appearance of VTE was also evaluated in both groups; sacral resection group and no-sacral

Table 5 Univariate analysis of clinical characteristics associated with VTE

Variables	Univariate		
	OR	95%CI	*p* value
Age (year-old) [≧50/ <50]	0.23	0.05–1.07	0.061
Sex [Female/ Male]	0.34	0.04–2.92	0.328
BMI [≧25/ <25]	1.72	0.32–9.30	0.529
Approach [laparotomy/ laparoscopy]	1.5	0.32–6.95	0.604
LLND [+/ -]	3.94	0.46–33.49	0.210
Blood loss (ml) [≧455/ <455]	6.39	0.75–54.29	0.089
Operating time (min) [≧619/ <619]	6.39	0.75–54.29	0.089
Postoperative complication [Clavien Dindo≧3a/ <3a]	2.99	0.65–13.88	0.161
Pharmacologic Prophylaxis of VTE [+/ -]	0.91	0.17–4.84	0.907
Pharmacologic Prophylaxis of VTE [FPX/ ENP]	1.61	0.26–10.06	0.612
TPE [+/ -]	0.87	0.16–4.65	0.873
Sacral resection [+/ -]	5.45	1.02–29.06	*0.047*

BMI Body Mass Index, *LLND* Lateral lymph node dissection, *VTE* Venous thromboembolism, *FPX* Fondaparinux sodium, *ENP* Enoxaparin sodium, *TPE* Total pelvic exenteration

Table 6 The appearance of VTE was also evaluated in both groups; sacral resection group and no-sacral resection group

	Sacral resection(+) *n* = 55	Sacral resection(-) *n* = 111	*p* value
			0.041
VTE +	5 (9.09%)	2 (1.80%)	
VTE -	50 (90.9%)	109 (98.2%)	

VTE Venous thromboembolism

resection group. The incidence of VTE was significantly higher in the sacral resection group than in the no-sacral resection group (9.09% vs. 1.80%, $p = 0.041$).

The details of VTE cases are shown in Table 7. Case 1–5 were the patients with sacral resection, case 6–7 were the patients without sacral resection. Two of these were non-symptomatic VTE cases, and pharmacologic prophylaxis of VTE was not administered in place in two patients. The operative methods were varied; highly invasive operations, such as resection involving multiple organs, were commonly performed. Operating time exceeded 521 min, and blood loss volume was often substantial, with transfusions performed in more than half of the patients. The onset of VTE varied in timing, ranging from 1 to 42 days after surgery. In six patients, the C-D classification of VTE was grade II, and they received anticoagulant therapy. In contrast, one patient's C-D classification of VTE was grade IIIa, and an IVC filter was placed.

Discussion

Significance of surgery for LRRC

Local recurrence is common after curative resections after rectal cancer, and it occurs at rates of 5.6–11% [4]. Surgical resection is considered a primary curative treatment option for patients with LRRC, with 5-year survival rates of 42.4–63% reported [8, 13–17].

A radical resection for locally recurrent rectal cancer (LRRC) often necessitates highly invasive procedures, such as concomitant resections of adjacent organs, including the sacral bone. This high invasiveness is usually associated with a significant risk of postoperative complications, including pelvic collections, perineal and abdominal wound infections, bowel obstruction or ileus, urologic complications, postoperative bleeding, and pelvic abscess [4]. Some of these complications can be fatal. Therefore, management of severe complications is indispensable [9].

VTE in colorectal surgery

Colorectal cancer surgery carries a high risk of postoperative venous thromboembolism, including pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT), with an incidence reported to be about 1.1–2.5%, significantly higher than in other surgical procedures [10]. Drawing on our unpublished data specific to colorectal cancer surgeries, we identified additional risk factors for postoperative VTE, such as open abdominal surgery and intraoperative bleeding. Within this cohort, our study reported an incidence rate of 1.01% (13 out of

Table 7 Details of VTE cases

Case	Sacral resection	Age	Sex	BMI	Details of VTE(symptomatic+/-)	Pharmacologic Prophylaxis	Timing of VTE (POD)	Operative method	Approach	Operating time (min)	Blood loss(ml)/ Blood transfusion+/-	Hospital stay(days)	Postoperative complication	C-D of VTE	Additional information
1	+	41	M	26.6	DVT(-)	FPX	14	Tumor resection, Total cystectomy, Phallectomy, Pubic bones excision, Ischiectomy, Sacrectomy, Ileal conduit, Rectus abdominis muscle skin valve	Open	928	4200/+	48	Pelvic abscess, SSI	2	Paralysis
2	+	46	M	23.6	DVT(+), PTE(-)	FPX	29	TPE, Ileal conduit, Rectus abdominis muscle skin valve, Inguinal lymph nodes dissection, Sacrectomy, LLND	Open	1280	4820/+	139	Ileus, Perforation, Pelvic abscess	3a	
3	+	51	M	20.4	DVT(+), PTE(-)	ENP	15	APR, Left uretectomy, LLND, Sacrectomy, Omentoplasty	Lap	915	1200/+	61	Lymphocyst	2	
4	+	62	M	22.9	DVT(+)	ENP	41	LAR, Small bowel resection, LLND, Sacrectomy	Lap	956	530/-	116	Postoperative hemorrhage, Bradder injury	2	
5	+	68	M	23.1	DVT(+)	-	42	LAR, LLND, Sacrectomy	Lap	835	630/-	68	SSI	2	CKD
6	-	47	F	15.9	DVT(+), PTE(-)	-	1	TPE, Left external iliac vein resection, para-aortic lymph nodes dissection, Ileal conduit, LLND	Open	804	7560/+	147	Pelvic abscess	2	
7	-	72	M	27.2	PTE(-)	ENP	6	LLND, Left internal iliac artery/ vein resection, Left piriformis muscle•coccyx muscle•levator muscle of anus resection	Lap	521	200/-	17	-	2	

BMI Body Mass Index, *VTE* Venous thromboembolism, *CD* Clavien-Dindo classification, *DVT* Deep vein thrombosis, *PTE* Pulmonary thromboembolism, *FPX* Fondaparinux sodium, *ENP* Enoxaparin sodium, *TPE* Total pelvic exenteration, *LLND* Lateral lymph node dissection, *APR* Abdominoperineal resection, *LAR* Low anterior resection, *SSI* Surgical site infection, *CKD* Chronic kidney disease

1279 patients) for postoperative VTE during the period from 2010 to 2018 (detailed data not shown).

VTE in highly invasive surgery; surgery for LRRC

There are reports regarding the relationship between intraoperative bleeding volume and postoperative complications in colorectal cancer surgeries. Significant bleeding alters hemodynamics and impacts the coagulation system. LRRC surgery is highly invasive procedure and involves high intraoperative bleeding, which may increase the risk of postoperative complications such as VTE and postoperative bleeding [4].

VTE can be a fatal complication following surgery for LRRC, which often involves highly invasive procedures. However, no reports have yet examined the risk factors for VTE in LRRC surgeries, leaving its incidence largely unknown. This study aims to evaluate the risk of postoperative VTE in patients undergoing surgery for LRRC. In our current study, the incidence of VTE in LRRC surgeries was 4.2%. The incidence of VTE in the group of patients undergoing combined sacral resection was 9.09%, which was significantly higher than the incidence of VTE in the group of patients undergoing surgery without sacral resection (1.80%) ($p=0.041$). Univariate analysis showed that VTE incidence was significantly higher in the patients who required sacral resection to secure the resection margin during surgery for LRRC, compared to those who did not need sacral resection ($p=0.047$). In our examination, we found that surgeries for LRRC, which are generally highly invasive, particularly those accompanied by sacral resection, were prone to VTE. These cases also showed a higher frequency of other serious complications [4, 9, 18], indicating that careful management of complications, including VTE, is necessary postoperatively.

Sacral resection

Surgery for LRRC, especially in cases of posterior recurrence, often requires a combined resection of the sacrum to secure the resection margin. This procedure may lead to sciatic nerve dysfunction, impacting function and mobility. Patients often experience pain that radiates from the buttocks to the lower leg [19, 20]. Postoperative weaning may be delayed, and they may tend to remain in bed for prolonged periods due to pain, limited mobility in the lower limb, and other complications. Generally, the procedure is associated with significantly heavier blood loss, longer operative time, more severe complications (of C-D grade IIIa or higher), and an extended hospital stay. These factors may also contribute to the higher incidence of postoperative VTE.

VTE prevention

The ninth edition of the American College of Chest Physicians (ACCP) Antithrombotic Therapy and Prevention of Thrombosis Guideline, published in 2012, provided a comprehensive presentation of primary studies and detailed discussions of the rationale for recommendations [21, 22]. This guidance recommended pharmacologic prophylaxis with low-molecular-weight heparin or low-dose unfractionated heparin for higher-risk major procedures in cancer cases. It also recommended combining pharmacologic methods with mechanical methods, such as elastic stockings or intermittent pneumatic compression (IPC). Regarding the duration of thromboprophylaxis, the guidance advised continuation until discharge, and for high-risk patients who underwent cancer surgery or had a past history of VTE, it recommended extending thromboprophylaxis for up to 28 days. The ENOXACAN II study further proposed that four weeks of enoxaparin prophylaxis after surgery for abdominal or pelvic cancer is safe and significantly reduces the incidence of VTE compared to one week of enoxaparin prophylaxis [23].

Since the frequency of VTE in Japan differs from that in Europe and the United States, several academic societies in Japan published their own guidelines in 2004, based on the ACCP guidelines, recommending risk-based preventive measures. In the Japanese Guideline for Prevention of Venous Thromboembolism, the overall risk level is determined by incorporating additional risk factors with the intensity of the risk of disease and surgery, and preventive measures are implemented based on that risk level. Additional risk factors are classified as: weak (obesity, etc.); moderate (advanced age, prolonged bed rest, malignant disease, central venous catheter placement, chemotherapy, severe infection, etc.); strong (previous history of VTE, leg paralysis, etc.) [24]. Cases of LRRC surgery, especially those involving sacral resection, often present many of these risk factors. In LRRC surgeries, postoperative complications are more frequent and the risk of postoperative bleeding is higher than in primary colorectal cancer surgeries. Based on unpublished data from our institution, covering the period from 1998 to 2020, 7.2% of patients with LRRC experienced postoperative bleeding requiring emergency hemostasis. Therefore, based on clinical research and experience, pharmacologic prophylaxis was administered only when the attending physician deemed it safe. As a result, in this study, the use of anticoagulant therapy was limited to 73.3% of cases.

Our study was unable to evaluate the appropriate duration of pharmacologic prophylaxis, but in LRRC cases with sacral resection, adequate pain control and aggressive rehabilitation must be provided for early

weaning. Moreover, IPC should be performed throughout the day until the patient can be adequately weaned, and elastic stockings should be worn all day during hospitalization. Furthermore, in our five cases with sacral resection, the onset of VTE occurred as late as 14–42 days after surgery. This information is considered significant when contemplating the duration of pharmacological prophylaxis. Especially in cases where weaning was delayed due to postoperative complications, long-term administration may be advisable.

This study had some limitations. First, the study was retrospective study. Second, the cohort was relatively small. Although 166 patients represented a relatively large cohort in LRRC clinical research, number of LRRC cases and VTE events may have been insufficient to identify the risk factors for VTE. Third, since no clear criteria for the implementation of anticoagulant therapy were established, and the decision to administer anticoagulant therapy was left to the discretion of the attending physician, we were unable to demonstrate the effectiveness of pharmacological prophylaxis for preventing VTE following LRRC surgery.

Conclusion

Our study showed that in patients undergoing surgery for LRRC, the incidence of postoperative VTE could be higher when sacral resection was performed than when it was not performed. Further accumulation of LRRC cases, including more data and prospective trials, is necessary to determine the appropriate prevention and treatment strategies for VTE after surgery for LRRC.

Acknowledgements
Not applicable.

Authors' contributions
Conception and design of the study, CK and MU; analysis and interpretation of data, CK and MU; acquisition of data, CK, MU, MO, NT, MK and MP; drafting of manuscript, CK and MU; critical revision of manuscript, CK, MU, YS, MT, TH, AH, TO, NM, MT, YK and TK; final approval of the article: HE and YD. All authors have read and approved the manuscript.

Funding
Not applicable.

Availability of data and materials
The datasets generated and analyzed during the current study are not publicly available due to data involving other facilities as a multiple analyses and publications are currently underway, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Osaka University, and it conforms to the provisions of the Declaration of Helsinki (Approval no. 20163-3). All informed consent was obtained from the participates.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 2 April 2024 Accepted: 13 August 2024
Published online: 20 August 2024

References

1. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. 2007;246(5):693–701.
2. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011;12(6):575–82.
3. Beppu N, Kimura F, Aihara T, Doi H, Tomita N, Yanagi H, et al. Patterns of local recurrence and oncologic outcomes in T3 low rectal Cancer (=5 cm from the anal verge) treated with short-course Radiotherapy with delayed surgery: outcomes in T3 low rectal Cancer treated with short-course Radiotherapy with delayed Surgery</at. Ann Surg Oncol. 2017;24(1):219–26.
4. Paku M, Uemura M, Kitakaze M, Fujino S, Ogino T, Miyoshi N, et al. Impact of the preoperative prognostic nutritional index as a predictor for postoperative complications after resection of locally recurrent rectal cancer. BMC Cancer. 2021;21(1):435.
5. Asoglu O, Karanlik H, Muslumanoglu M, Igci A, Emek E, Ozmen V, et al. Prognostic and predictive factors after surgical treatment for locally recurrent rectal cancer: a single institute experience. Eur J Surg Oncol. 2007;33(10):1199–206.
6. Uemura M, Ikeda M, Yamamoto H, Kitani K, Tokuoka M, Matsuda K, et al. Clinicopathological assessment of locally recurrent rectal cancer and relation to local re-recurrence. Ann Surg Oncol. 2011;18(4):1015–22.
7. Dresen RC, Gosens MJ, Martijn H, Nieuwenhuijzen GA, Creemers GJ, Daniels-Gooszen AW, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol. 2008;15(7):1937–47.
8. Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. Ann Surg Oncol. 2007;14(2):447–54.
9. Uemura M, Ikeda M, Sekimoto M, Haraguchi N, Mizushima T, Yamamoto H, et al. Prevention of severe pelvic abscess formation following extended radical surgery for locally recurrent rectal cancer. Ann Surg Oncol. 2009;16(8):2204–10.
10. Emoto S, Nozawa H, Kawai K, Hata K, Tanaka T, Shuno Y, et al. Venous thromboembolism in colorectal surgery: incidence, risk factors, and prophylaxis. Asian J Surg. 2019;42(9):863–73.
11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.
12. Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA. 2014;311(11):1117–24.
13. McKigney N, Houston F, Ross E, Velikova G, Brown J, Harji DP. Systematic review of patient-reported outcome measures in locally recurrent rectal Cancer. Ann Surg Oncol. 2023;30(7):3969–86.
14. Huang Y, Steffens D, Koh CE, Young JM, Solomon MJ. Differences in Surgical outcomes and Quality-of-life outcomes in pelvic exenteration between locally Advanced Versus locally recurrent rectal cancers. Dis Colon Rectum. 2022;65(12):1475–82.
15. Hagemans JAW, van Rees JM, Alberda WJ, Rothbarth J, Nuyttens J, van Meerten E, et al. Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre. Eur J Surg Oncol. 2020;46(3):448–54.

16. Westberg K, Palmer G, Hjern F, Johansson H, Holm T, Martling A. Management and prognosis of locally recurrent rectal cancer - A national population-based study. Eur J Surg Oncol. 2018;44(1):100–7.
17. You YN, Roses RE, Chang GJ, Rodriguez-Bigas MA, Feig BW, Slack R, et al. Multimodality salvage of recurrent disease after local excision for rectal cancer. Dis Colon Rectum. 2012;55(12):1213–9.
18. Uemura M, Ikeda M, Kawai K, Nishimura J, Takemasa I, Mizushima T, et al. Laparoscopic surgery using a Gigli wire saw for locally recurrent rectal cancer with concomitant intraperitoneal sacrectomy. Asian J Endosc Surg. 2018;11(1):83–6.
19. Kitakaze M, Uemura M, Kobayashi Y, Paku M, Miyo M, Takahashi Y, et al. Postoperative pain management after concomitant sacrectomy for locally recurrent rectal cancer. Surg Today. 2022;52(11):1599–606.
20. Phukan R, Herzog T, Boland PJ, Healey J, Rose P, Sim FH, et al. How does the level of Sacral Resection for primary malignant bone tumors affect physical and Mental Health, Pain, mobility, incontinence, and sexual function? Clin Orthop Relat Res. 2016;474(3):687–96.
21. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):eS227–77.
22. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest. 2008;133(6 Suppl):s381-453.
23. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med. 2002;346(13):975–80.
24. Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis(JCS. 2017). https://www.j-circ.or.jp/cms/wp-content/uploads/2017/09/JCS2017_ito_h.pdf. 2017.

Publisher's Note