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Outcomes and failure patterns after chemoradiotherapy for locally advanced rectal cancer with positive lateral pelvic lymph nodes: a propensity score-matched analysis

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Abstract

Purpose This study aimed to use propensity score matching (PSM) to explore the long-term outcomes and failure patterns in locally advanced rectal cancer (LARC) patients with positive versus negative lateral pelvic lymph node (LPLN).

Materials and methods Patients with LARC were retrospectively divided into LPLN-positive and LPLN-negative groups. Clinical characteristics were compared between the groups using the chi-square test. PSM was applied to balance these differences. Progression-free survival (PFS) and overall survival (OS), and local–regional recurrence (LRR) and distant metastasis (DM) rates were compared between the groups using the Kaplan–Meier method and log-rank tests.

Results A total of 651 LARC patients were included, 160 (24.6%) of whom had positive LPLN and 491 (75.4%) had negative LPLN. Before PSM, the LPLN-positive group had higher rates of lower location (53.1% vs. 43.0%, $P=0.025$), T4 stage (37.5% vs. 23.2%, $P=0.002$), mesorectal fascia (MRF)-positive (53.9% vs. 35.4%, $P<0.001$) and extramural venous invasion (EMVI)-positive (51.2% vs. 27.2%, $P<0.001$) disease than the LPLN-negative group. After PSM, there were 114 patients for each group along with the balanced clinical factors, and both groups had comparable surgery, pathologic complete response (pCR), and ypN stage rates. The median follow-up was 45.9 months, 3-year OS (88.3% vs. 92.1%, $P=0.276$) and LRR (5.7% vs. 2.8%, $P=0.172$) rates were comparable between LPLN-positive and LPLN-negative groups. Meanwhile, despite no statistical difference, 3-year PFS (78.8% vs. 85.9%, $P=0.065$) and DM (20.4% vs. 13.3%, $P=0.061$) rates slightly differed between the groups. 45 patients were diagnosed with DM, 11 (39.3%) LPLN-positive and 3 (17.6%) LPLN-negative patients were diagnosed with oligometastases ($P=0.109$).

Conclusions Our study indicates that for LPLN-positive patients, there is a tendency of worse PFS and DM than LPLN-negative patients, and for this group patients, large samples are needed to further confirm our conclusion.

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Keywords Locally advanced rectal cancer, Lateral pelvic lymph nodes, Propensity score matching, Progression-free survival, Recurrence patterns, Oligometastases

Introduction

For proficient mismatch repair (pMMR) locally advanced rectal cancer (LARC), neoadjuvant chemoradiotherapy (NCRT) combined with total mesorectal excision (TME) is one of the standard treatment options, clinical studies adding neoadjuvant chemotherapy or immunotherapy to this treatment paradigm are emerging and are cited in the international guidelines [1, 2]. Meanwhile, pelvic magnetic resonance imaging (MRI) with diffusion-weighted sequences is valuable in the pre-treatment assessment of LARC and the evaluation of the efficacy of neoadjuvant treatment, some tumor features demonstrated by pelvic MRI such as mesorectal fascia (MRF) status, extramural venous invasion (EMVI) status, and T-staging are associated with long-term prognosis [3–6]. Thus, the European Society for Medical Oncology (ESMO) guidelines use these factors to determine the suitability of LARC patients for specific treatments. Meanwhile, some investigators have suggested that these high-risk factors occur in the natural progression of rectal cancer and some LARC patients have multiple high-risk factors [7].

Approximately 15–25% of LARC patients present with positive lateral pelvic lymph node (LPLN), and this rate is higher in the lower rectal cancer than that in other location types [8–11]. Consequently, the Japanese guidelines recommend lateral pelvic lymph node dissection (LPLD) for rectal cancer located below the peritoneal reflection [12]. If LPLD is performed, it needs longer operation time, it may increases blood loss volume and the risk of toxic side effects, specifically at cancer centers with relatively little experience with this procedure [13]. Although local recurrence rates are comparable between NCRT + TME and TME + LPLD [14], standard doses of radiotherapy are often inadequate for patients with positive LPLN defined as the short axis of lymph node was more than or equal to 7 mm [15, 16], meanwhile those patients may benefit from treatment with increased radiotherapy doses, which may achieve better local control without increasing the risk of side effects [17–19].

In LARC patients treated with NCRT, clinical factors such as lower tumor location, extramural depth for T3 stage, and elevated carcinoembryonic antigen levels have been associated with their worse prognosis, these clinical factors are also associated with positive-LPLN, and positive LPLN in LARC patients are associated with poor prognosis [20–22]. However, it is still unclear whether this poor prognosis is directly related to the status of the LPLN or mainly related to other clinical risk factors. Since the most common failure pattern of LARC after NCRT is distant metastasis (DM), while most studies on positive LPLN focused on local–regional recurrence (LRR) [16, 23], and the impact of positive LPLN on DM risk remains unclear. Herein, we aimed to assess the independent prognostic value of positive LPLN in LARC patients by propensity score matching (PSM), and explore their failure patterns, specially focused on DM.

Materials and methods

Patient selection

This retrospective study was based on the clinical data of LARC patients treated at our center. Patients were eligible for this study if they met the following criteria: pathologically confirmed rectal adenocarcinoma (biopsy), the tumor located less than or equal to 8 cm from the anal verge on colonoscopy or MRI, pre-treatment MRI scan with a diagnosis of cT3-4 or N-positive disease, absence of DM on abdominopelvic and chest computed tomography (CT) scans, Eastern Cooperative Oncology Group performance status of 0–1, age ≥ 18 years, absence of any serious medical comorbidities or any other cancers, completed NCRT with good compliance and follow-up assessments.

All patients were informed the risks and benefits of NCRT and signed informed consent before treatment. This study was approved by the institutional review board of the Beijing Cancer Hospital Ethics Committee (approval number: 2020YJZ71) and was conducted according to the Declaration of Helsinki.

MRI evaluation

All patients underwent pelvic MRI scanning before NCRT, and the sequence of scans included axial, axial oblique, coronal, and sagittal T2-weighted and diffusion-weighted images [24]. All MRI scans were evaluated by one senior radiologist and one radiation oncologist. The T/N stage, T3 subgroup, EMVI, and MRF status were recorded according to the ESMO guidelines. The LPLN areas were defined as the lymph node located in the internal iliac and obturator lymphatic drainage areas, all lymph nodes visible in those areas were evaluated, including short diameter, margins, and signal values. The criteria of positive LPLN were short diameter more than or equal to 7 mm combined with irregular margin and mixed signal findings [16, 25]. Patients were divided into

LPLN-positive and LPLN-negative groups based on the LPLN status.

About 4–8 weeks after NCRT, repeat MRI scans were acquired to re-evaluate MRF, EMVI status and T/N stage, and to provide a reference for subsequent surgery. Lateral pelvic lymph nodes were re-evaluated to determine the suitability of LPLD [26]. For patients undergoing non-surgical treatments after NCRT, MRI scanning was used as a routine part of follow-up assessments.

Neoadjuvant chemoradiotherapy

All patients underwent computed tomography (CT) scan simulation after filling the bladder. Thermoplastic membrane and abdominal plate board, supine position, enhanced CT scanning, and MRI scan simulation were used. All patients were recommended intensity-modulated radiotherapy (IMRT), and most patients underwent simultaneous integrated boost (SIB) technique. The target area outline was previously described in recent study [27]. Briefly, the primary gross tumor volume (GTVp) contained the primary rectal tumor and enlarged lymph nodes in the rectal mesentery, and clinical target volume (CTV) contained the primary tumor and anterior sacral area, rectal mesenteric area, and internal iliac and obturator lymphatic drainage areas. These target areas were expanded by 5 mm to form planing primary gross tumor volume (PGTVp) and planning target volume (PTV). The total radiation doses were 50–50.6 Gy/22–25 F and 41.8–45 Gy/22–25 F delivered to PGTVp and PTV. For the patients with positive LPLN, gross lymph node tumor volume (GTVn) was outlined, and the planning gross lymph node tumor volume (PGTVn) was the GTVn with a 5-mm margin. The dose delivered to PGTVn was 56–60 Gy/22–25 F, this radiation therapy dose began to apply since 2016, at 2019 this dose strategy was used for all positive LPLN patients who receiving NCRT in our hospital.

Synchronous chemotherapy included oral capecitabine with or without oxaliplatin. The dose of capecitabine was 825 mg/m^2 twice daily for 5 days/week; when combined with oxaliplatin therapy, the dose of oxaliplatin was 85 mg/m^2 for every 2 weeks.

Chemotherapy

Post-surgery, all patients were recommended to receive adjuvant chemotherapy. Chemotherapy regimens included CapOX, FOLFOX, or oral capecitabine. The specific adjuvant chemotherapy regimen is based on the recommendations of a multidisciplinary consultation. We recommend 10 cycles or more for biweekly chemotherapy regimens and 6 cycles or more for three-weekly chemotherapy regimens, and 6 months of oral administration for single agent capecitabine.

The results of several recent studies indicated that the addition of chemotherapy prior to surgery improves pathologic complete response (pCR) rate [28, 29], based on these results and the strong desire of some patients to preserve their anus, we have adopted a treatment plan of concurrent chemoradiotherapy combined with induction or consolidation chemotherapy with a regimen of CapOX (oxaliplatin 130 mg/m^2, d1; capecitabine 1000 mg/m^2 twice daily, d1-14/Q21d).

Surgery and pathology

At approximately 5–12 weeks after NCRT, patients were recommended to receive surgery if imaging and clinical examination findings revealed no contraindications. Radical surgery was performed following the TME principle, surgical procedures included low anterior resection, abdominoperineal resection, and Hartmann procedure. LPLD was recommended for patients whose short LPLNs were still greater than 5 mm after NCRT. Intentional watch & wait strategy can be used for those who have been critically evaluated for complete clinical response and do not wish to undergo surgery. If the patient's staging is assessed as ycT0-2N0 and they have a strong desire to preserve their anus, local excision may be considered.

Surgical specimens were evaluated by specialized pathologists. A structured pathology report was issued, the report including tumor volume, upper and lower margins, circumferential margins, T/N stage, number and location of metastatic lymph nodes, presence of cancer nodes, presence of vascular thrombi and nerve invasion, and tumor regression grade (assessed according to the AJCC criteria) [2]. R0 resection was confirmed when the outer edge of the tumor or positive lymph node was more than 1 mm from the circumferential resection margin and both upper and lower margins were negative [30].

Follow-up

During NCRT, all patients were recommended weekly outpatient visits to assess and manage toxicities, which were graded based on the Common Terminology Criteria of Adverse Events Version 4.0.

Subsequently, patients were recommended to undergo follow-up visits every 3 months for the first 2 years, every 6 months for the subsequent 3 years and then yearly thereafter. Follow-up assessments included medical history taking, chest and abdominopelvic CT, serum carcinoembryonic antigen, and colonoscopy if necessary. As required, digital rectal examination, colonoscopy and

MRI were performed for patients who had undergone non-surgical treatments.

Prognostic indicators

The primary outcome was progression-free survival (PFS), which accounted for local regional recurrence (LRR) and distant metastases (DM). PFS was measured from the end of NCRT to the date of any evidence of progression or death from any cause or the last follow-up. The oligometastases were defined the amount of metastatic lesions was one to five [31]. DM were divided into oligometastases and non-oligometastases, and DM were observed from the end of NCRT to the date of any evidence of DM confirmed by radiology or pathology findings. LRR was divided into lateral pelvic recurrence and other local recurrence type, LRR was observed from the end of NCRT to the date of any evidence of recurrence.

Statistical analysis

The patients' clinical and follow-up characteristics were recorded. All statistical analyses were performed in Statistical Package for the Social Sciences (IBM Corp. SPSS Statistics for Windows, v.22.0, Armonk, NY, USA). The chi-square test was used to compare the groups. Propensity score matching (PSM) was used to balance group characteristics and was performed in Statistics and Data Science (STATA Corp. STATA for Windows, v.17.0, Texas, USA). Clinically relevant variables included tumor location, tumor length, tumor thickness, T/N stage, MRF status, and EMVI status. The caliper width was equal to 0.1 of the logit standard deviation of the propensity score. Survival curves were generated using the Kaplan–Meier method and were compared by using the log-rank test. *P*-values of < 0.05 were considered indicative of statistically significant findings.

Results

Patients characteristics

A total of 651 patients with middle-low LARC met the eligibility criteria and were included in the study from October 2014 to December 2019. The median age was 59 (range, 24–84) years, and the median distance from the anal verge was 5 cm (range, 0–8 cm). A total of 174 (26.7%) patients had cT4 disease. In addition, 260 (40.0%) and 217 (33.3%) patients had MRF-positive and EMVI-positive disease based on MRI findings. Moreover, 160 (24.6%) patients had positive LPLN. The patients' characteristics are presented in Table 1.

The proportions of cases with the primary tumor located less than or equal to 5 cm from the anal verge (53.1% vs. 43.0%, $P=0.025$), those with primary tumor of more than 45 mm in length (55.0% vs. 41.5%, $P=0.003$), and primary tumor of more than 15 mm in thickness (54.1% vs. 41.1%, $P=0.003$) were higher in the LPLN-positive group than in the LPLN-negative group. MRI findings revealed that the rates of cT4 (37.5% vs. 23.2%, $P=0.002$), MRF-positive (53.9% vs. 35.4%, $P<0.001$), and EMVI-positive (51.2% vs. 27.5%, $P<0.001$) disease were higher in the LPLN-positive group than LPLN-negative group.

Treatment regime

During NCRT, 559 (85.9%) patients received concurrent oral capecitabine alone. The remaining patients received 2-week CapOX regimen. Moreover, 126 (19.6%) patients received induction or consolidation chemotherapy before or after NCRT. The number of chemotherapy cycles ranged from one to six, with a median of four cycles. A total of 86 (68.3%) patients received more than or equal to four cycles of chemotherapy (Table 1). The LPLN-positive group was more likely to receive CapOX concurrent chemotherapy regimens (25.0% vs. 10.6%, $P<0.001$) and induction or consolidation chemotherapy (33.8% vs. 14.7%, $P<0.001$) than LPLN-negative group.

Short-term prognosis after PSM

After PSM, there were 114 patients in each of the LPLN-positive and LPLN-negative groups, and there were no significant differences in the clinical and therapeutic characteristics (Table 2). For LPLN-positive patients, 55 (48.2%) received SIB-IMRT technique and the dose for LPLN was 56–60 Gy, and 9 (7.9%) received LPLD after neoadjuvant treatment.

After neoadjuvant treatment, subsequent treatment regimens were comparable between the groups. A total of 93 (81.6%) and 96 (84.2%) patients in the LPLN-positive and LPLN-negative groups received surgery treatment, respectively. The R0 resection was achieved in 97.8% and 99.0% of the LPLN-positive and LPLN-negative patients. And the corresponding post-surgical pathologic complete response (pCR) rate was 29.3% and 31.3%, respectively ($P=0.777$). Meanwhile the proportions of ypN0 (74.5% vs. 82.3%, $P=0.333$) were comparable between the groups.

Long-term prognosis after PSM

The overall median follow-up duration was 45.9 months. The corresponding values for the LPLN-positive and LPLN-negative groups were 44.9 months and 45.9 months, respectively. Overall, 47 patients experienced tumor progression, including 45 cases of DM and 10 cases of LRR. The PFS, OS, DM, and LRR rates of both groups are shown in Fig. 1. Three-year OS (88.3% vs. 92.1%, $P=0.276$) and LRR (5.7% vs. 2.8%, $P=0.172$) rates were comparable between LPLN-positive and

Table 1 Patients' clinical and treatment characteristics

	LPLN-positive group (n = 160)	LPLN-negative group (n = 491)	*P* value
Age			
Median (Range)	58 (25–83) year	59 (24–84) year	-
Sex			
Male	112 (70.0%)	332 (67.6%)	0.574
Female	48 (30.0%)	159 (32.4%)	
Tumor location (Range)			
Median (Range)	4 (0–8) cm	5 (0–8) cm	0.025
Middle (> 5 cm)	75 (46.9%)	280 (57.0%)	
Low (≤ 5 cm)	85 (53.1%)	211 (43.0%)	
Clinical T stage			0.002
T2	6 (3.8%)	24 (4.9%)	
T3	94 (58.8%)	353 (71.9%)	
T4	60 (37.5%)	114 (23.2%)	
T3 subgroup[#]			
T3a	4 (4.3%)	40 (11.3%)	0.016
T3b	76 (80.9%)	286 (81.0%)	
T3c	14 (14.9%)	24 (6.8%)	
T3d	0 (0)	3 (0.8%)	
Clinical N stage			< 0.001
N −	0 (0)	45 (9.2%)	
N +	160 (100%)	446 (90.8%)	
CEA (ng/ml)			0.133
< 5 ng/ml	79 (49.4%)	275 (56.0%)	
≥ 5 ng/ml	68 (42.6%)	166 (33.8%)	
Unidentified	13 (8.1%)	50 (10.2%)	
MRF status			< 0.001
Positive	86 (53.7%)	174 (35.4%)	
Negative	74 (46.3%)	317 (64.6%)	
EMVI status			< 0.001
Positive	82 (51.2%)	135 (27.5%)	
Negative	78 (48.8%)	356 (72.5%)	
Tumor length (mm)			0.003
Median (Range)	47.5 (18–105) mm	45 (15–105) mm	
> 45 mm	88 (55.0%)	204 (41.5%)	
≤ 45 mm	72 (45.0%)	287 (58.5%)	
Tumor thickness (mm)			0.003
Median (Range)	16 (8–50) mm	15 (7–53) mm	
> 15 mm	87 (54.4%)	202 (41.1%)	
≤ 15 mm	73 (45.6%)	289 (58.9%)	
Concurrent Chemotherapy			< 0.001
Capecitabine	120 (75.0%)	439 (89.4%)	
CapOX	40 (25.0%)	52 (10.6%)	
Induction or consolidation Chemotherapy			< 0.001
Yes	54 (33.8%)	72 (14.7%)	
No	106 (66.2%)	419 (85.3%)	
Induction or consolidation Chemotherapy Cycles*			0.082
< 4 Cycles	22 (40.7%)	18 (25.0%)	
≥ 4 Cycles	32 (59.3%)	54 (75.0%)	

[#] n = 447 for cT3 diagnosis; *n = 126 for inductive or consolidating chemotherapy. *LPLN* lateral pelvic lymph node, *CEA* carcinoembryonic antigen, *MRF* mesorectal fascia, *EMVI* extramural venous invasion

Table 2 Distribution of clinical and treatment characteristics after propensity score matching

	LPLN-positive group (n = 114)	LPLN-negative group (n = 114)	*P* value
Sex			0.672
Male	75 (65.8%)	78 (68.4%)	
Female	39 (34.2%)	36 (31.6%)	
Tumor location			0.596
Middle	57 (50.0%)	53 (46.5%)	
Low	57 (50.0%)	61 (53.5%)	
Clinical T stage			0.642
T2	4 (3.5%)	7 (6.1%)	
T3	77 (67.5%)	76 (66.7%)	
T4	33 (28.9%)	31 (27.2%)	
T3 subgroup[#]			0.787
T3a	4 (5.2%)	5 (6.6%)	
T3b	62 (80.5%)	62 (81.6%)	
T3c	11 (14.3%)	8 (10.5%)	
T3d	0	1 (1.3%)	
Clinical N stage			0.081
N −	0	3 (2.6%)	
N +	114 (100%)	111 (97.4%)	
CEA (ng/ml)			0.296
< 5 ng/ml	54 (47.4%)	58 (50.9%)	
≥ 5 ng/ml	54 (47.4%)	45 (39.5%)	
Unidentified	6 (5.2%)	11 (9.6%)	
MRF status			0.484
Positive	56 (49.1%)	47 (41.2%)	
Negative	58 (50.9%)	67 (58.8%)	
EMVI status			0.405
Positive	43 (37.7%)	37 (32.5%)	
Negative	71 (62.3%)	77 (67.5%)	
Tumor length (mm)			0.289
> 45 mm	60 (52.6%)	52 (45.6%)	
≤ 45 mm	54 (47.4%)	62 (54.4%)	
Tumor thickness (mm)			0.287
> 15 mm	59 (51.8%)	67 (58.8%)	
≤ 15 mm	55 (48.2%)	47 (41.2%)	
Concurrent chemotherapy			0.187
Capecitabine	87 (76.3%)	95 (83.3%)	
CapOX	27 (23.7%)	19 (16.7%)	
Induction or consolidation Chemotherapy			0.166
Yes	33 (28.9%)	23 (20.2%)	
No	81 (71.1%)	91 (79.8%)	
*Induction or consolidation Chemotherapy Cycles**			0.777
< 4Cycles	12 (36.4%)	7 (30.4%)	
≥ 4Cycles	21 (63.6%)	16 (69.6%)	
Post-NCRT Treatment			0.788
Surgery	93 (81.6%)	96 (84.2%)	
Wait and See for cCR	10 (8.8%)	11 (9.6%)	
Refuse surgery	7 (6.1%)	4 (3.5%)	
Tumor Progression	4 (3.5%)	3 (2.6%)	
Excision Type[&]			0.542

Table 2 (continued)

	LPLN-positive group (n = 114)	LPLN-negative group (n = 114)	*P* value
R0	91 (97.8%)	95 (99.0%)	
Non R0	2 (2.2%)	1 (1.0%)	
pCR[&]			0.770
Yes	27 (29.0%)	30 (31.2%)	
No	66 (71.0%)	66 (68.8%)	
pT Stage[&]			0.124
pT0	29 (31.2%)	32 (33.3%)	
pT1	8 (8.6%)	5 (5.2%)	
pT2	18 (19.4%)	31 (32.3%)	
pT3	36 (38.7%)	28 (29.2%)	
pT4	2 (2.1%)	0	
pN Stage[&]			0.316
pN0	69 (74.2%)	79 (82.3%)	
pN1	21 (22.6%)	16 (16.7%)	
pN2	3 (3.2%)	1 (1.0%)	
TRG group[&]			0.515
TRG 0	29 (31.2%)	32 (33.3%)	
TRG 1	28 (30.1%)	35 (36.5%)	
TRG 2	33 (35.5%)	28 (29.2)	
TRG 3	3 (3.2%)	1 (1.0%)	

[#] n = 149 for cT3 disease; *n = 56 for inductive and consolidating chemotherapy; [&]n = 189 for surgery. *LPLN* lateral pelvic lymph nodes, *CEA* carcinoembryonic antigen, *MRF* mesorectal fascia, *EMVI* extramural venous invasion, *pCR* pathologic complete response, *cCR* clinical complete response, *TRG* tumor regression grade

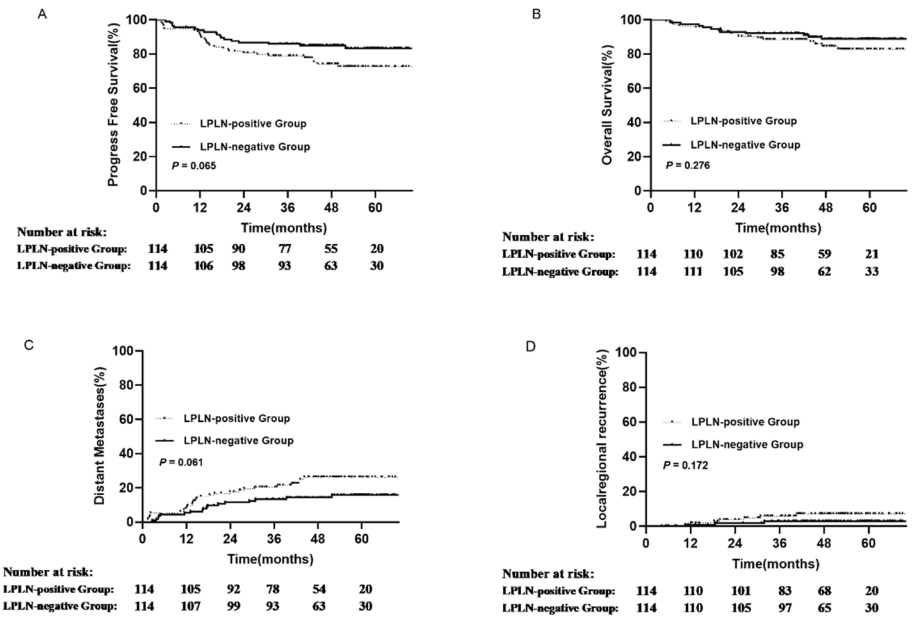

Fig. 1 Kaplan–Meier curves stratified by lateral pelvic lymph node status. **A** Progression-free survival. **B** Overall survival. **C** Distant metastases. **D** Localregional recurrence.

LPLN-negative groups. Although not statistically different, there was a higher tendency towards 3-year PFS (85.9% vs.78.8%, $P=0.065$) in the LPLN-negative group, while their 3-year DM (13.3% vs. 20.4%, $P=0.061$) had a lower tendency towards than LPLN-positive group.

The univariate analysis indicated that EMVI-positive patients (74.6% vs. 86.5%, $P=0.039$) had poorer 3-year PFS rates than EMVI-negative group patients, no other factors were associated with 3-year PFS (Table 3).

Patterns of treatment failure

Among 10 patients with LRR, seven (70.0%) had lateral pelvic recurrence (including one case combined with anastomosis and one combined with recurrence located in the anterior sacral region), two patients had recurrence around the anastomosis region, and one patient presented with recurrence in the anterior sacral region. In whole LRR group included seven LPLN-positive patients; among them, five experienced lateral pelvic recurrence, four (80.0%) of these patients did not receive SIB-IMRT (Fig. 2). Meanwhile in whole LRR group three patients were LPLN-negative, two (66.6%) of them had suffered lateral pelvic recurrence.

Finally, 45 patients suffered DM, 28 of which were LPLN-positive. For patients suffered DM, 11 (39.3%) LPLN-positive and 3 (17.6%) LPLN-negative patients were diagnosed with oligometastases ($P=0.109$). The median detection time of oligometastases (14.7 months) was comparable to that of non-oligometastases (15.1 months). Lung and liver were the most common DM sites, affecting 17 (7.5%) and 11 (4.8%) for whole group patients, respectively (Fig. 3). DM site rates were comparable between the LPLN-positive and LPLN-negative groups (lung, 9.6% vs. 5.3%, $P=0.207$; liver, 5.3% vs. 4.4%, $P=0.757$).

Discussion

In this study, LPLN-positive patients tended to present with several high-risk clinical factors, we then used PSM to balance the differences between groups and evaluate the long-term prognosis, the 3-year PFS rates were 78.8% and 85.9% in the LPLN-positive and LPLN-negative groups, respectively ($P=0.065$). In addition, even the difference was not statistically significant, the LPLN-positive group had a tend towards higher 3-year DM rate compared to the LPLN-negative group (20.4% vs. 13.3%, $P=0.061$).

Previous studies have used the short diameter of lymph nodes as a criterion to define the positive LPLN. A large multicenter study by Ogura et al. included 1216 LARC cases, showing that lymph node short axis of ≥7 mm increased the risk of pelvic recurrence (hazard ratio, 2.060; $P=0.045$) [16]. Meanwhile, Brown et al. have found that border characteristics or signal intensity can help determine the risk of lymph node metastases in LARC patients [25], in subsequent studies these morphological features helped determine LPLN status [32, 33]. In our study, we chose the combination of short diameter of ≥7 mm and morphological features to diagnose positive LPLN, the rate of positive LPLN was 24.6% in LARC

Table 3 Univariate analysis of factors associated with 3-year progression-free survival

Characteristics	3-year PFS	*P* Value	Characteristics	3-year PFS	*P* Value
Sex		0.674	EMVI status		0.039
Male	81.4%		Positive	74.6%	
Female	84.2%		Negative	86.5%	
Tumor location			Tumor length (mm)		0.497
Middle	82.9%	0.955	>45 mm	78.7%	
Low	81.8%		≤45 mm	85.6%	
Clinical T stage		0.088	Tumor thickness (mm)		0.153
T2-3	86.3%		>15 mm	78.2%	
T4	72.7%		≤15 mm	87.3%	
CEA (ng/ml)		0.235	Concurrent chemotherapy		0.560
<5 ng/ml	87.8%		Capecitabine	82.1%	
≥5 ng/ml	77.2%		CapOX	83.5%	
MRF status		0.184	Induction or consolidation Chemotherapy		0.840
Positive	75.0%		Yes	80.3%	
Negative	87.6%		No	83.3%	

CEA carcinoembryonic antigen, *MRF* mesorectal fascia, *EMVI* extramural venous invasion

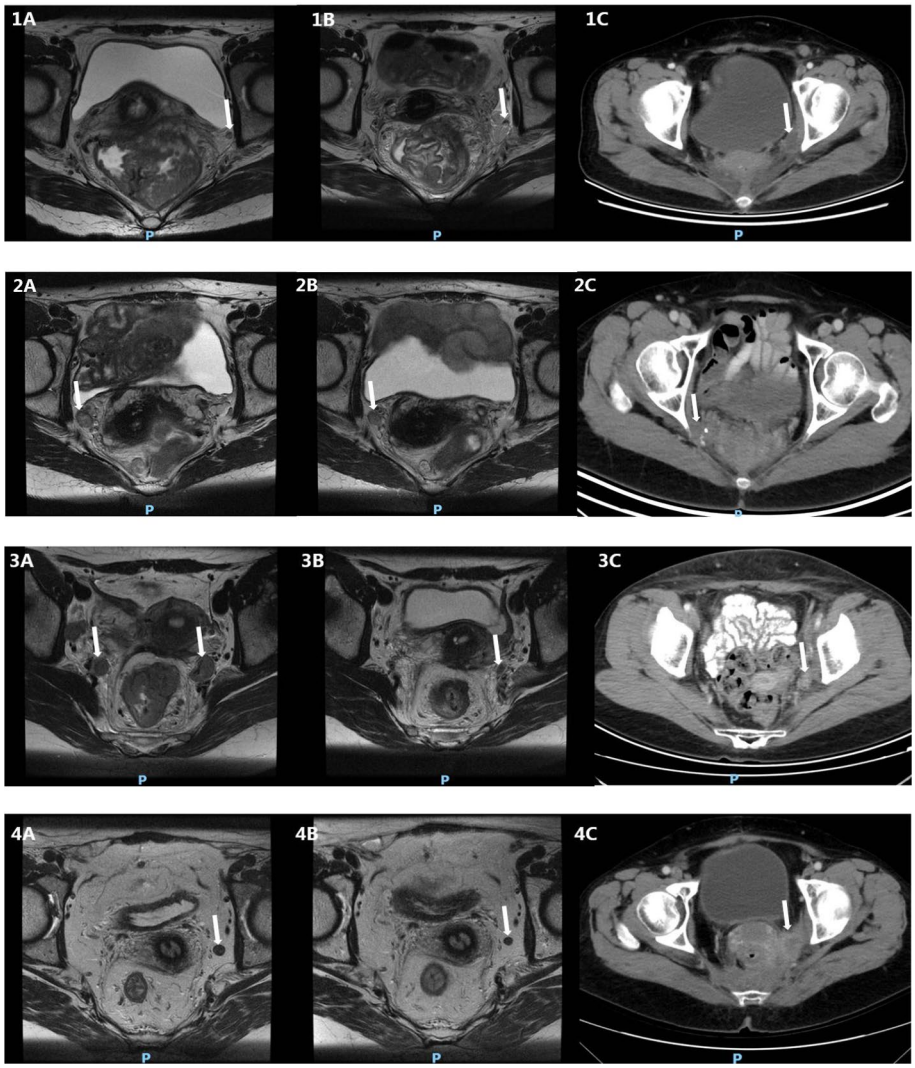

Fig. 2 Patients with lateral pelvic recurrence. Patient 1 had positive LPLN in the left obturator lymphatic drainage area, size 7×7 mm (**1A**). After NCRT, the LPLN regressed to 6×3 mm (**1B**). However, 18 months thereafter, the lateral pelvic recurrence combined with inguinal lymph node metastases (**1C**). Patient 2 had positive LPLN in the right internal iliac region, size 15×13 mm (**2A**). After NCRT, the LPLN regressed to 13×8 mm (**2B**). Although this patient refused to undergo LPLD, the lymph node continued to SD after surgery. But forty months later, the patient developed lung metastasis and the primary lymph node increased in size (**2C**). Patient 3 had positive LPLNs in the bilateral internal iliac region; the left and right lymph node sizes were 21×15 mm and 14×10 mm, respectively (**3A**). After NCRT, the right LPLN disappeared and the left LPLN shrank to 8×5 mm (**3B**). The patient then underwent LPLD. Eight lateral pelvic lymph nodes were removed and no evidence of residual tumor was found. After 26 months, the patient experienced lateral pelvic recurrence in the left lateral pelvic region combined with retroperitoneal and inguinal lymph node metastases (**3C**). Patient 4 had positive LPLN in the left obturator lymphatic drainage area, size 10×9 mm (**4A**). After NCRT, the LPLN regressed to 7×5 mm (**4B**). After 19 months, the patient had lateral pelvic recurrence combined with tumor recurrence in the anterior sacral region (**4C**)

which located less than or equal to 8 cm from the anal verge, which was similar to previous studies [8–11].

In our study, before PSM, the LPLN-positive group had a higher rate of low LARC (less than or equal to 5 cm from the anal edge) than the LPLN-negative group, in addition, the LPLN-positive group had a higher rate of longer and thicker tumors, cT4 disease, MRF-positive and EMVI-positive status. Pelvic MRI scanning is the standard pre-treatment radiology examination for LARC. In addition to the LPLN status, the risk stratification of the ESMO guidelines refers to T-stage, MRF, and EMVI status [1]. Pre-treatment MRF status and the presence of T4 are associated with the possibility of obtaining R0 resection by TME after NCRT [34, 35], At the same time, multiple studies have shown a correlation between EMVI positivity and long-term prognosis [36]. Herein, we used PSM to ensure comparable distribution of characteristics between the groups. As a result, we found that 3-year

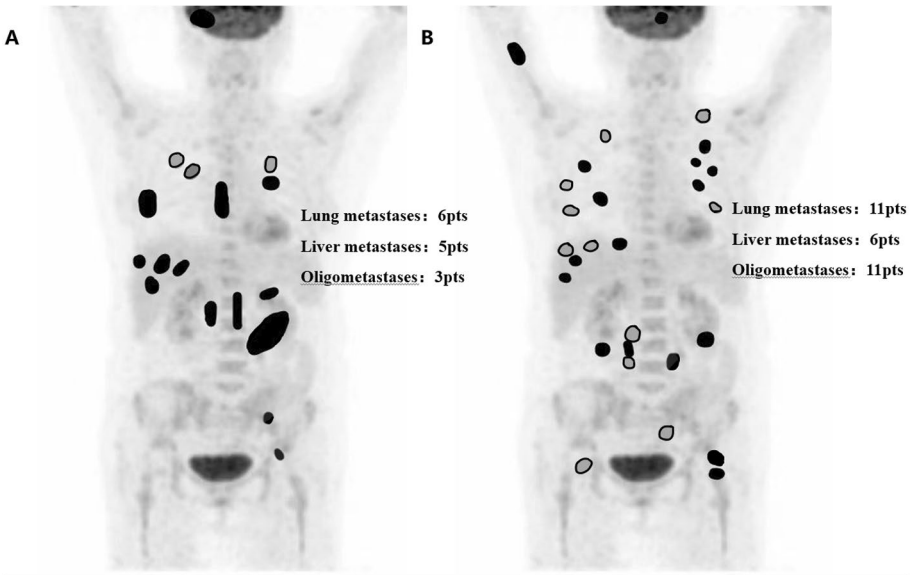

Fig. 3 Distribution of metastatic lesions in the LPLN-negative (**A**) *and LPLN-positive (**B**) #group. Black dots represent non-oligometastases, black circles represent oligometastases. *: One patient presented with malignant peritoneal effusion and liver metastases, and we drew Black dots in the abdominal cavity. #: One patient presented with multiple retroperitoneal lymph node metastases and multiple liver metastases, and we drew Black dots in the abdominal cavity

PFS rates were poorer in EMVI-positive patients than in their counterparts (74.6% vs. 86.5%, $P=0.039$).

The correlation between LPLN-positive status and long-term prognosis remains controversial [15, 37]. Since current studies have proven that for patients with positive pathological mesorectal lymph nodes after NCRT, the overall prognosis is relatively poor [38, 39], which implied that the LPLN-positive patients may have a poorer prognosis. Dongha et al. reported 52 LARC patients who receive NCRT and surgery, 37 patients receive combined LPLD, and the 5-year recurrence-free survival was significantly lower (56.8% vs. 85.7%, $P=0.038$) in patients whose short axis of LPLN was more than or equal to 7 mm [40]. Meanwhile, Ogura et al. reported that there was no evidence that pretreatment LPLN status could affect DM risk or survival rates [16], afterwards, Schaap et al. also found that the positive internal iliac lymph node status was associated with an increased LLR, whereas positive obturator lymph nodes are associated with increased distant metastasis [23]. In our study, the LPLN- positive patients also had a trend of lower 3-year PFS rates than LPLN- negative patients, and the correlation between the location, number, volume of LPLN and long-term prognosis deserves further study.

DM and LRR are commonly used in long-term prognostication of LARC after NCRT. However, few studies have analyzed the detail of failure patterns. For patients with oligometastases, if local control can be obtained by appropriate local treatment timely, a favorable long-term prognosis can be achieved [31, 41, 42]. In our study, in LPLN-positive patients with DM, oligometastases accounted for 39.3% of cases, and the corresponding rate in the LPLN-negative group was 17.6%. And now, a growing number of studies have confirmed that local therapies (such as surgery or radiation) can be used to cure patients with oligometastases [42, 43]. Meanwhile, for LPLN-positive patients, lateral pelvic recurrence was a major LRR pattern, especially for patients receiving conventional radiation therapy doses, thus the efficacy of LPLD is definite for these patients [26]. However, LPLD extends surgical time and blood loss volume, and it may also affect urinary and sexual function [13]. If the radiotherapy dose can be increased by new radiotherapy techniques, it can improve the LPLN regression without increasing treatment-related toxicity [19, 44]. In our center, the SIB-IMRT technique has been used to treat LPLN-positive patients, and the results demonstrated better efficacy and safety [17, 18].

In fact, based on some objective factors this study still has some limitations. Firstly, Our study is a retrospective study and may be subject to selection bias. Secondly, some LPLN-positive patients who did not undergo SIB-IMRT, their positive LPLN only received radiation doses of 41.8–45 Gy/22–25 F, which are relatively low. However, all LPLN-positive patients have been treated with SIB-IMRT since the beginning of 2019. Thirdly, this was a single-center study, and the sample size after PSM

was relatively small. Large multicenter studies on the prognosis in LPLN-positive patients are ongoing.

In conclusion, LPLN-positive patients often have a combination of other risk factors, and the present study indicates that there is a tendency of worse PFS and DM than LPLN-negative patients after PSM.

Abbreviations

PSM	Propensity score matching
LARC	Locally advanced rectal cancer
LPLN	Lateral pelvic lymph node
MRF	Mesorectal fascia
EMVI	Extramural venous invasion
pCR	Pathologic complete response
NCRT	Neoadjuvant chemoradiotherapy
TME	Total mesorectal excision
ESMO	European Society for Medical Oncology
LPLD	Lateral pelvic lymph node dissection
CT	Computed tomography
MRI	Magnetic resonance imaging
IMRT	Intensity-modulated radiotherapy
SIB	Simultaneous integrated boost
GTVp	Primary gross tumor volume
CTV	Clinical target volume
PGTVp	Planing primary gross tumor volume
PTV	Planning target volume
GTVn	Gross lymph node tumor volume
PGTVn	Planning gross lymph node tumor volume
PFS	Progression-free survival
OS	Overall survival
LRR	Local-regional recurrence
DM	Distant metastasis

Author contributions

Conception and study design: WWH and LYH, Development of methodology: SMXW, TJ, THJ and SX, Analysis and interpretation of data: CY, LZY, GJH, ZYZ and ZXG, Writing and review of the manuscript: LS and SMXW, Study supervision: CY, LYH and WWH. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of the Beijing Cancer Hospital Ethics Committee (approval number: 2020YJZ71).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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