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## Venous Thromboembolism Following Lateral Lymph Node Dissection for Rectal Cancer

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**Abstract.** *Background/Aim:* Postoperative venous thromboembolism (VTE) is a well-recognized complication that leads to morbidity and mortality. Lateral lymph node dissection (LLND) for rectal cancer is thought to potentially increase the risk of VTE due to its technical complexity. However, the relationship between LLND and VTE remains inadequately understood. The aim of this study was to elucidate the impact of LLND on the incidence of postoperative VTE. *Patients and Methods:* This is a retrospective analysis of patients who underwent rectal cancer resection between 2010 and 2018 to identify the risk factors associated with postoperative VTE. Patients were divided into two groups: those who underwent surgery with LLND (LLND+ group) and those who underwent surgery without LLND (LLND- group). *Results:* A total of 543 patients were enrolled in this study, and 113 patients underwent surgery for rectal cancer with LLND. VTE developed in 8 patients (1.47%), with the incidence rates being 4.42% in the LLND+ group and 0.69% in the LLND- group, respectively ( $p=0.012$ ). Three of 8 patients had developed severe postoperative complications, and the other two patients needed intraoperative repair of the iliac vein during LLND procedure. Multivariate analysis identified the incidence of postoperative complications and LLND as the independent risk factors of VTE. *Conclusion:* Patients undergoing rectal cancer surgery with LLND should be closely monitored for signs of VTE.

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**Key Words:** Venous thromboembolism, surgery for rectal cancer, lateral lymph node dissection.

Postoperative venous thromboembolism (VTE) is a well-known complication that leads to morbidity and mortality (1). VTE includes pulmonary embolism (PE) and deep vein thrombosis (DVT). Since VTE is one of the major postoperative complications, identifying its risk factors and conducting proper prophylaxis are important to reduce the risk of subsequent death (2).

Postoperative VTE is more frequently observed after colorectal cancer surgery (3) and the rate of VTE following colorectal operations has been reported to be as much as four times higher than that after general abdominal surgery (4). Many previous studies have been conducted to identify the risk factors of postoperative VTE (3, 5-9) and several VTE predictors have been identified, such as age >50 years, diabetes, obesity, malignancy, and history of myocardial infarction (MI) (10). Colorectal surgery often carries those risk factors of VTE, with a reported prevalence ranging between 0.63-2.4% (3, 7).

Lateral lymph node dissection (LLND) is recommended for advanced lower rectal cancer in Japanese guidelines (11, 12). Recent multicenter studies involving multiple countries are increasingly validating the importance of LLND in reducing lateral local recurrence rates for patients with advanced low rectal cancer (13, 14). Although it is important to perform LLND for achieving radical cure and decreasing recurrence rate, several disadvantages arise from performing LLND, such as hemorrhage and prolonged surgical time due to its technical complexity (15). In addition, LLND often involves physical irritation to the iliac venous system. It is thought that direct venous endothelial damage by surgical maneuvers can be a cause of VTE (16, 17). These factors potentially increase the risk of VTE compared to other colorectal surgeries. However, the relationship between LLND and VTE remains inadequately understood.

Thus, the aim of the study was to identify the risk factors of VTE after surgery for rectal cancer and clarify the impact of LLND on the incidence of postoperative VTE.

## Patients and Methods

**Patients.** From April 2010 to March 2018, a total of 543 patients who underwent a resection for primary rectal cancer or locally recurrent rectal cancer in Osaka University Medical Hospital were retrospectively analyzed. All surgical procedures were performed by two qualified and board-certified colorectal surgeons with established endoscopic surgical skills at Osaka University.

**The criteria of neoadjuvant treatment in rectal cancer.** Neoadjuvant treatment was performed for patients who underwent LLND and were considered to be able to tolerate neoadjuvant therapy based on performance status (PS) and their age. Chemotherapy or chemoradiotherapy were indicated as neoadjuvant therapy.

**Indication of LLND.** LLND was performed for patients satisfying the following criteria: a) tumor is located in lower rectum at or below the peritoneal reflection, and b) clinically diagnosed as T3 or T4, or c) positive lymph nodes are suspected in the lateral pelvic regions by preoperative computed tomography (CT) or magnetic resonance imaging (MRI). Bilateral LLND (internal iliac and obturator nodes dissection) was basically performed in the patients who satisfied the criteria above.

**Perioperative management.** All patients were generally encouraged to start walking from postoperative day (POD) 1 unless they could not move due to the heavy pain, or a doctor-in-charge decided it was better not to leave bed to reduce the risk of postoperative complications. Blood tests including D-dimer assessment were routinely performed at POD1 and POD3. Additional blood tests and CT scan were performed if needed.

**Prophylaxis protocol of VTE.** Our VTE prophylaxis protocol has been described previously (9, 18). All of the patients wore elastic stockings before surgery and underwent intermittent pneumatic compression (IPC) immediately after induction of anesthesia until they began to walk again. For the patients who underwent postoperative pharmacologic prophylaxis, either fondaparinux (Arixtra; GlaxoSmithKline, Middlesex, UK) or enoxaparin (Kurekisan; Kaken Pharmaceutical Co., Ltd., Tokyo, Japan) was given.

**Diagnosis of DVT and PE.** Assessment of DVT and PE was performed as described previously (9). If patients suffered from symptoms clinically suspecting VTE, such as chest pain or decreasing percutaneous arterial oxygen saturation (SpO<sub>2</sub>), enhanced multi-detector helical CT with contrast medium, pulmonary scintigraphy, or pulmonary arteriography were immediately performed to diagnose PE. If the deep vein thrombosis was observed by chance in the postoperative follow-up CT, the patients were diagnosed with DVT.

**Statistical analysis.** Statistical analysis was performed using JMP Pro 16 software (SAS Institute, Irvine, CA, USA) and R v4.3.0 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as medians (interquartile range), while categorical variables are presented as numbers (frequency). The chi-square test was performed for categorical variables and

Wilcoxon rank-sum test was used for differences in parameters, such as blood loss and operating time. To identify independent risk factors associated with postoperative DVT and to obtain adjusted odds ratios (OR) and a 95% confidence interval (CI), we performed a multivariate logistic regression analysis that included variables with  $p < 0.05$  in the univariate analysis. The factors which were considered to be obviously confounding with LLND, such as multivisceral resection and blood loss, were excluded from the univariate and multivariate analysis. All  $p$ -values  $< 0.05$  were considered significant.

**Ethics approval.** This retrospective study was approved by our institutional review board, Ethics Committees of the Osaka International Cancer Institute, Osaka University Hospital, and Minoh City Hospital. Written informed consent was obtained from all patients (approval code: 20163-2).

## Results

**Patient characteristics of the study population.** A total of 543 patients were enrolled in this study. Of these, 113 (20.7%) patients underwent surgeries with LLND (LLND+ group), and 432 (79.3%) patients underwent surgeries without LLND (LLND- group). Table I summarizes the baseline clinical characteristics. The median age at the time of surgery was significantly lower in the LLND+ group than the LLND- group (62 vs. 64, respectively;  $p = 0.005$ ). The number of patients who had the American Society of Anesthesiologists physical status (ASA-PS) classification  $\geq 3$  was significantly lower in the LLND+ group than in the LLND- group [2/113 (1.13%) vs. 32/432 (7.40%), respectively;  $p = 0.05$ ]. In addition, the number of patients who underwent surgery for locally recurrent rectal cancer was significantly higher in the LLND+ group than in the LLND- group [24/113 (21.2%) vs. 15/432 (3.47%), respectively;  $p < 0.001$ ]. The number of patients whose tumor location was rectum/below the peritoneal reflection (Rb), and anal canal (P) was significantly higher in the LLND+ group than in the LLND- group [76/113 (85.4%) vs. 138/432 (33.1%), respectively;  $p < 0.001$ ].

Table II summarizes the clinical factors associated with treatment. As for the surgical procedures, 20 patients (17.7%) underwent laparoscopic surgery in the LLND+ group and 20 patients (4.6%) underwent laparoscopic surgery in the LLND- group. The rate of the patients who underwent multivisceral resection was significantly higher in the LLND+ group than the LLND- group [40/113 (35.4%) vs. 48/432 (11.1%), respectively;  $p < 0.001$ ]. The LLND+ group exhibited more blood loss and longer operating times during surgery compared to the LLND- group [340 (0-18,400) vs. 30 (0-6,390), respectively, 625 (182-1,280) vs. 302 (84-878), respectively]. The rate of the indications of pharmacologic prophylaxis of VTE, preoperative chemotherapy, and preoperative radiotherapy were significantly higher in the LLND+ group than the LLND- group [68 (60.2%) vs. 149 (34.5%), 88 (77.9%) vs. 43

Table I. Clinical characteristics of the 543 patients who underwent a resection for primary or locally recurrent rectal cancer.

	LLND+ group (n=113)	LLND- group (n=432)	p-Value
Age (years), median (range)	62 (19-79)	64 (26-104)	0.005
Sex, [male/female]	72/41	259/173	0.53
Body mass index, median (range)	22.2 (15.4-32.9)	22.2 (14.5-48.5)	0.43
ASA-PS $\geq 3$	2	32	0.05
Cardiovascular disease	20	92	0.46
Atrial fibrillation	1	23	0.071
VTE history	2	0	0.058
Primary or locally recurrent			
Locally recurrent	24	15	<0.001
Primary	89	417	
Tumor Location (RS, Ra/Rb, P)	13/76	279/138	<0.001
AJCC stage (0, I, II/III, IV))	48/41	255/162	0.25

LLND: Lateral lymph node dissection; ASA-PS: American society of anesthesiologists physical status; VTE: venous thromboembolism; RS: rectosigmoid; Ra: rectum above the peritoneal reflection; Rb: rectum below the peritoneal reflection; P: anal canal; AJCC: the American Joint Committee on Cancer.

Table II. Clinical factors associated with treatment of the 543 patients who underwent a resection for primary or locally recurrent rectal cancer.

	LLND+ group (n=113)	LLND- group (n=432)	p-Value
Approach, n (%)			
Laparotomy	20 (17.7%)	20 (4.6%)	<0.001
Laparoscopy	93 (82.3%)	412 (95.4%)	
Multivisceral resection, n (%)	40 (35.4%)	48 (11.1%)	<0.001
Blood loss, ml (range)	340 (0-18,400)	30 (0-6,390)	<0.001
Operating time, min (range)	625 (182-1,280)	302 (84-878)	<0.001
Pharmacologic Prophylaxis of VTE, n (%)	68 (60.2%)	149 (34.5%)	<0.001
Preoperative chemotherapy, n (%)	88 (77.9%)	43 (10.0%)	<0.001
Preoperative radiotherapy, n (%)	27 (23.9%)	10 (2.3%)	<0.001
Postoperative complication, Clavien-Dindo $\geq 3$ , n (%)	13 (11.5%)	27 (6.3%)	0.09
Immobilization $\geq 3$ days, n (%)	39 (34.5%)	57 (13.2%)	<0.001
POD3 D-dimer, $\mu\text{g/ml}$ (range)	4.37 (1.61-53.34)	2.37 (0.44-18.63)	<0.001
Peak D-dimer, $\mu\text{g/ml}$ (range)	5.36 (0.2-53.34)	3.05 (0.44-39.16)	<0.001

LLND: Lateral lymph node dissection; VTE: venous thromboembolism; POD: postoperative day.

(10.0%), 13 (11.5%) vs. 27 (6.3%), respectively]. The rate of the patients who took over three days to mobilize was higher in the LLND+ group than the LLND- group [39 (34.5%) vs. 57 (13.2%);  $p < 0.001$ ]. Plasma D-dimer at POD3 and peak D-dimer during hospitalization were significantly higher in the LLND+ group than in the LLND- group [4.37 (1.61-53.34) vs. 2.37 (0.44-18.63), 5.36 (0.2-53.34) vs. 3.05 (0.44-39.16), respectively].

*Incidence of VTE after for primary rectal cancer or locally recurrent rectal cancer.* Table III represents the incidence of VTE in all included patients subjected to surgeries with or without LLND. A total of eight (1.47%) out of the 543

patients developed either symptomatic or asymptomatic VTE. The frequencies of VTE were 4.42% and 0.69% in the LLND+ group and the LLND- group, respectively ( $p = 0.01$ ).

Detailed clinicopathological characteristics of the eight patients who experienced VTE or PE after surgery are summarized in Table IV. Of those eight patients, five patients underwent LLND. The median onset of VTE, operative time and blood loss during surgery in patients who experienced VTE were 14.5 days (2-91), 672.5 min (192-1,280), and 930 ml (20-11,150), respectively. As shown in Table IV, three of those eight patients had developed severe postoperative complications, such as perforation and postoperative bleeding before the onset of VTE. Notably, two of five patients who

Table III. Association between lateral lymph node dissection (LLND) and venous thromboembolism (VTE).

	LLND+ group (n=113)	LLND- group (n=432)	p-Value
VTE (+), n (%)	5 (4.42%)	3 (0.69%)	0.01
VTE (-), n (%)	108 (95.6%)	429 (99.3%)	

Table IV. Detailed clinicopathological characteristics of the eight patients who experienced venous thromboembolism (VTE) or pulmonary embolism (PE) after surgery.

Patient	LLND	Details of VTE (Location of thrombosis)	Onset of VTE (POD)	Surgical procedure	Operating time (min)	Blood loss (ml)	Postoperative complication	Additional information
1	+	DVT (Femoral), PE	91	TPE	496	11,150	-	-
2	+	DVT (Popliteal)	7	APR	729	910	-	-
3	+	DVT (Femoral)	2	LAR	846	950	-	Intraoperative repair of external iliac vein
4	+	DVT (Femoral)	28	TPE	1,280	4,820	Perforation (Small intestine)	-
5	+	DVT (Popliteal)	36	APR	712	420	-	Resection of internal iliac veins
6	-	PE, Portal thrombosis	7	LAR	192	20	-	-
7	-	PE	8	LAR	633	180	Intraabdominal abscess	-
8	-	DVT (Peripheral)	21	TPE	607	3,700	Intraperitoneal bleeding	-

LLND: Lateral lymph node dissection; DVT: deep venous thrombosis; TPE: total pelvic exenteration; APR: abdominoperineal resection; LAR: low anterior resection.

did not develop postoperative complications required intraoperative repair of external iliac vein or combined resection of internal iliac veins during LLND procedure.

*Risk factors for DVT after surgery for rectal cancer.* Next, to identify the risk factors for VTE after surgery for rectal cancer, both univariate and multivariate analysis were performed (Table V). Univariate analysis identified the incidence of postoperative complications (Clavien-Dindo classification  $\geq 3$ ), immobilization of three days or longer, and LLND as significant risk factors for the development of DVT. Then, multivariate analysis was performed using these factors with  $p$ -values  $<0.05$ . Multivariate analysis revealed that the incidence of postoperative complications and LLND were the independent risk factors for VTE.

## Discussion

In this retrospective study, 543 patients underwent a resection for primary rectal cancer or locally recurrent rectal cancer, and an overall DVT incidence of 1.4% was observed in the cohort. Five of eight patients who experienced DVT underwent LLND, and the frequency of DVT was significantly higher in the LLND+ group than the LLND- group. According to the multivariate analysis, the incidence of postoperative

complications and LLND were identified as significant risk factors of VTE. Though several recent reports discuss the associations between colorectal surgery and postoperative VTE (6-9), there have been no studies focusing on the associations between LLND and postoperative VTE. To the best of our knowledge, this is the first report to identify LLND procedure as an independent risk factor for VTE.

Our group previously conducted a multicenter randomized controlled trial to identify the risk factors for VTE following the laparoscopic colorectal cancer surgery (9). In this previous study, blood loss and tumor location were identified as the risk factors of VTE (19, 20). A long operation time is also a well-known risk factor for postoperative complications after colorectal surgery (21). The surgeries with LLND usually carry the risks of a larger amount of blood loss and a longer operating time due to their complicated procedure. Thus, LLND may potentially enhance the risk of postoperative complications including VTE compared the other colorectal surgery. In fact, our cohort demonstrated that the LLND+ group had longer operation time and larger amount of intraoperative blood loss than the LLND- group. However, no statistically significant differences of the rate of postoperative complications between the LLND+ group and the LLND- group were observed. Several previous studies reported that the incidence of severe postoperative



Table V. Univariable and multivariable analysis of factors associated with venous thromboembolism.

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	p-Value	OR	95%CI	p-Value
Age (year-old) [≥66/<66]	1.33	0.32-5.65	0.78			
Sex [Female/Male]	4.60	0.56-37.67	0.15			
Body mass index [≥25/<25]	1.23	0.24-6.21	0.80			
Location [RS, Ra/Rb, P]	2.13	0.50-8.98	0.30			
Operation time (min) [≥300/<300]	4.57	0.56-37.38	0.090			
ASA-PS [≥3/<3]	0.00	0-0	0.31			
Pharmacologic prophylaxis of VTE [+/-]	2.55	0.60-10.80	0.20			
Postoperative complication [+/-]	8.11	1.86-35.26	0.0053	5.05	1.02-24.94	0.05
Surgery for locally recurrent rectal cancer [+/-]	1.88	0.22-15.65	0.56			
POD3 D-dimer [≥4.37/<4.37]	5.35	0.47-60.78	0.18			
Immobilization (day) [≥3/<3]	4.83	1.19-19.69	0.0022	2.08	0.44-9.87	0.36
Surgery for locally recurrent rectal cancer [+/-]	1.88	0.22-15.65	0.59			
Multivisceral resection [+/-]	3.24	0.76-13.80	0.14			
LLND [+/-]	6.62	1.56-28.13	0.0105	4.96	1.11-22.25	0.04

LLND: Lateral lymph node dissection; OR: odds ratio; CI: confidence interval; POD: postoperative day.

complications after LLND was from 12.5% to 22.0% (21-24). Our current study presented that the incidence rates of severe postoperative complications after LLND were 11.5%, which is lower than those reported in previous studies. Additionally, the multivariate analysis in the current study identified LLND as an independent risk factor for VTE. There are no strict guidelines how to follow up patients who underwent surgery for rectal cancer with LLND. Our results suggested that patients after LLND may warrant close follow-up such as CT scan to identify an asymptomatic VTE and extended postoperative prophylaxis of VTE.

Furthermore, colorectal surgeons need to compress the iliac vein during surgery to perform LLND and sometimes repair or resect it. Interestingly, two of the patients who had VTE after surgery required to repair external iliac vein intraoperatively for preventing bleeding or to resect internal iliac veins for the achievement of radical resection. The associations between compression of iliac vein and VTE have been frequently discussed in the field of orthopedics (25, 26). It has been also reported that May-Thurner syndrome, in which the iliac vein is mechanically compressed between the artery and the bone should be a risk factor for VTE (27, 28). Though those two patients in the present study did not have the postoperative stenosis of iliac vein, it is possible that the physical irritation of iliac vein during the procedure may have influenced the development of VTE. Our study suggested that the patients may warrant careful monitoring to identify VTE earlier if intraoperative repair or complicated resection of the iliac vessels is required.

A limitation of this study was that the background in the LLND+ group differed from that of the LLND- group including the surgical approach, operating time, blood loss, and

various other factors. These results suggest that LLND procedures are considered highly invasive. Because extensive surgical procedures, involving longer operating times and greater blood loss, have been reported as risk factors for VTE, this study alone may not be sufficient to conclude that LLND is a direct risk factor for VTE. To assess the associations between LLND and postoperative VTE more accurately, a prospective study with a larger cohort is necessary. However, considering that five of eight patients in whom DVT was observed underwent LLND, and two of these five patients also required intraoperative repair of the iliac vein during the LLND procedure, we consider that our study provides an important suggestion that patients undergoing LLND procedures should be monitored closely for signs of VTE.

## Conclusion

In conclusion, undergoing LLND as part of rectal cancer surgery and experiencing postoperative complications are the independent risk factors for VTE. Based on our findings, patients undergoing LLND, especially those requiring repair of iliac vein during surgery, should be closely monitored for signs of VTE.

## Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

## Authors' Contributions

All Authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yuta

Kobayashi, Mamoru Uemura, Masakatsu Paku, and Masatoshi Kitakaze. The first draft of the manuscript was written by Yuta Kobayashi and all authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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