Journal of Gastrointestinal Surgery (2021) 25:1866–1874
https://doi.org/10.1007/s11605-020-04825-x

ORIGINAL ARTICLE

The Significance of Lateral Lymph Node Metastasis in Low Rectal Cancer: a Propensity Score Matching Study

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Received: 23 June 2020 / Accepted: 3 October 2020 / Published online: 19 October 2020

Abstract

Background The indications for lateral lymph node dissection (LLND) in rectal cancer have been controversial. The purpose of this study was to clarify the significance of lateral lymph node metastasis in low rectal cancer.

Methods This was a retrospective study at a high-volume cancer center in Japan. In this study, 40 patients with pathologically positive LLN (LLN+) were matched with 175 negative (LLN−) patients by propensity score matching (PSM). COX regression analysis was used to identify independent risk factors related to prognosis. The relapse-free survival rate (RFS) and overall survival rate (OS) of the 2 groups before and after matching were analyzed.

Results Of the 64 patients undergoing LLND, 40 (62.5%) patients had LLN+ disease. The LLN+ patients showed deeper infiltration of the primary tumor than the LLN− patients (T3-T4: 87.5% vs. 72.0%; $p = 0.044$), a greater number of metastatic lymph nodes (N2: 75.0% vs. 35.4%; $p < 0.001$), and a higher rate of local recurrence (30% vs. 9.1%; $p < 0.001$). Adjuvant chemotherapy was more common in the 40 LLN+ patients than in the 175 LLN− patients (70.0% vs. 46.8%; $p = 0.008$). After relapse, the rate of first-line chemotherapy administration for LLN+ patients was higher than that for the LLN− patients (62.5% vs. 29.5%; $p = 0.005$). The RFS of LLN+ patients was shorter than that of the LLN− patients ($p = 0.005$). After PSM, although more LLN+ patients received adjuvant chemotherapy than the LLN− patients (70.0% vs. 40.0%; $p = 0.007$), the local recurrence rate remained higher (30% vs. 10%; $p = 0.025$). The differences between RFS ($p = 0.655$) and OS rates ($p = 0.164$) of the 2 patient groups were not significant.

Conclusion Even after LLND, patients with LLN+ low rectal cancer still showed an elevated local recurrence rate. Controlling local recurrence by adjuvant chemotherapy alone is difficult, and the additional strategic treatments are needed.

Keywords Lateral lymph node dissection · Low rectal cancer · Propensity score matching

Introduction

Lateral lymph node (LLN) metastasis associated with advanced low rectal cancers poses a major challenge to the treatment of this disease. Although LLN dissection (D) for patients with rectal cancer can be traced back to the 1930s, and western surgeons have performed LLND as early as the 1950s to improve patient treatment, it is currently only popular in Japan.[1,2]

According to a Japanese retrospective study, 16–23% of patients with low rectal cancer have LLN metastases.[3] For patients with a preoperative diagnosis of low rectal cancer without an obvious LLN metastasis and a tumor infiltrating deeper than the muscle propria, the decision to perform LLND remains controversial. In western countries, adjuvant chemo-radiation therapy is recommended, because LLN metastasis is considered to be a reflection of systemic metastatic disease, rather than locoregional metastatic lymph nodes.[4] Although the latest Japanese guidelines for the treatment of colorectal cancer suggest that each case of advanced low rectal cancer should undergo bilateral LLND, the evidence level remains relatively low because of the absence of data from large-scale prospective clinical trials.[5]

Propensity score matching (PSM) is becoming increasingly used for retrospective studies in clinical research because it

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can reduce the imbalance between background confounders in study groups.[6] Therefore, to clarify the significance of lateral lymph node metastasis in low rectal cancer, we used PSM to conduct a retrospective cohort study to compare the short-term and long-term differences in the outcomes of patients with low rectal cancer and LLN-positive (LLN+) versus LLN-negative (LLN−) disease.

Materials and Methods

This was a retrospective single-center study at a high-volume cancer center in Japan. From April 2007 to December 2016, 899 patients at Saitama Medical University International Medical Center were diagnosed with colorectal cancer and metastatic lymph nodes by histopathological examination. The Ethics Committee of the Saitama Medical University International Medical Center approved the study. All the study participants provided informed consent. Patients with recurrent colorectal cancer, malignant tumors associated with inflammatory colitis, and failure to undergo surgical resection were excluded.

Low rectal cancer was defined as a tumor with a lower margin that was lower than the peritoneal reflex. A finding of multiple primary colorectal cancers was termed "multiple cancers." Concomitant malignant tumors found in other organs were regarded as "duplicate cancers." A lymph node with a long axis measuring 7 mm on a multi-slice spiral CT (MDCT) scan or a magnetic resonance imaging (MRI) scan was considered to be a clinically positive LLN.

Of the 899 stage III patients, 215 patients had low rectal cancer, of which 64 had a clinical diagnosis of LLN-positive low rectal cancer (cLLN+). Patients with low rectal cancer who were cLLN+ underwent total mesenteric resection (TME) and lateral lymph node dissection (LLND). The remaining 151 patients who were clinically negative for LLN metastasis (cLLN-) only undergo TME (Fig. 1).

Patients with pathologically positive LLNs (pLLN+) were called LLN+ patients, and those with pathologically negative LLN (pLLN−) or a negative preoperative imaging diagnosis (cLLN−) were called the LLN− patients. Propensity score weighting was used to balance the following variables between the 2 groups: patient age, gender, surgical method, depth of tumor invasion, lymph node metastasis, lymphatic invasion, peripheral nerve infiltration, vascular infiltration, and preoperative carcinoembryonic antigen (CEA) level. Overall survival (OS) and relapse-free survival (RFS) were compared between the 2 groups both before and after matching.

Statistical analysis was performed by SPSS version 22 (IBM Corporation, Tokyo, Japan). COX regression analysis was used to identify independent risk factors related to prognosis. The chi-square test and Fisher exact test were used to test for differences between categorical variables. $p < 0.05$ was considered statistically significant.

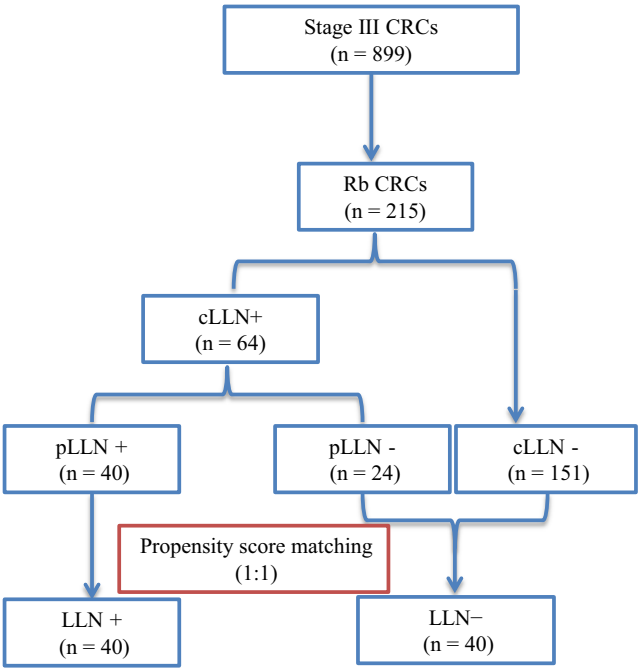

Fig. 1 Research flowchart. LLN -:Lateral Lymph Node negative; LLN +: Lateral Lymph Node positive; cLLN: Clinical LLN, pLLN: Pathological LLN; CRCs: Colorectal Cancers. Rb: rectum below the peritoneal reflection.

Results

Of 899 patients with colorectal cancer and lymph node metastasis, 215 (23.9%) patients had low rectal cancer. Sixty four were diagnosed with cLLN+ disease by preoperative imaging, and 40 (18.6%) were postoperatively diagnosed with pLLN+ by histopathological evaluation. The accuracy of the preoperative imaging diagnosis of LLN metastasis is 62.5% (Fig. 1).

Among the 40 LLN+ patients, 30 (75%) patients had perirectal lymph node metastases (Region 251), with a mean number of 6.1 ± 5.1 positive nodes; 4 (10%) patients had inferior mesenteric trunk lymph node metastases (Region 252); and only 2 (5%) patients had metastatic inferior mesenteric nodes (Region 253). Region 283L, comprised of the left obturator lymph nodes, was the most frequently involved metastatic site (47%). The second most common site was Region 263R, comprised of the right internal iliac lymph nodes (27.5%). Only 4 (10%) patients had metastatic disease involving the common iliac lymph nodes (Region 273) or the external iliac lymph nodes (Region 293) (Fig. 2).

Univariate analysis was performed on 40 LLN+ and 175 LLN− patients. LLN+ patients vs LLN− patients underwent open surgery more frequently (45.0% vs. 22.3%, respectively; $p = 0.005$), showed deeper infiltration (T3-T4: 87.5% vs.

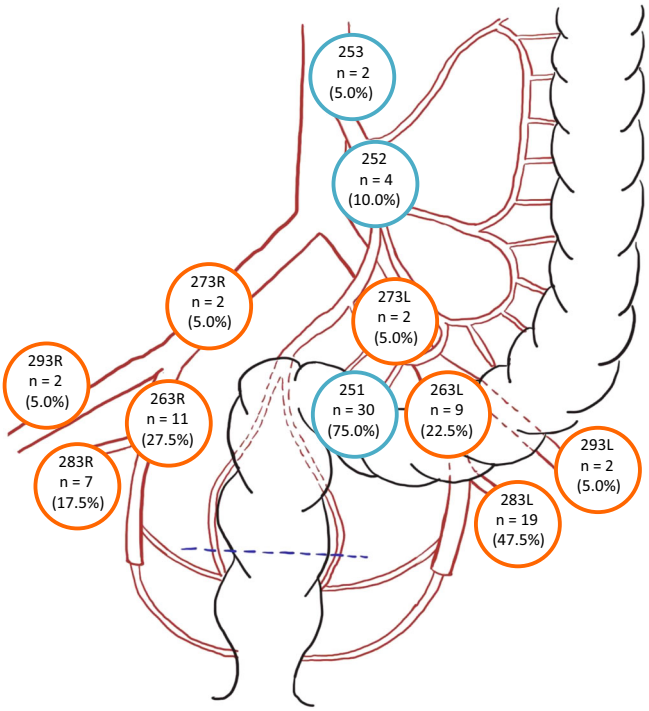

Fig. 2 Distribution of lymph node metastases in LLN+ patients. 251 (perirectal nodes), 252 (inferior mesenteric trunk nodes) 253 (inferior mesenteric nodes); 263(internal iliac nodes), 273 (common iliac node), 283 (obturator nodes), 293 (external iliac nodes); L: left, R: right. LLND: lateral lymph node dissection; Rb: rectum below the peritoneal reflection; Dotted line: Peritoneal reflection.

72.0%, respectively; $p = 0.044$) and had more than 4 metastatic lymph nodes (N2: 75.0% vs. 35.4%, respectively; $p < 0.001$) (Table 1). Perioperatively, LLN+ patients vs LLN− patients underwent more abdominoperineal resections (APR) (22.5% vs. 10.9%, respectively; $p = 0.048$), had longer operative times (371.6 ± 17.8 min vs. 279.2 ± 5.7 min, respectively; $p < 0.001$), lost higher amounts of blood during surgery (362.9 ± 76.2 mL vs. 117.8 ± 17.0 mL respectively; $p < 0.001$), and had higher numbers of resected lateral lymph nodes (6.7 ± 1.0 vs. 3.7 ± 0.3, respectively; $p < 0.001$). Although the incidence of postoperative dysuria was higher among the LLN+ patients, the difference between the rates of dysuria is not significant (Table 2).

The postoperative recurrence and local recurrence rates were higher in the LLN+ than in the LLN− patients (overall recurrence: 60% vs. 34.8%, respectively; $p = 0.002$; local recurrence: 30.0% vs. 9.1%, respectively; $p < 0.001$). The difference between the rates of development of distant metastasis was not significant.

The rate of administration of adjuvant chemotherapy to the LLN+ patients was significantly higher than that of the LLN− patients (70.0% vs. 46.8%, respectively; $p = 0.008$). When patients relapsed, more LLN+ patients receive first-line chemotherapy than LLN− patients (62.5% vs. 29.5%, respectively; $p = 0.005$) (Table 3).

The long-term outcomes of the 2 groups were analyzed. The RFS of the LLN+ patients was significantly worse than that of the LLN− patients ($p = 0.005$). The difference between the OS of the 2 groups is not significant ($p = 0.851$) (Figs. 3 and 4).

The LLN+ and LLN− group were then matched 1:1 for propensity scores. After matching, the LLN+ patients compared with the LLN− patients still showed a longer operative time (371.6 ± 17.8 min vs. 290.1 ± 12.1 min, respectively; $p < 0.001$) and higher volume of blood loss (362.9 ± 76.2 mL vs. 189.6 ± 39.9 mL respectively; $p = 0.048$) (Table 2).

The difference between the recurrence rates in the 2 patient groups was not significant. More LLN+ than LLN− patients developed local recurrence (30.0% vs. 10.0%, respectively; $p < 0.001$). More LLN+ than LLN− patients receive adjuvant chemotherapy (70.0% vs. 40.0%, respectively; $p = 0.007$) (Table 3). Unexpected findings are that the differences between the rates of RFS and the rates of OS in the 2 patient groups were not significant ($p = 0.655$, $p = 0.164$, respectively) (Figs. 5 and 6).

COX regression analysis was used to identify prognostic factors. Before PSM, a CEA level ≥ 5 ng/mL was not only a significant risk factor for RFS (odds ratio [OR] = 6.942; 95% confidence interval [CI] = 0.313–0.843; $p = 0.008$) but also for OS (OR = 7.78; 95% CI = 0.149–0.717; $p = 0.005$). The other independent risk factors for OS include the following: female gender; age; duplicate cancers; intraoperative bleeding; pathological typing; lymphatic infiltration; vascular infiltration; and number of lymph nodes harvested (Table 4).

After PSM, COX regression analysis found that CEA (OR = 4.053; 95% CI = 0.178–0.977; $p = 0.044$), MUC/Sig/Poor (OR = 4.02; 95% CI = 0.054–0.967; $p = 0.045$), and vascular infiltration (OR = 7.939; 95% CI = 1.691–28.682; $p = 0.005$) were also independent risk factors for RFS. Female gender, duplicate cancers, postoperative complications, operative

Table 1 Clinicopathological parameters of patients with stage III Rb rectal cancer

Parameters	Before matching			After matching		
	LLN+	LLN−	*p* value	LLN+	LLN−	*p* value
Gender (Total *n* =)	40	175		40	40	
Male	30 (75.0)	118 (67.4)		30 (75.0)	32 (80.0)	
Female	10 (25.0)	57 (32.6)	N.S.	10 (25.0)	8 (20.0)	N.S.
Age (year)	63.3 ± 1.22	64.3 ± 0.81	N.S.	63.3 ± 1.22	63.8 ± 2.15	N.S.
CEA (ng/mL)						
≥ 5	20 (50.0)	65 (37.1)		20 (50.0)	19 (47.5)	
< 5	20 (50.0)	110 (62.9)	N.S.	20 (50.0)	21 (52.5)	N.S.
Duplicate cancer						
No	37 (92.5)	156 (89.1)		37 (92.5)	35 (87.5)	
Yes	3(7.5)	19 (10.9)	N.S.	3(7.5)	5 (12.5)	N.S.
Multiple cancer						
No	36 (90.0)	158 (90.3)		36 (90.0)	36 (90.0)	
Yes	4 (10.0)	17 (9.7)	N.S.	4 (10.0)	4 (10.0)	N.S.
Approach of operation						
Laparoscopic	22 (55.0)	136 (77.7)		22 (55.0)	26 (65.0)	
Open	18 (45.0)	39 (22.3)	0.005	18 (45.0)	14 (35.0)	N.S.
Pathological type						
ADC	36 (90.0)	162 (92.6)		36 (90.0)	37 (92.5)	
MUC, SRC, poor	4 (10.0)	13 (7.4)	N.S.	4 (10.0)	3 (7.5)	N.S.
Gross type						
Protruding	2 (5.0)	28 (16.0)		2 (5.0)	2 (5.0)	
Infiltrate and ulcerative	38 (95.0)	147 (84.0)	N.S.	38 (95.0)	38 (95.0)	N.S.
Perineural infiltration						
No	10 (25.0)	35 (20.0)		10 (25.0)	9 (22.5)	
Yes	30 (75.0)	140 (80.0)	N.S.	30 (75.0)	31 (77.5)	N.S.
Infiltration lymphatic vessels						
No	19 (47.5)	85 (48.6)		19 (47.5)	13 (32.5)	
Yes	21(52.5)	90 (51.4)	N.S.	21(52.5)	27 (67.5)	N.S.
Vascular invasion						
No	5 (12.5)	29 (16.6)		5 (12.5)	5 (12.5)	
Yes	35 (87.5)	146 (83.4)	N.S.	35 (87.5)	35 (87.5)	N.S.
Infiltration type						
Inflated	2 (5.0)	11 (6.3)		2 (5.0)	2 (5.0)	
Infiltrating	38 (95.0)	164 (93.7)	N.S.	38 (95.0)	38 (95.0)	N.S.
Infiltration depth						
T1-2	5 (12.5)	49 (28.0)		5 (12.5)	4 (10.0)	
T3-4	35 (87.5)	126 (72.0)	0.044	35 (87.5)	36 (90.0)	N.S.
Metastatic lymph node						
N1	10 (25.0)	113 (64.6)		10 (25.0)	12 (30.0)	
N2	30 (75.0)	62 (35.4)	< 0.001	30 (75.0)	28 (70.0)	N.S.

ADC adenocarcinoma; *CEA* carcinoembryonic antigen; *Muc* mucinous adenocarcinoma; *Poor:* poorly differentiated adenocarcinoma; *SRC* Signet ring cell carcinoma

time, intraoperative bleeding, number of lymph nodes harvested, and metastatic disease are all independent risk factors for OS (Table 4). Before and after PSM, metastatic LLN is not an independent risk factor for either OS or RFS (Tables 4 and 5).

Discussion

The complicated anatomy of the pelvis poses a major challenge to LLND. There are 2 main routes for lymphatic drainage in the

Table 2 Surgical results and postoperative complications before and after matching

Variables	Before matching			After matching		
	LLN+ (n = 40)	LLN− (n = 175)	p value	LLN+ (n = 40)	LLN− (n = 40)	p value
Surgical approach						
LAR	17 (42.5)	102 (58.3)	N.S.	17 (42.5)	20 (50.0)	N.S.
Hartmann	0 (0.0)	6 (3.4)	N.S.	0 (0.0)	1 (2.5)	N.S.
ISR	13 (32.5)	47 (26.9)	N.S.	13 (32.5)	11 (27.5)	N.S.
APR	9 (22.5)	19 (10.9)	0.048	9 (22.5)	8 (20.0)	N.S.
TPE	1 (2.5)	2 (1.1)	N.S.	1 (2.5)	0 (0.0)	N.S.
Metastatic lymph nodes	6.7 ± 1.0	3.7 ± 0.3	< 0.001	6.7 ± 1.0	5.8 ± 0.7	N.S.
Lymph node positivity rate	0.17 ± 0.02	0.152 ± 0.01	N.S.	0.17 ± 0.02	0.22 ± 0.02	N.S.
Operative time	371.6 ± 17.8	279.2 ± 5.7	< 0.001	371.6 ± 17.8	290.1 ± 12.1	< 0.001
Surgical bleeding	362.9 ± 76.2	117.8 ± 17.0	< 0.001	362.9 ± 76.2	189.6 ± 39.9	0.048
Postop complication	11 (27.5)	66 (37.7)	0.03	11 (27.5)	14 (35.0)	N.S.
Bowel obstruction	2 (5.0)	22 (12.6)	N.S.	2 (5.0)	4 (10.0)	N.S.
SSI or abscess	3 (7.5)	16 (9.1)	N.S.	3 (7.5)	7 (17.5)	N.S.
Anastomotic leakage	4 (10)	18 (10.3)	N.S.	4 (10)	3 (7.5)	N.S.
Dysuria	3 (7.5)	4 (2.3)	N.S.	3 (7.5)	2 (5.0)	N.S.
Others	0 (0.0)	9 (5.1)	N.S.	0 (0.0)	2 (5.0)	N.S.

LLN−, lateral lymph node negative; *LLN+*, lateral lymph node positive; *No.*, number; *Postop*, postoperative; *LAR*, low anterior resection; *ISR*, intersphincteric resection; *TPE*, total pelvic exenteration; *APR*, abdominoperineal resection

lower rectum. A drainage system along the superior rectal and inferior mesenteric arteries drains into the lymph nodes around the abdominal aorta. The other route is along the middle rectal artery and enters the obturator and internal and external iliac lymph nodes. Our study found that among 215 patients with stage III low rectal cancer, 40 (18.6%) patients had LLN metastases, similar to previously reported results.[3] Thirty (75%) patients had metastatic perirectal nodes, with a mean number of 6.1 positive nodes. This suggests that the majority of low rectal cancer metastases still occurred in the mesenteric region.[7]

For patients with low rectal cancer without LLN metastasis, high-level evidence for LLND is lacking. This study found that 30% of the LLN+ patients developed local recurrence. Some papers reported that the LLNs are the main sites of recurrence, which is consistent with our findings.[8–10] Even after LLND, local recurrence still occurred. Perhaps this should lead us to consider other comprehensive treatment methods. However, many other studies have shown that LLND-related reduction of local recurrence is possible.[5] Another Japanese report concluded that LLND did not affect the rate of local recurrence.[11] The conflicting results of these reports might be accounted for by the different diagnostic criteria that were used for the imaging findings regarding the LLNs.

Table 3 Postoperative recurrence and treatment after recurrence before and after matching

Variables	Before matching			After matching		
	LLN+ (n = 40)	LLN− (n = 175)	p value	LLN+ (n = 40)	LLN− (n = 40)	p value
Adjuvant chemotherapy	28 (70.0)	82 (46.8)	0.008	28 (70.0)	16 (40.0)	0.007
Total recurrence	24 (60.0)	61 (34.8)	0.002	24 (60.0)	20 (50.0)	N.S.
Local recurrence	12 (30.0)	16 (9.1)	< 0.001	12 (30.0)	4 (10.0)	0.025
Liver metastasis	4 (10.0)	21 (12.0)	N.S.	4 (10.0)	7 (17.5)	N.S.
Lung metastasis	10 (25.0)	24 (13.7)	N.S.	10 (25.0)	8 (20.0)	N.S.
Others	1 (2.5)	5 (2.8)	N.S.	1 (2.5)	3 (7.5)	N.S.
Postrecurrence treatment						
1st line chemotherapy	15 (62.5)	18 (29.5)	0.005	15 (62.5)	9 (45.0)	N.S.
2nd surgical resection	5 (20.8)	17 (27.8)	N.S.	5 (20.8)	1 (5.0)	N.S.
Best supportive care	4 (16.6)	8 (13.1)	N.S.	4 (16.6)	5 (25.0)	N.S.

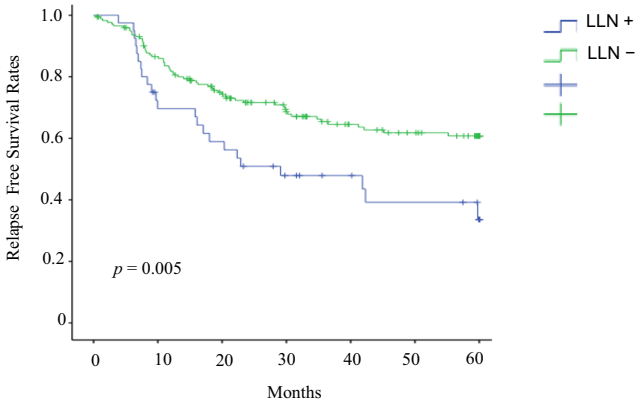

Fig. 3 Relapse-free survival rates of patients before propensity score matching

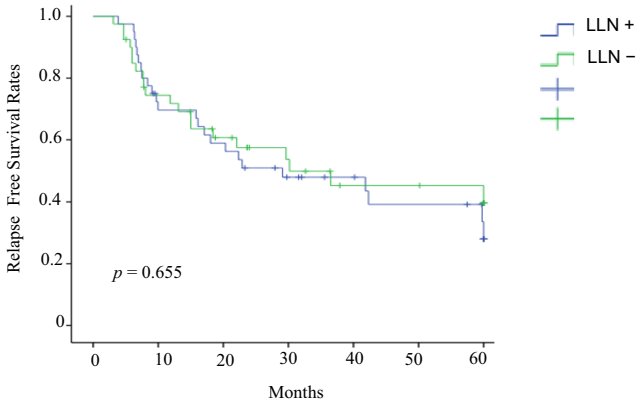

Fig. 5 Relapse-free survival rates of patients after propensity score matching

High-resolution CT and MRI are widely used in the diagnosis of lateral lymph node metastasis. Lymph nodes larger than 7 mm are diagnosed as positive for lymph node metastasis. In this report, we found that the accuracy of preoperative diagnostic imaging was only 62.5%, suggesting that a more reliable diagnostic standard is still needed. Beyond the size of a lymph node as a criterion, evaluation of the borders of the lateral lymph nodes might provide increased accuracy for preoperative imaging.[12,13]

The depth of cancer invasion as assessed by diagnostic preoperative imaging is also important for deciding to perform LLND. Generally, we can observe the depth of invasion by MRI or contrast-enhanced CT. Among all 215 patients, there were 13 cases of T4 (6.0%) and 6 cases (2.8%) of T4b disease. Of these cases, 2 showed infiltration of the vagina, and the rest showed infiltration of the bladder, prostate, cervix, or pelvic muscles. Even so, most of these underwent successful R0 radical resections (LLN+: 92.5% vs. LLN−: 95.4%). Of the 13 cases with T4 disease, 6 (46%) developed distant metastases. Therefore, performing an accurate preoperative diagnosis of imaging results regarding the depth of invasion is particularly important. Additionally, routine endoscopic ultrasonography for rectal cancer may improve the diagnostic assessment of the depth of malignant invasion.

Total mesenteric resection (TME) after neoadjuvant chemoradiotherapy (CRT) is currently the standard for the treatment of low rectal cancer treatment in North America and Europe.[14,15] The primary reason is that LLND does change the prognosis and may also cause excessive intraoperative bleeding and postoperative difficulty in urination because of nerve damage.[15] Our study also found that both before and after PSM, the intraoperative bleeding was significantly increased and the operative time was significantly prolonged in LLN+ patients.

The frequency of laparoscopic resection of colorectal cancer has gradually increased in Japan.[16] There have been reports that laparoscopic LLND is safer than LLND performed during open surgery.[17] The magnification provided by the laparoscope contributes to the protection of nerves during surgery.[18] Our research suggests that when special attention is focused on protecting nerves during surgery, the rate of postoperative urinary retention should not be excessive.

Some studies have reported significant improvement in RFS after LLND.[9] Our study found that before PSM, patients with LLN+ were more likely to relapse even after LLND. However, when patient backgrounds were rendered equivalent after PSM, the difference between the relapse rates of the 2 patient groups was not significant. These results indicate that

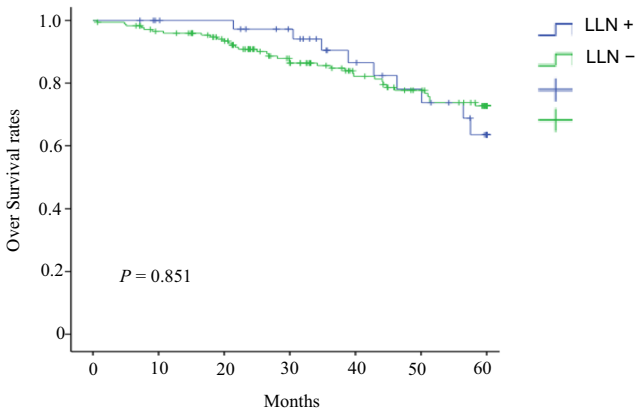

Fig. 4 Overall survival rates of patients before propensity score matching

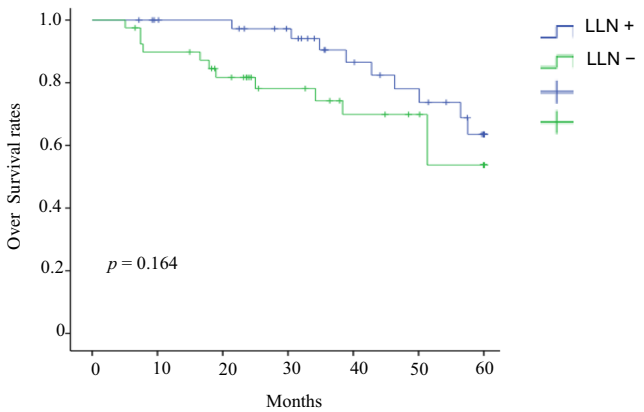

Fig. 6 Overall survival rates of patients after propensity score matching

Table 4 Cox regression model comparing the outcome of patients before matching

Variable	Relapse free survival			Overall survival		
	Odds ratio	HR(95% CI)	*p* value	Odds ratio	HR(95% CI)	*p* value
LLN metastasis, Yes vs. No	0.054	0.351–3.788	0.815	2.148	0.042–1.579	0.143
Gender, male vs. female	3.166	0.342–1.053	0.075	12.244	0.039–0.401	0
Age	0.763	0.986–1.037	0.382	10.306	1.027–1.117	0.001
Duplicate cancer, Yes vs. No	0.001	0.427–2.403	0.976	10.615	0.053–0.481	0.001
Postop complications, Yes vs. No	0.872	0.755–2.205	0.35	0.11	0.512–2.564	0.74
CEA level (ng/mL), ≥ 5 vs. < 5	6.942	0.313–0.843	0.008	7.78	0.149–0.717	0.005
Operative time	2.146	0.999–1.005	0.143	2.561	0.991–1.001	0.11
Surgical bleeding	0.289	0.999–1.001	0.591	5.693	1–1.003	0.017
MUC, SRC, Poor vs. ADC	2.849	0.239–1.113	0.091	8.19	0.084–0.629	0.004
Perineural invasion, Yes vs. No	1.454	0.292–1.341	0.228	0.008	0.253–3.501	0.929
Lymphatic invasion, Yes vs. No	0.145	0.546–1.504	0.703	5.521	0.148–0.842	0.019
Vascular invasion, Yes vs. No	1.293	0.737–3.16	0.255	10.574	1.99–16.06	0.001
Number of lymph nodes metastasis	0.145	0.913–1.144	0.703	0.293	0.834–1.109	0.588
Number of lymph nodes harvested	0.361	0.961–1.021	0.548	7.705	1.017–1.1	0.006
Lymph node positivity rate	0.94	0.138–346.88	0.332	2.162	0.294–5288.04	0.141

ADC adenocarcinoma; *CEA* carcinoembryonic antigen; *CI* confidence interval; *HR* hazard ratio; *Muc* mucinous adenocarcinoma; *Poor* poorly differentiated adenocarcinoma; *SRC* Signet ring cell carcinoma; *vs.* versus

metastatic LLNs did not affect RFS when LLND was performed. What exactly will affect the prognosis of patients? Our results, which were consistent with other studies, showed that the preoperative CEA level and pathological type reflected RFS.[19–21]

Although Japanese guidelines recommend preventive LLND,[3] high-volume cancer centers in Japan are inconsistent with regard to the guidelines on the diagnostic criteria and treatment. The Cancer Research Ariake Hospital, which is the largest cancer center in Japan, prefers neoadjuvant CRT.[11,13] Our cancer center routinely

Table 5 Cox regression model comparing the outcomes of patients after matching

Variable	Relapse free survival			Overall survival		
	Odds ratio	HR(95% CI)	*p* value	Odds ratio	HR(95% CI)	*p* value
LLN metastasis, Yes vs. No	0.271	0.325–6.93	0.602	3.709	0.002–1.057	0.054
Gender, male vs. female	0.31	0.249–2.169	0.578	9.272	0.001–0.218	0.002
Age	1.977	0.987–1.083	0.16	1.497	0.965–1.165	0.221
Duplicate cancer, Yes vs. No	2.438	0.68–30.09	0.118	5.13	0–0.469	0.024
Postop complications, Yes vs. No	0.041	0.357–2.307	0.839	7.272	0.01–0.48	0.007
CEA level (ng/mL), ≥ 5 vs. < 5	4.053	0.178–0.977	0.044	1.07	0.079–2.193	0.301
Operative time	2.691	0.999–1.01	0.101	7.157	0.966–0.995	0.007
Surgical bleeding	0.017	0.999–1.002	0.895	9.378	1.001–1.007	0.002
MUC, SRC, Poor vs. ADC	4.02	0.054–0.967	0.045	0.129	0.002–76.304	0.719
Perineural invasion, Yes vs. No	3.311	0.912–11.887	0.069	0.006	0.053–15.049	0.936
Lymphatic invasion, Yes vs. No	0.006	0.458–2.336	0.936	0.172	0.12–25.913	0.678
Vascular invasion, Yes vs. No	7.939	1.691–28.682	0.005	0.013	0.017–37.413	0.908
Number of lymph nodes metastasis	1.808	0.938–1.409	0.179	4.533	0.539–0.975	0.033
Number of lymph nodes harvested	1.219	0.905–1.028	0.269	8.889	1.06–1.323	0.003
Lymph node positivity rate	0.62	0–77.896	0.431	5.14	8.205–3799.38	0.023

ADC adenocarcinoma; *CEA* carcinoembryonic antigen; *CI* confidence interval; *HR* hazard ratio; *Muc* mucinous adenocarcinoma; *Poor* poorly differentiated adenocarcinoma; *SRC* Signet ring cell carcinoma; *vs.* versus.

performed prophylactic bilateral LLND 5 years ago but has subsequently only performed therapeutic unilateral LLND. We changed our treatment approach, because we found that after prophylactic surgery, the original pelvic anatomy was disrupted, which resulted in a difficult surgical field for second operations for local recurrence.

Local recurrence after LLND was relatively difficult to control. Among 12 (30%) LLN+ patients with local recurrence, para-aortic lymph node metastases accounted for 6 cases (15%). Among the 16 (9.1%) LLN− patients with local recurrence, only 4 (2.3%) patients developed para-aortic lymph node metastases. This finding indicates that the occurrence of metastatic disease in a LLN+ likely indicates an increase in chance of recurrence involving the lymph nodes around the abdominal aorta, which is a difficult region to treat by radiotherapy. Adjuvant chemotherapy should be used for these cases. In the LLN+ group, the remaining 6 cases (15%) had local recurrence. Regions 263 and 283 each had 2 cases, anastomoses and pelvic muscles each had 1 case. Compared with 12 cases (6.8%) of local recurrence in the LLN- group, the local recurrence rate in the LLN+ group was still relatively high. Fortunately, local radiotherapy can be performed in this area.

Our research has limitations. Patients who were diagnosed with cLLN− before surgery might still harbor LLN metastases. Although our analysis looked at cases occurring over a 10-year period at a high-volume cancer center in Japan, there were few LLN+ patients. We anticipate participating in international prospective clinical studies in the future.

Conclusion

Even after lateral lymph node dissection, patients with LLN+ low rectal cancer still showed an elevated local recurrence rate. Local recurrence is difficult to control by adjuvant chemotherapy alone, and additional strategic treatments are needed.

Acknowledgments Our thanks are extended to BioMed Proofreading, LLC for English copyediting.

Authors' contributions LMW and YH drafted the manuscript. TI, HK, KH, NO, MA, GH, and SY reviewed its content. All authors have read and approved the final submission.

Compliance with ethical standards

Disclosure of Interest None to disclose

Consent for Publication All patients have agreed to use their medical data for research and publication.

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