Prognostic Significance of Lateral Pelvic Lymph Node Dissection for Middle-Low Rectal Cancer Patients with Lateral Pelvic Lymph Node Metastasis: A Propensity Score Matching Study

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Abstract

Background

There is still controversy regarding whether the addition of lateral pelvic lymph node dissection (LPND) to total mesorectal excision (TME) confers survival benefits to rectal cancer patients with clinical lateral pelvic node metastasis (LPNM).

Methods

Patients who underwent TME+LPND were systematically reviewed and divided into the LPNM group (n=29) and the non-LPNM group (n=112). The LPNM group were further subdivided into a high-risk LPNM group (n=14) and a low-risk LPNM group (n=15). Propensity score matching (PSM) was performed to minimize selection bias.

Results

Of the 141 patients undergoing LPND, the local recurrence rate of patients with LPNM was significantly higher than that of patients without LPNM both before (27.6% vs. 4.5%, *P*=0.001) and after (27.6% vs 3.4%, *P*=0.025) PSM. Multivariate analysis revealed that LPNM was an independent risk factor for not only OS (HR: 3.06; 95% CI, 1.15–8.17; *P*=0.025) but also DFS (HR: 2.39; 95% CI, 1.18–4.87; *P*=0.016) in patients with LPNM after TME+LPND. When the LPNM group was further subdivided, multivariate logistic regression analysis showed that OS and DFS were significantly better in the low-risk group (obturator/internal iliac artery region and < 2 positive LPNs).

Conclusion

Even after LPND, LPNM patients have a high local recurrence rate and poor prognosis. Moreover, LPNM is an independent poor prognostic factor affecting OS and DFS after TME+LPND. However, LPND appears to confer survival benefits to specific patients with single LPN involvement in the obturator region or internal iliac vessel region.

Introduction

The lateral lymph node metastasis (LPNM) pathway of middle and low rectal cancer was first proposed by Gerota in 1895[1], and the anatomical theoretical system of lateral pelvic lymphatic drainage of rectal cancer gradually formed in the 1950s[2]. LPNM has been reported in approximately 16–23% of patients with middle to low rectal cancer[3], and it is an important predictive factor for local recurrence and long-term survival[4,5]. Lateral pelvic lymph node dissection (LPND), as a potential radical surgery, is still controversial worldwide. In Western countries, LPNM (except internal iliac lymph nodes) is considered a systemic disease. Even if LPND is performed, the five-year survival rate is only 20–45%[6], and it may increase the possibility of sexual function and urinary dysfunction. Therefore, NCCN guidelines and ESMO guidelines recommend neoadjuvant chemoradiotherapy (nCRT) combined with total mesorectal resection (TME) as the standard treatment mode for advanced rectal cancer, rather than prophylactic LPND alone[7]. However, in Japan, the lateral pelvic lymph nodes (LPNs) in the area of the obturator, external iliac, and common iliac were regarded as regional lymph

nodes, which were considered within the scope of the N3 stage. The JSCCR guidelines clearly indicate that prophylactic LPND should be performed for patients with T3-T4 rectal cancer that is below the peritoneal reflection[8]. However, the level of evidence is relatively low, and thus, this procedure is not widely implemented.

Several Japanese studies have suggested that the overall benefit related to local recurrence and survival of LPND is not promising in patients with LPNM[9–13]. Therefore, it is necessary to clarify the effectiveness of LPND with regard to increasing local control and prolonging survival. Our study found that some patients with LPNM could survive more than 5 years after LPND, so it is important to explore which types of patients with LPNM may receive some prognostic benefit from LPND. In the present study, we used propensity score matching (PSM) and designed a retrospective cohort study to investigate the clinical significance of LPND in rectal cancer patients with LPNM and to clarify which patients with LPNM might benefit from LPND.

Materials And Methods

Patients and methods

We reviewed records of 141 consecutive middle-lower rectal adenocarcinoma patients with clinically suspected LPNM who underwent TME + LPND at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, between January 2015 and January 2021. Patients with a history of other malignancies or distant metastases were excluded from this study. This retrospective study was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences (NCC 2017-YZ-026, Oct 17, 2017), and all enrolled patients provided informed consent.

Routine preoperative investigations for all patients included laboratory examination, endoscopy, abdominal computed tomography (CT), and pelvic magnetic resonance imaging (MRI). Clinical LPNM was diagnosed by two imaging specialists who specialized in gastrointestinal cancer based on MRI before treatment. Meeting one or more of the following criteria was considered clinically LPNM, and TME + LPND was performed: (1) short diameter of LPN > 0.8 cm; (2) inhomogeneous or intense enhancement; and (3) irregular shape with rough edges. Patients with pathological LPNM were divided into the LPNM group (n = 29), and those without pathological LPNM were divided into the non-LPNM group (n = 112). Twenty-nine patients in the LPNM group were further divided into two groups based on the actual number and region of LPNMs. According to the JSCCR guidelines, LPNs were divided into 5 regions: the common iliac vessel region, the proximal iliac vessel region, the distal iliac vessel region, the obturator region and the external iliac vessel region[8]. Patients with < 2 positive LPNs and positive LPNs in the obturator or internal iliac artery region were assigned to low-risk LPNM group (n = 15), and patients without any of these factors were assigned to the high-risk LPNM group (n = 14).

After the operation, all patients were followed up by telephone or outpatient visits until death due to recurrence or metastasis of rectal cancer or February 1, 2021, whichever came first. The follow-up examination consisted of serum tumour marker measurements, abdominal CT, and pelvic MRI 3–6 months for the first three years and every 6 months for the next two years. The long-term endpoints of this study were 5-year overall survival (OS) and disease-free survival (DFS), and the data were collected based on this follow-up survey.

Statistical analysis

Clinical and pathological factors are expressed as frequencies and percentages or means ± standard deviations and were analysed separately using the χ^2 test or Fisher's exact test and a t-test. PSM was performed by logistic regression to reduce the imbalance in these 2 groups. The matching ratio was 1:1, and the covariates included age, sex, body mass index (BMI), CEA level, CA19-9 level, American Society of Anesthesiologists (ASA) category, preoperative chemotherapy, histology, T stage, N stage, perineural invasion, lymphatic invasion, vascular invasion and adjuvant chemotherapy. OS and DFS were calculated by the Kaplan-Meier method and compared by the log–rank test. The variables determined to have a *P* value < 0.05 in univariate analysis were subsequently tested by multivariate analysis through a Cox regression model, and an odds ratio with a 95% confidence interval was calculated for each variable. A *P* value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows version 20.0 (SPSS, Chicago, Illinois, USA).

Results

Clinical and pathological characteristics

Of 141 patients with rectal cancer and clinical LPNM, 29 (20.6%) patients were postoperatively diagnosed with pathological LPNM by histopathological evaluation. Region 283, the lymph nodes around the obturator, was the most common LPN metastatic site (n=14, 48.3%). The second most frequently involved LPN metastatic site was region 263, which consisted of the proximal and distal internal iliac lymph nodes (n=8, 27.6%). Six patients (20.7%) had metastatic disease involving the common iliac lymph nodes (Region 273), and 5 patients (17.2%) had LPN metastatic sites in the external iliac lymph nodes (Region 293) (**Figure 1**).

The clinicopathological characteristics of the patients are listed in **Table 1**. Before matching, patients in the LPNM group were diagnosed with poor/mucinous/signet adenocarcinoma more frequently (44.8% vs. 25.9%, *P* = 0.047), showed deeper infiltration (T3-T4: 93.1% vs. 70.5%, *P*=0.012), had more than 4 metastatic lymph nodes (N2: 48.3% vs. 20.5%, *P* <0.001), and were more likely to develop lymphatic invasion (44.8 vs. 25.0%, *P*=0.036). After matching, the LPNM group and non-LPNM group were well balanced in terms of age, sex, BMI, CEA level, CA19-9 level, ASA category, preoperative chemotherapy, histology, pT stage, pN stage, perineural invasion, lymphatic invasion, vascular invasion, and adjuvant chemotherapy.

Table 1 Clinical and pathological characteristics of 141 rectal cancer patients with or without pathological LPNM before and after matching

Variables	Original cohort			Matched cohort		
	LPNM (n=29)	Non-LPNM (n=112)	*P*	LPNM (n=29)	Non-LPNM (n=29)	*P*
Age (years, mean±SD)	57.5 ± 11.7	56.2 ± 10.4	0.551	57.5 ± 11.7	58.8 ± 10.2	0.667
Gender			0.462			0.788
Male	18 (62.1)	61 (54.5)		18 (62.1)	17 (58.6)	
Female	11 (37.9)	51 (45.5)		11 (37.9)	12 (41.4)	
BMI (kg/m^2, mean±SD)	24.3 ± 3.0	25.0 ± 3.2	0.295	24.3 ± 3.0	24.4 ± 2.5	0.933
CEA level (ng/mL, mean ± SD)	15.0 ± 32.0	8.4 ± 15.1	0.124	15.0 ± 32.0	12.6 ± 22.7	0.793
CA19-9 level (ng/mL, mean ± SD)	47.9 ± 101.8	19.0 ± 17.3	0.169	47.9 ± 101.8	31.4 ± 23.4	0.273
ASA category			0.580			1.000
I-II	26 (89.7)	106 (94.6)		26 (89.7)	27 (93.1)	
III-IV	3 (10.3)	6 (5.4)		3 (10.3)	2 (6.9)	
Preoperative chemotherapy	16 (55.2)	58 (51.8)	0.745	16 (55.2)	17 (58.6)	0.791
Histology			0.047			0.788
Moderate	16 (55.2)	83 (74.1)		17 (58.6)	18 (62.1)	
Poor/Mucinous/signet	13 (44.8)	29 (25.9)		12 (41.4)	11 (37.9)	
pT stage			0.012			0.666
T1-T2	2 (6.9)	33 (29.5)		2 (6.9)	4 (13.8)	
T3-T4	27 (93.1)	79 (70.5)		27 (93.1)	25 (86.2)	
pN stage			<0.001			0.514
N0	3 (10.3)	56 (50.0)		3 (10.3)	5 (17.2)	
N1	12 (41.4)	33 (29.5)		12 (41.4)	14 (48.3)	
N2	14 (48.3)	23 (20.5)		14 (48.3)	10 (34.5)	
Perineural invasion	14 (48.3)	41 (36.6)	0.251	14 (48.3)	11 (37.9)	0.791
Lymphatic invasion	13 (44.8)	28 (25.0)	0.036	13 (44.8)	12 (41.4)	
Vascular invasion	13 (44.8)	33 (29.5)	0.116	13 (44.8)	10 (34.5)	0.421
Mesorectal lymph nodes harvested	15.6 ± 8.2	18.7 ± 10.2	0.137	15.6 ± 8.2	19.5 ± 11.6	0.200

LPLNs harvested	9.3 ± 5.5	9.9 ± 6.1	0.773	9.3 ± 5.5	10.4 ± 6.3	0.602
Adjuvant chemotherapy	23 (79.3)	68 (60.7)	0.062	23 (79.3)	18 (62.1)	0.149

Operative And Perioperative Data

Perioperative outcomes including surgical outcomes, postoperative complications, and postoperative recovery are shown in Table 2. Patients in both groups had comparable types of operations, LPND, operative time, estimated blood loss, postoperative complications, time to first flatus, and postoperative hospital stay before and after matching ($P > 0.05$). No deaths were recorded during the perioperative period in either group.

Table 2
Perioperative outcomes of 141 rectal cancer patients with or without pathological LPNM before and after matching

Variables	Original cohort			Matched cohort		
	LPNM (n = 29)	Non-LPNM (n = 112)	*P*	LPNM (n = 29)	Non-LPNM (n = 29)	*P*
Types of operation (%)			0.428			0.890
Low anterior resection	11 (37.9)	54 (48.2)		11 (37.9)	11 (37.9)	
Abdominoperineal resection	16 (55.2)	55 (49.1)		16 (55.2)	15 (51.7)	
Hartmann procedure	2 (6.9)	3 (2.7)		2 (6.9)	3 (10.4)	
LPND			0.997			0.517
Unilateral dissection	22 (75.9)	85 (75.9)		22 (75.9)	24 (82.8)	
Bilateral dissection	7 (24.1)	27 (24.1)		7 (24.1)	5 (17.2)	
Operative time, min (mean ± SD)	275.4 ± 72.8	265.8 ± 76.5	0.542	275.4 ± 72.8	283.1 ± 77.1	0.699
Estimated blood loss, ml (mean ± SD)	83.1 ± 61.9	84.3 ± 108.7	0.955	83.1 ± 61.9	80.3 ± 91.7	0.894
Postoperative complications	4 (13.8)	21 (18.8)	0.533	4 (13.8)	6 (20.7)	0.487
Postoperative bleeding	0 (0)	2 (1.8)		0 (0)	1 (3.4)	
Ileus	1 (3.4)	2 (1.8)		1 (3.4)	1 (3.4)	
Anastomosis leakage	0 (0)	3 (2.7)		0 (0)	1 (3.4)	
Pelvic cavity abscess	1 (3.4)	2 (1.8)		1 (3.4)	1 (3.4)	
Pneumonia	1 (3.4)	8 (7.1)		1 (3.4)	2 (6.9)	
Wound infection	1 (3.4)	4 (3.6)		1 (3.4)	1 (3.4)	
Urinary retention	0 (0)	2 (1.8)		0 (0)	0 (0)	
Time to first flatus (day, mean ± SD)	3.1 ± 1.3	3.1 ± 1.4	0.868	3.1 ± 1.3	3.2 ± 1.6	0.715
Postoperative hospital stay (day, mean ± SD)	8.9 ± 4.5	8.7 ± 5.1	0.872	8.9 ± 4.5	9.2 ± 5.6	0.817
Re-operation	0 (0)	1 (0.9)	1.000	0 (0)	0 (0)	-
Mortality	0 (0)	0 (0)	-	0 (0)	0 (0)	-

Postoperative Recurrence Pattern

Postoperative recurrence is shown in Table 3. The postoperative overall recurrence rate (51.7% vs 21.4%, P = 0.001) and local recurrence rate (27.6% vs. 4.5%, P = 0.001) were significantly higher in the LPNM group than in the non-LPNM group before matching. Although the proportion of patients with distant metastases in the LPNM group was higher (27.6% vs 17.0, P = 0.195), the difference was not statistically significant. After eliminating confounding factors through matching, the differences in the total recurrence rate (51.7% vs 31.0%, P = 0.110) and distant metastasis rate (27.6% vs 27.6%, P = 1.000) were not significant between the two groups. Notably, more patients in the LPNM group developed local recurrence (27.6% vs 3.4%, P = 0.025) after surgery.

Table 3
Postoperative recurrence of 141 rectal cancer patients with or without pathological LPNM before and after matching

Variables	Original cohort			Matched cohort		
	LPNM (n = 29)	Non-LPNM (n = 112)	*P*	LPNM (n = 29)	Non-LPNM (n = 29)	*P*
Overall recurrence (%)	15 (51.7)	24 (21.4)	0.001	15 (51.7)	9 (31.0)	0.110
Local recurrence	8 (27.6)	5 (4.5)	0.001	8 (27.6)	1 (3.4)	0.025
Distant metastasis	8 (27.6)	19 (17.0)	0.195	8 (27.6)	8 (27.6)	1.000
Liver metastasis	5 (17.2)	11 (9.8)		5 (17.2)	5 (17.2)	
Lung metastasis	1 (3.4)	11 (9.8)		1 (3.4)	5 (17.2)	
Bone metastasis	2 (6.9)	2 (1.8)		2 (6.9)	2 (6.9)	
Peritoneal metastasis	1 (3.4)	0 (0)		1 (3.4)	0 (0)	
Others	0 (0)	2 (1.8)		0 (0)	0 (0)	

Survival Analysis

The median follow-up period of the whole group was 25.0 (range, 2–66) months. In total, 22 (15.6%) patients died and 43 (30.5%) patients developed local recurrence or distant metastasis during follow-up. Before matching, the OS and DFS of patients in the LPNM group were significantly worse than those of patients in the non-LPNM group (Figs. 2 and 3). The 1-, 2- and 3-year OS rates were 92.0% vs. 97.9%, 71.7% vs. 92.4% and 57.9% vs. 85.7% in the LPNM group and non-LPNM group, respectively (P< 0.001) (Table 4). The 1-, 2- and 3-year DFS rates were 52.3% vs. 85.3%, 43.2% vs. 77.9% and 36.0% vs. 68.4% in the LPNM group and non-LPNM group, respectively (P< 0.001) (Table 4). After matching, the DFS of patients in the LPNM group was also found to be significantly worse than that in the non-LPNM group (P = 0.044) (Fig. 5), while there was no significant difference in OS between the two groups (P = 0.168) (Fig. 4). The 1-, 2- and 3-year OS rates were 92.0% vs. 96.0%, 71.7% vs. 85.3 and 73.0% vs. 56.5% in the LPNM group and non-LPNM group, respectively (P = 0.168)

(Table 4). The 1-, 2- and 3-year DFS rates were 52.3% vs. 81.4%, 43.2% vs. 77.3% and 36.0% vs. 49.2% in the LPNM group and non-LPNM group, respectively (P = 0.044) (Table 4).

Table 4
Overall survival and disease-free survival of 141 rectal cancer patients with or without pathological LPNM before and after matching

	N	Overall survival			Disease-free survival		
		1-year	2-year	3-year	1-year	2-year	3-year
Before matching							
LPNM	29	92.0%	71.7%	57.9%	52.3%	43.2%	36.0%
Non-LPNM	112	97.9%	92.4%	85.7%	85.3%	77.9%	68.4%
After matching							
LPNM	29	92.0%	71.7%	56.5%	52.3%	43.2%	36.0%
Non-LPNM	29	96.0%	85.3%	73.0%	81.4%	77.3%	49.2%

Univariate and multivariate regression analyses were performed to identify prognostic factors for OS and DFS of patients with clinical LPNM who underwent TME + LPND. In univariate analysis, histology, perineural invasion, lymphatic invasion, N stage, and LPNM significantly affected OS (P < 0.05). In addition, DFS was significantly affected by the preoperative CEA level, perineural invasion, lymphatic invasion, N stage, and LPNM (P < 0.05). In multivariate regression analysis, LPNM was an independent risk factor not only for OS (HR: 3.06; 95% CI, 1.15–8.17; P = 0.025) but also for DFS (HR: 2.39; 95% CI, 1.18–4.87; P = 0.016). Moreover, lymphatic invasion was another independent risk factor for OS (HR: 3.34; 95% CI, 1.13–9.88; P = 0.003) (Table 5).

Table 5
Univariate and multivariate analyses for overall survival and disease-free survival of the 141 rectal patients with clinical LPNM who underwent TME + LPND

Variables	Overall survival				Disease-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P
Gender: male/female	0.86 (0.37–1.98)	0.716			0.85 (0.46–1.56)	0.600		
Age	1.02 (0.97–1.06)	0.459			0.99 (0.97–1.03)	0.817		
Preoperative chemotherapy	1.70 (0.65–4.48)	0.283			1.59 (0.85-3.00)	0.149		
Preoperative CEA level	1.01 (0.98–1.03)	0.587			1.01 (1.00-1.03)	0.050	1.01 (0.99–1.02)	0.165
Preoperative CA19-9 level	1.00 (0.99–1.01)	0.160			1.00 (0.99–1.01)	0.512		
Histology	2.83 (1.21–6.64)	0.017	1.38 (0.55–3.44)	0.489	1.77 (0.95–3.29)	0.073		
Perineural invasion	2.78 (1.19–6.46)	0.018	1.48 (0.54–4.09)	0.450	2.06 (1.13–3.76)	0.019	1.77 (0.86–3.65)	0.121
Vascular invasion	1.29 (0.52–3.19)	0.589			0.98 (0.50–1.91)	0.953		
Lymphatic invasion	6.00 (2.42–14.89)	< 0.001	3.34 (1.13–9.88)	0.003	2.31 (1.24–4.29)	0.008	1.48 (0.70–3.12)	0.303
T stage: T3-4/T1-2	2.36 (0.70-8.00)	0.168			1.24 (0.61–2.51)	0.557		
N stage								
N0	Reference		Reference		Reference		Reference	
N1	1.67 (0.51–5.50)	0.398	1.08 (0.30–3.89)	0.905	1.38 (0.66–2.90)	0.390	0.87 (0.38–2.03)	0.751
N2	5.06 (1.74–14.76)	0.003	2.68 (0.84–8.54)	0.096	2.32 (1.12–4.83)	0.024	1.16 (0.48–2.85)	0.741

Variables	Overall survival				Disease-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P
LPN metastasis	4.49 (1.82–11.12)	0.001	3.06 (1.15–8.17)	0.025	2.95 (1.59–5.50)	0.001	2.39 (1.18–4.87)	0.016
Mesorectal LN harvested	0.98 (0.93–1.03)	0.411			0.99 (0.96–1.03)	0.698		
LPN harvested	0.99 (0.98–1.01)	0.345			1.00 (0.99–1.01)	0.264		
Adjuvant chemotherapy	0.58 (0.25–1.35)	0.209			0.72 (0.39–1.33)	0.292		
Postoperative complications	0.49 (0.14–1.68)	0.255			0.82 (0.38–1.79)	0.618		

Univariate and multivariate regression analyses were performed to identify prognostic factors for OS and DFS of patients with pathological LPNM. These patients were divided into a high-risk LPNM group and a low-risk LPNM group according to the site (obturator or internal iliac artery region) and number (< 2 positive LPNs) of LPNMs. The OS and DFS of the patients in the high-risk LPNM group were significantly worse than those of patients in the low-risk LPNM group and non-LPNM group (Figs. 6 and 7). In univariate analysis, lymphatic invasion and high-risk LPNM significantly affected both OS and DFS ($P < 0.05$). According to multivariate analysis, high-risk LPNM was an independent risk factor affecting both OS (HR: 9.23; 95% CI, 1.46–87.35; $P = 0.032$) and DFS (HR: 4.39; 95% CI, 1.33–13.16; $P = 0.041$) (Table 6).

Table 6
Univariate and multivariate analyses for overall survival and disease-free survival of the 29 rectal patients with pathological LPNM.

Variables	Overall survival				Disease-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P
Gender: male/female	0.72 (0.19–2.71)	0.625			0.99 (0.37–2.71)	0.998		
Age	1.01 (0.95–1.06)	0.811			0.99 (0.96–1.03)	0.767		
Preoperative chemotherapy	2.73 (0.56–13.34)	0.214			1.78 (0.65–4.94)	0.265		
Preoperative CEA level	0.99 (0.93–1.05)	0.705			1.01 (1.00-1.02)	0.181		
Preoperative CA19-9 level	1.00 (0.99–1.01)	0.858			1.00 (0.99–1.01)	0.677		
Histology	0.89 (0.22–3.64)	0.870			1.00 (0.36–2.78)	0.999		
Perineural invasion	3.89 (0.34–18.10)	0.083			2.03 (0.70–5.90)	0.195		
Vascular invasion	1.06 (0.28–3.99)	0.935			0.77 (0.28–2.14)	0.612		
Lymphatic invasion	6.64 (1.35–32.78)	0.020	2.74 (0.44–17.15)	0.280	3.03 (1.01–9.10)	0.048	1.65 (0.45–5.99)	0.447
T stage: T3-4/T1-2	1.17 (0.15–9.42)	0.884			0.50 (0.14–1.80)	0.289		
N stage								
N0	Reference				Reference			
N1	0.17 (0.15–185)	0.145			0.62 (0.15–2.63)	0.517		
N2	1.83(0.35–9.68)	0.477			1.38 (0.34–5.57)	0.654		

Variables	Overall survival				Disease-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P
Mesorectal LN harvested	0.98 (0.91–1.06)	0.638			1.00 (0.94–1.06)	0.994		
LPN harvested	1.01 (0.95–1.08)	0.742			0.98 (0.92–1.05)	0.605		
Adjuvant chemotherapy	0.69 (0.17–2.77)	0.598			0.39 (0.14–1.08)	0.071		
Postoperative complications	0.52 (0.06–4.33)	0.547			0.42 (0.09–1.93)	0.263		
High risk LPNM	15.33 (1.77-133.46)	0.013	9.23 (1.46–87.35)	0.032	4.46 (1.38–14.46)	0.013	4.39 (1.33–13.16)	0.041

Discussion

The clinical value of LPND is controversial because LPNM represents systemic disease in Western countries, and R0 resection for tumours cannot be achieved, while LPNM is considered a regional disease amenable to surgical cure in Japan. This study discovered that 20.6% of patients who underwent TME + LPND were pathologically confirmed to have LPNM. Previous studies have reported LPNM rates varying from 8.6–18.6% [12,14,15], similar to our results. In addition, the most common site of LPNM was the obturator lymph node (48.3%), followed by the internal iliac lymph node (27.6%), the common iliac lymph node (20.7%), and the external iliac lymph node (17.2%), which is also consistent with previous literature reports[16].

Several studies have demonstrated that LPNs are the most common site of postoperative recurrence[12,13,17]. In the present study, even after TME + LPND, the postoperative overall recurrence rate (51.7% vs 21.4%, $P = 0.001$) and local recurrence rate (27.6% vs 4.5%, $P = 0.001$) of patients with LPNM were significantly higher than those of patients without LPNM. After the elimination of confounding factors by PSM, the local control effect of LPND for patients with LPNM was still worse (27.6% vs 3.4%, $P = 0.025$). A retrospective study involving 899 colorectal cancer patients at a high-volume cancer centre in Japan conducted by Wang et al. revealed that even with LPND, patients with LPNM still showed an elevated risk of local recurrence (30.0% vs 10.0, $P = 0.025$)[12]. Similarly, Numata et al. suggested that additional LPND based on TME cannot achieve obvious local control compared with TME alone (27.8% vs 26.4%, $P = 1.000$), while increasing the R0 resection rate is crucial to maximizing the potential merits of LPND[13]. The literature has shown that both chemotherapy and TME combined with LPND have the same long-term survival outcomes in rectal cancer patients with LPNM and that even the former can achieve a reduction in local recurrence[18]. Therefore, we suggest that LPND alone is not

sufficient to achieve local control, and comprehensive treatment methods, including chemoradiotherapy during the perioperative period, should be considered to confer overall survival benefits for rectal cancer patients with LPNM.

We investigated prognostic factors in 141 patients with TME + LPND, and the results showed that the OS and DFS of patients with LPNM were significantly poorer even after LPND and that LPNM was an independent predictive value affecting OS (HR: 3.06; 95% CI, 1.15–8.17; *P* = 0.025) and DFS (HR: 2.39; 95% CI, 1.18–4.87; *P* = 0.016). Similarly, Sato et al. also proved that LPNM results in a higher recurrence rate and a poor prognosis after LPND in patients with rectal carcinoma below the peritoneal reflection[19]. The above results suggested that the potential benefits of routine use of LPND are limited or even ineffective. It has been reported in the literature that LPND may provide survival benefits for patients with certain specific LPN involvement[19–22]. Yokoyama et al. classified LPNs according to the actual number and region of LPNMs and found that LPND is an effective treatment for patients with a single LPNM in the internal iliac vessel region or the obturator region[20]. Moreover, Ueno and colleagues considered that the internal iliac vessel region and the obturator region are “vulnerable fields”, and the value of LPND can be effectively assessed by estimating the nodal diameter in this “vulnerable field”[22]. Similar to the above literature, our study also demonstrated that patients in the low-risk group (obturator/internal iliac artery region and < 2 positive LPNs) achieved better survival benefits in terms of OS and DFS. The 8th edition of the AJCC indicated that lymph nodes around the internal iliac artery should be regarded as regional lymph nodes for rectal cancer, and the N stage should be included in staging considerations, which also supports our results to a certain extent.

There are several potential limitations to this study that should be considered. First, the accuracy of MRI in the diagnosis of LPNM was only 20.6% (29/141), which was related to our relatively loose diagnostic criteria for clinical LPNM. Therefore, we do not recommend that this imaging diagnostic standard be used in clinical practice, as it could result in a high false positive rate. The second potential limitation is the retrospective nature of this study, and only 141 patients were included; in particular, only 29 patients with pathological LPNM were included in the prognostic analysis, which may have caused some bias. However, we conducted PSM according to clinical and pathological characteristics to minimize selection bias. Despite these limitations, we believe that our results will improve the understanding of issues related to LPND and provide a basis for the management of LPNM in clinical practice.

In conclusion, our data demonstrated that even after performing LPND, patients with LPNM still have a high postoperative local recurrence rate and poor long-term survival. Moreover, LPNM was found to be an independent poor prognostic factor affecting OS and DFS in patients with LPNM after TME + LPND. However, LPND appears to confer survival benefits to certain patients with single LPN involvement in the obturator region or internal iliac vessel region.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. The ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College approved this study. Prior written informed consent was obtained from all study participants.

Consent for publication

Not applicable

Availability of data and materials

The data that support the fndings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Conception and design were performed by Liang Jianwei and Zhou Zhixiang. Material preparation, data collection and analysis were performed by Zhou Sicheng , Jiang Yujuan and Pei Wei.The first draft of the manuscript was written by Zhou Sicheng and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Not available.

Statement

All methods were carried out in accordance with relevant guidelines and regulations.

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Figures

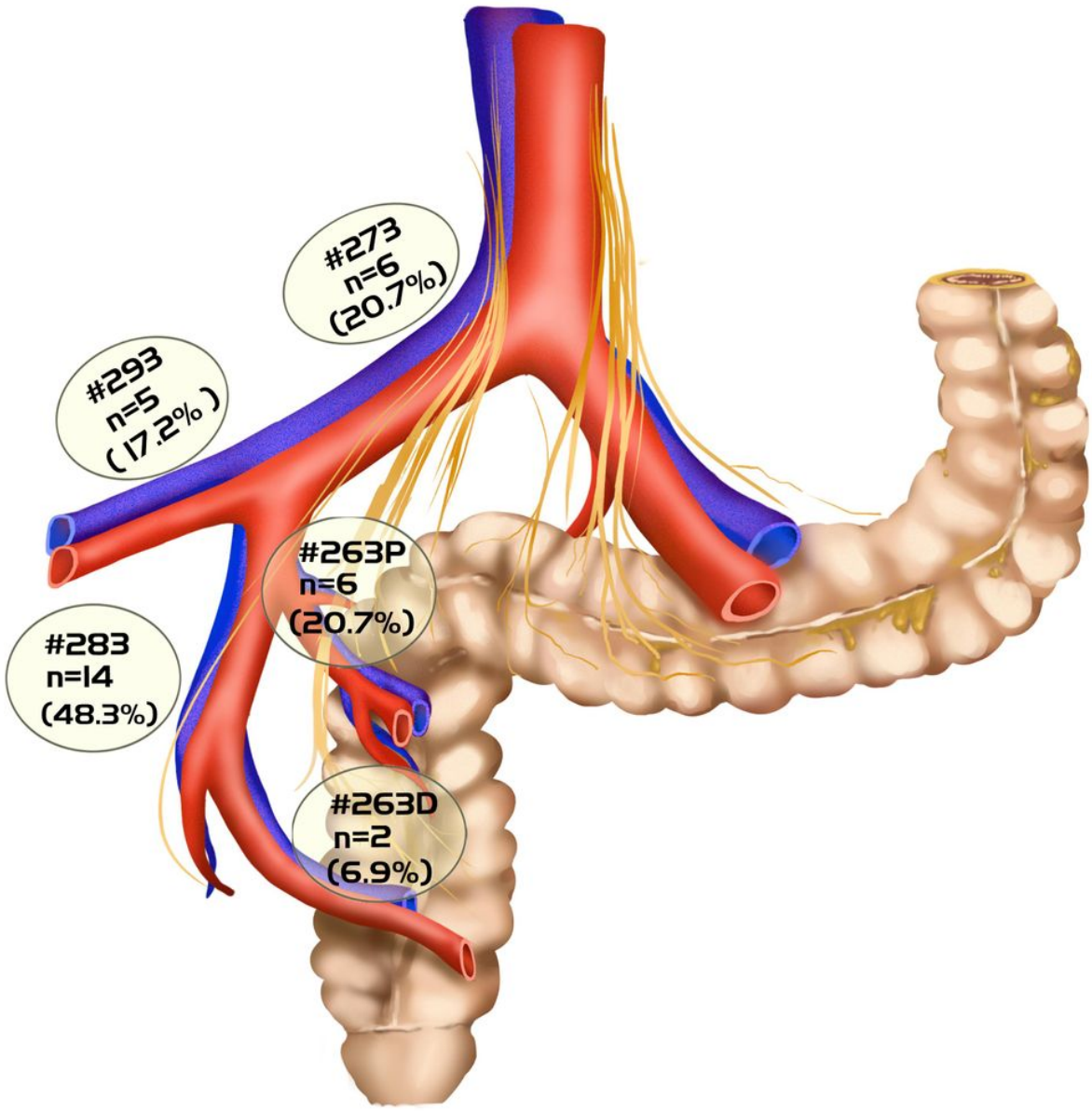

Figure 1

Distribution of lateral lymph node metastases of 29 patients in LPNM group. #263P (proximal internal iliac lymph nodes), #263D (distal internal iliac lymph nodes), #273 (common iliac lymph nodes), #283 (lymph

nodes around obturator), #293 (external iliac lymph nodes)

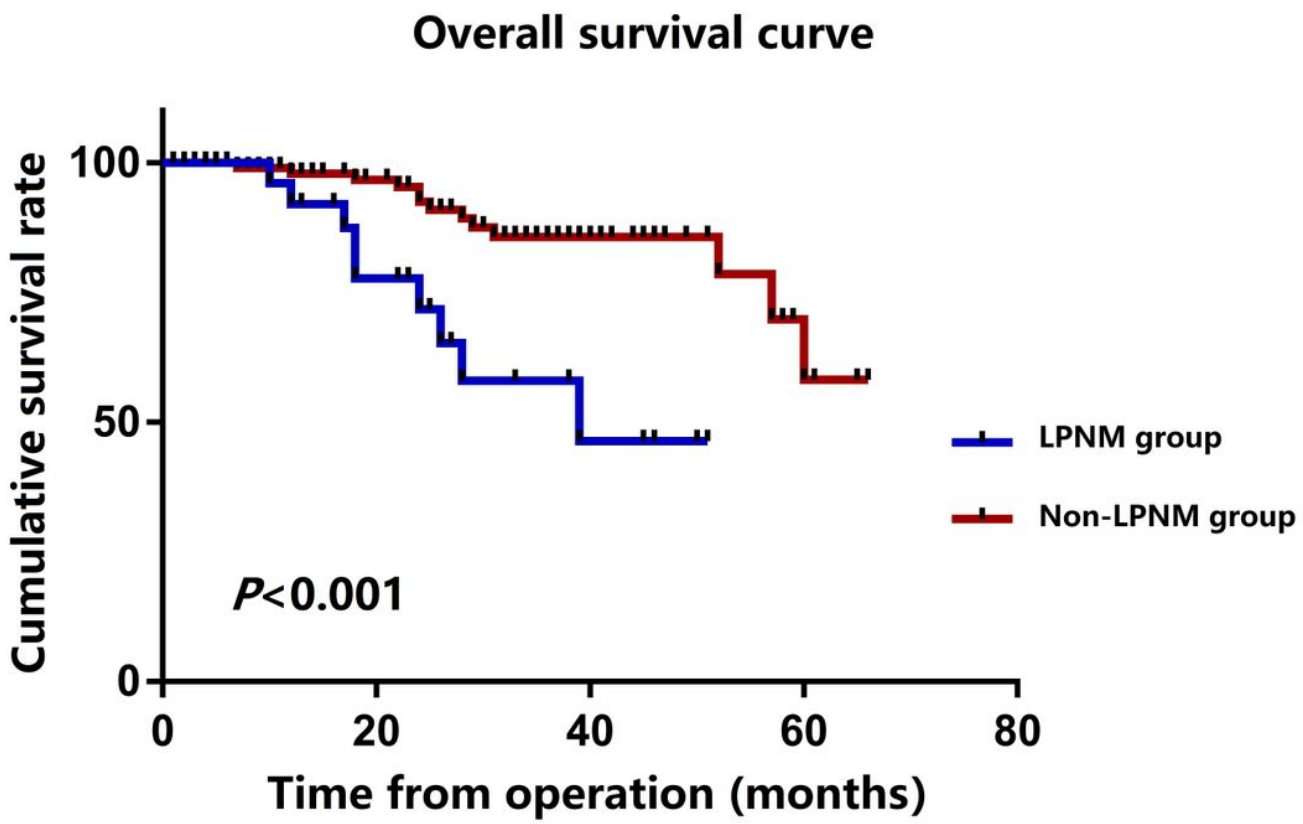

Figure 2

Overall survival rate of patients in the LPNM group and non-LPNM group before propensity score matching

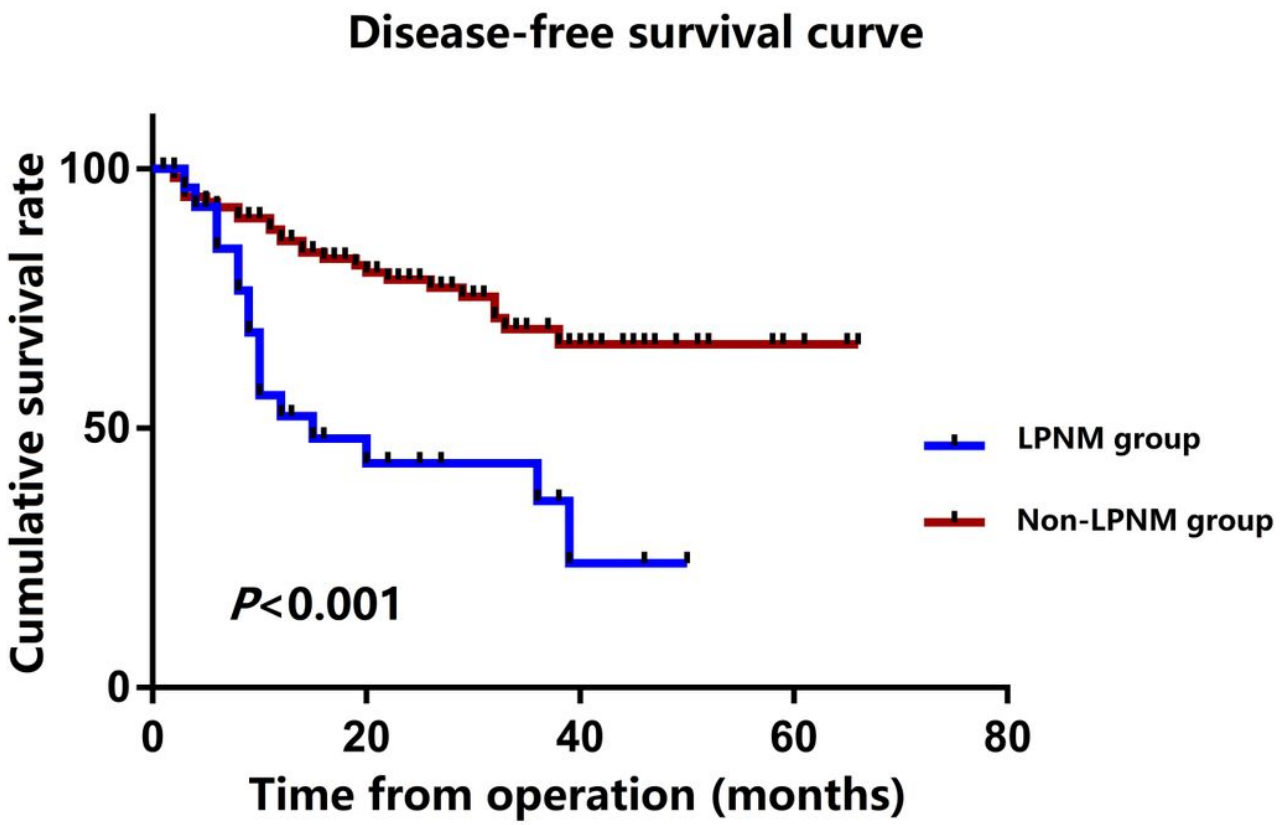

Figure 3

Disease-free survival rate of patients in the LPNM group and non-LPNM group before propensity score matching

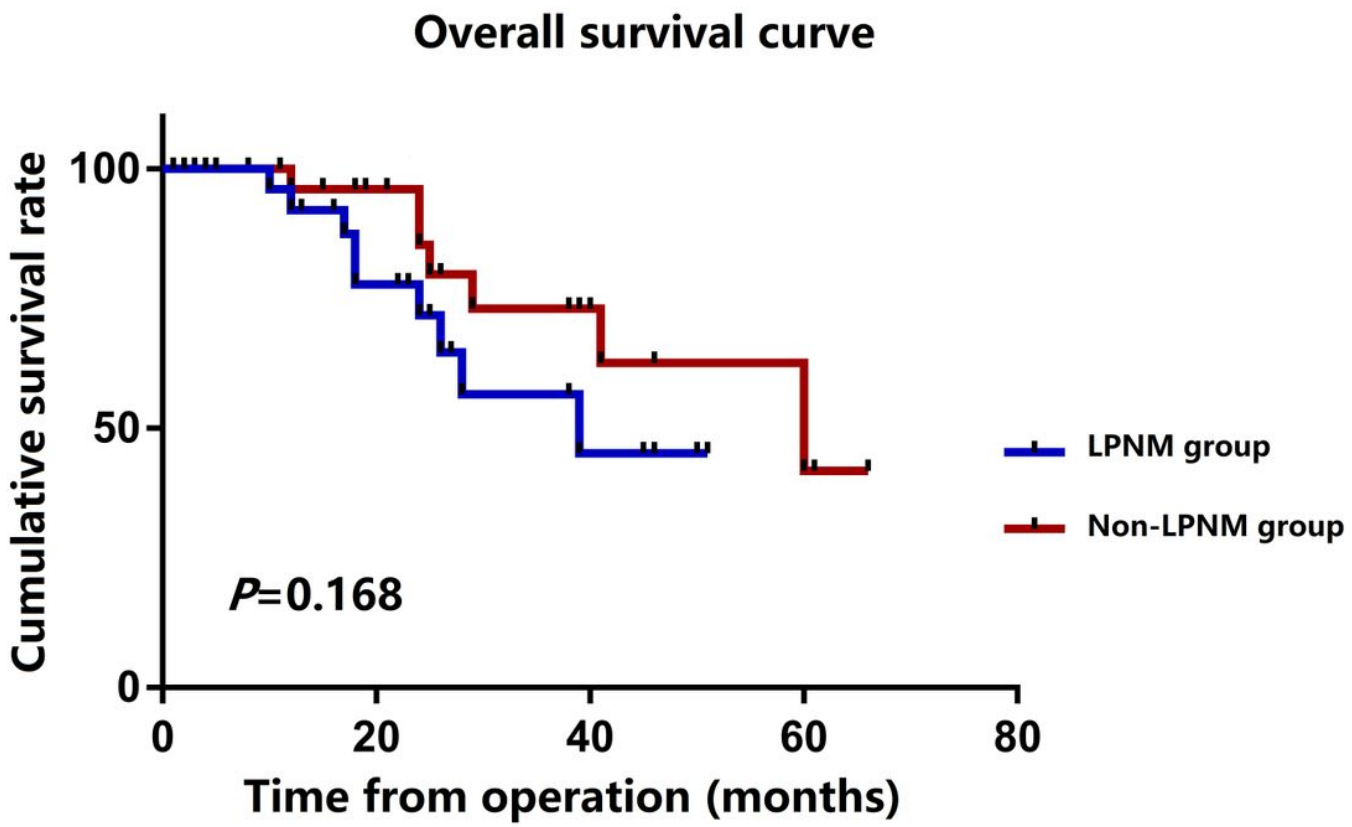

Figure 4

Overall survival rate of patients in the LPNM group and non-LPNM group after propensity score matching

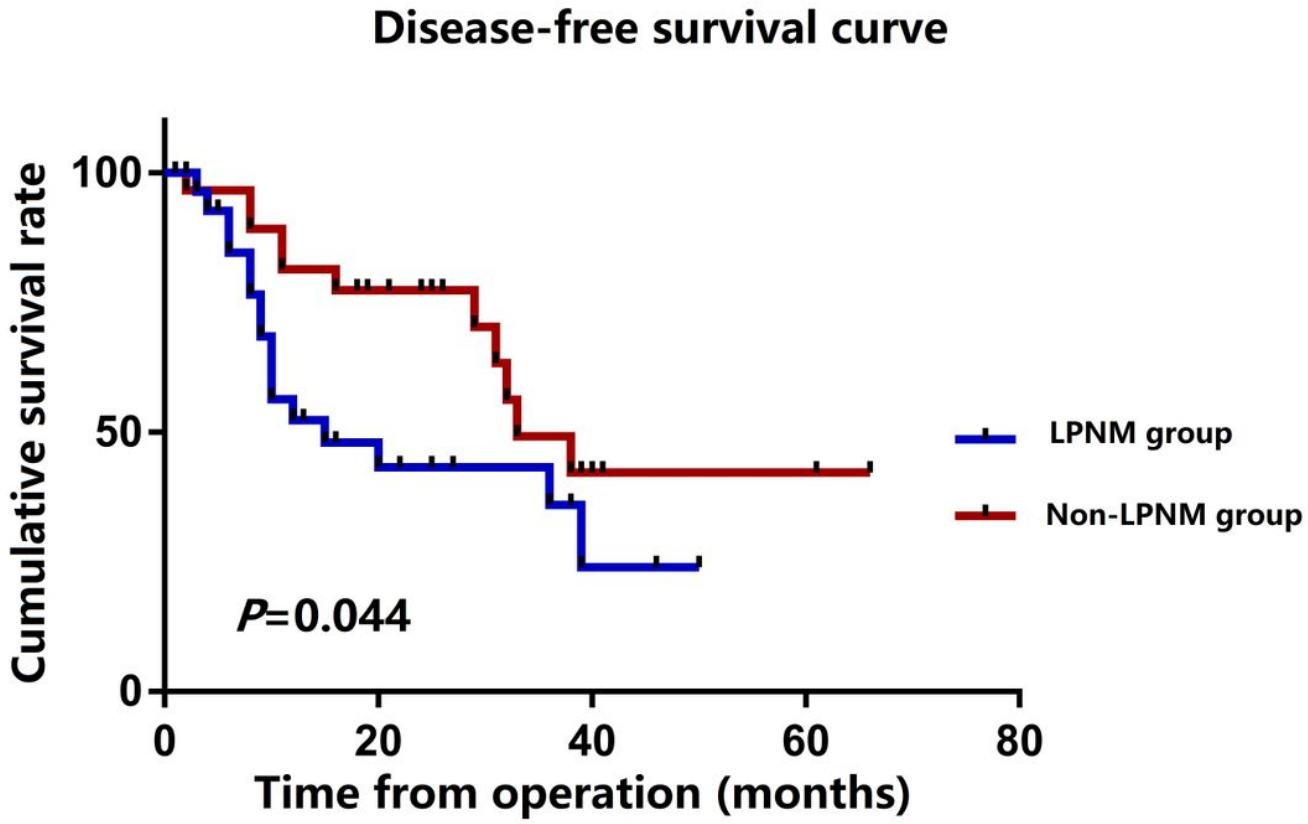

Figure 5

Disease-free survival rate of patients in the LPNM group and non-LPNM group after propensity score matching

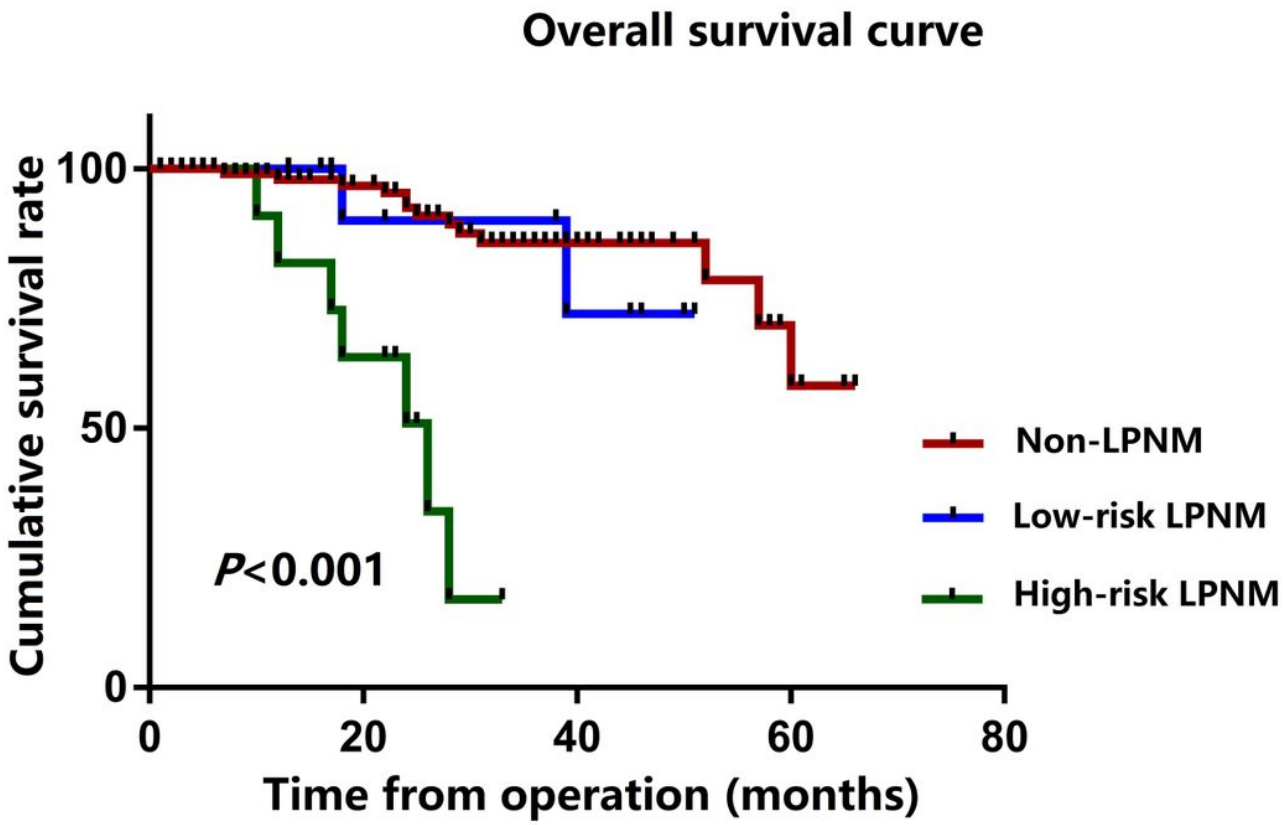

Figure 6

Overall survival rate of patients in the high-risk LPNM group, low-risk LPNM and Non-LPNM group

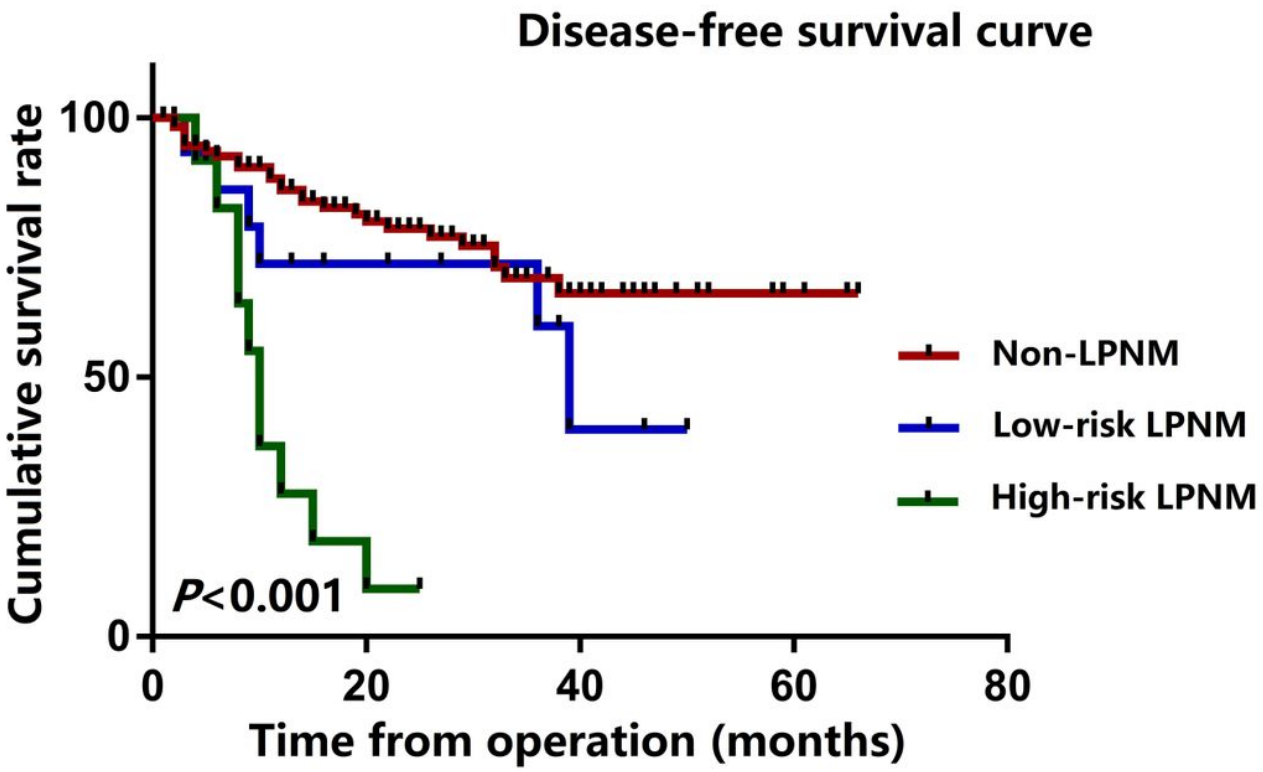

Figure 7

Disease-free survival rate of patients in the high-risk LPNM group, low-risk LPNM and Non-LPNM group