Metastatic lymph node ratio as a prognostic factor after laparoscopic total mesorectal excision for extraperitoneal rectal cancer

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Abstract
Background
The lymph node ratio (LNR; number of positive nodes divided by total nodes harvested) has been demonstrated to be a prognostic factor in colon cancer, but its role in extraperitoneal rectal cancer is still debated; furthermore, no data are available on laparoscopic rectal resection. The aim of this study was to evaluate the prognostic impact of LNR on long-term outcomes after laparoscopic total mesorectal excision (LTME) for extraperitoneal cancer in consecutive patients with a 5-year minimum follow-up.
Methods
This study is a prospective analysis of consecutive patients who underwent LTME for adenocarcinoma of the extraperitoneal rectum.
Results
LTME was performed in 158 patients. The median number of LN harvested was 12 (range = 3–25). The proportion of specimens with fewer than 12 examined LN was significantly higher in patients who had neoadjuvant chemoradiotherapy ($p < 0.001$). During a median follow-up period of 122 months, the local recurrence rate was 8 %. At univariate analysis, disease-free survival and overall survival significantly decreased with increasing LNR ($p < 0.001$). Multivariate analysis showed that the distal margin ≤1 cm was the only independent predictor of local recurrence ($p = 0.028$). LNR (cutoff value = 0.25) and lymphovascular invasion were significant prognostic factors for both disease-free ($p = 0.015$ and $p = 0.046$, respectively) and overall survival ($p = 0.031$ and $p = 0.040$, respectively). Even in the subgroup of patients in whom fewer than 12 LN were examined, LNR confirmed its prognostic role, with a statistical trend toward worse disease-free survival and overall survival.
Conclusion
Metastatic LNR is an independent prognostic factor for disease-free survival and overall survival after LTME for extraperitoneal rectal cancer.
Keywords
Lymph node ratio Survival Laparoscopy Total mesorectal excision Rectal cancer
Excellence of surgical technique is of particular relevance in the treatment of extraperitoneal rectal cancer. Routine excision of the intact mesorectum during resection of cancer of the middle and lower rectum has resulted in a significant decrease in local recurrence rates [*1*]. Developed and popularized by Heald and co worker [*1*], total mesorectal excision (TME) is presently the surgical gold standard, with a 4 % local recurrence rate and a 78 % tumor-free survival rate in curative cases at 5 years [*2*].
A recent meta-analysis by Huang et al. [*3*] of randomized controlled trials that included small numbers of patients with upper or mid-to-low rectal cancer did not show differences between laparoscopic and open surgery in terms of the number of lymph nodes (LN) harvested, local recurrence, 3-year disease-free survival, and overall survival. Although a minimum of 12 LN in the

tumor specimen is recommended for an adequate assessment of tumor staging, the number of resected LN after TME is highly variable.
While the prognostic role of the lymph node ratio (LNR) in colon cancer patients has been demonstrated, its role in extraperitoneal rectal cancer is still under debate. Furthermore, no cutoff values have been clearly identified, and no prospective data are available in patients who underwent laparoscopic TME.
The aim of this study was to prospectively evaluate the prognostic value of the LNR in consecutive patients who underwent laparoscopic TME for extraperitoneal rectal cancer with a 5-year minimum follow-up.

Materials and methods

The data of all patients admitted to our institution with histologically proven adenocarcinoma of extraperitoneal (mid and low) rectum were entered into a prospective database. In the absence of specific contraindications to laparoscopy (e.g., severe cardiopulmonary disease and glaucoma), patients with tumors in the extraperitoneal rectum were selected for laparoscopic TME based on the following criteria: elective surgery, absence of acute intestinal occlusion or perforation, and American Society of Anesthesiologists (ASA) status of I–III. Neither morbid obesity nor prior pelvic surgery was considered a contraindication to laparoscopic TME.
The preoperative workup included clinical evaluation, total colonoscopy, chest and upper abdominal computed tomography (CT) scan, endoscopic ultrasound and pelvic CT scan until 2003, then pelvic magnetic resonance imaging (MRI), and tumor marker assay for carcinoembryonic antigen (CEA) and cancer antigen 19-9.
Neoadjuvant chemoradiotherapy (CRT) was discussed in a multidisciplinary setting. Patients preoperatively staged as T3-4 N0-1 without distant metastases received preoperative CRT (45 Gy over 4 weeks, together with systemic 5-fluorouracil intravenous infusion) and were reevaluated by clinical examination, rigid rectoscopy, endoscopic ultrasound, and CT or MRI 4 weeks after the completion of CRT. Definitive inclusion in the study was decided at this point, but patients with T4 tumors that did not show clinical downstaging or downsizing were excluded as they were considered a contraindication to the laparoscopic approach.
All surgical procedures were performed by surgeons experienced in colorectal and laparoscopic advanced surgery. They followed the same oncologic principles as described by Heald and co worker [*1*]: adequate resection margins; en bloc high ligation of the inferior mesenteric artery (IMA) and lymphadenectomy; and minimal intraoperative manipulation of the tumor mass. Our technique of laparoscopic anterior resection with TME has been previously described [*4*]. When digital examination revealed that the neoplasm reached the anatomic anal canal or was fixed to the pelvic floor, a laparoscopic abdominoperineal resection was performed.
Only patients with a minimum follow-up of 60 months were included in the study. For this prospective study, a database was created to contain the patient's characteristics (age, gender, and ASA status), preoperative assessment, operative variables, pathological examination, and short-term and long-term outcomes. Operative variables included duration of the operation (from skin incision to the application of dressings), intraoperative morbidity and mortality, and conversion rate to abdominal surgery. Conversion to laparotomy was defined as an unplanned incision or an incision made longer or earlier than planned. Pathological examination included stage of disease (TNM), length of the surgical specimen, number of LN harvested, LNR (defined as the number of positive nodes divided by total nodes harvested), and longitudinal and radial margins of excision. Lymph nodes in the mesorectal fatty tissue were identified after formalin fixation of the specimen. Long-term outcomes included the local recurrence rate, incidence of abdominal wall and distant metastases, disease-free survival, and overall survival for rectal cancer.

Patients were classified in four groups according to the LN metastases distribution (LND): (1) LND0, no LN metastasis; (2) LND1, metastases in the perirectal nodes; (3) LND2, metastases in the intermediate nodes; and (4) LND3, metastases in nodes at the origin of the IMA. Stage III patients were divided into four categories according to quartiles for the LNR: 0.01–0.10, 0.11–0.25, 0.26–0.43, and ≥0.44.
All patients who received neoadjuvant CRT and stage II–III–IV patients were offered an adjuvant treatment after a clinical oncologic evaluation within 8 weeks after surgery:
Follow-up assessment consisted of a digital examination, rectoscopy, and tumor marker assay every 3 months for the first 2 years, then every 6 months thereafter. A full colonoscopy was performed at 12 months and then every 3 years, and chest and abdominopelvic CT scans were performed at 6 and 12 months and every year thereafter. The data were collected prospectively from the time of diagnosis.

Statistical analysis

Quantitative data are given as median and range and qualitative data as frequency and percentage. Patients with a minimum follow-up of 60 months were included in the analysis. Univariate analyses of 5-year overall survival and disease-free survival rates were performed using the Kaplan–Meier method, and the differences between the groups were analyzed using the log-rank test. Patients' observations were censored on the date of last examination or death.
A multivariable Cox regression analysis was performed to identify predictive factors of local recurrence, disease-free survival, and overall survival using both forward and backward stepwise selection. Explanatory variables with univariable $P \leq 0.200$ were included in the multivariable analysis. This significance level was chosen to incorporate all potentially important predictor variables in the final modeling process. All sets of variables were analyzed: age, gender, type of surgery, conversion to open surgery, pT stage, tumor grade, number of LN harvested, LNR, LND, peritumoral lymphocytic infiltrate, lymphovascular invasion, distal resection margins, postoperative anastomotic leakage, neoadjuvant treatment, and postoperative treatment. A level of 5 % was set as the criterion for statistical significance. The data were collected in an Excel spreadsheet. The statistical analysis was performed using SYSTAT ver. 10 (Systat Software, Inc., Chicago, IL, USA).

Results

Between July 1996 and July 2006, 158 patients with extraperitoneal rectal adenocarcinoma underwent laparoscopic TME (Table 1). One hundred twenty-six (79.7 %) patients underwent a "sphincter-saving" procedure and 32 (20.3 %) underwent abdominoperineal resection. There were 21 (13.3 %) conversions to laparotomy. The 30-day postoperative morbidity rate was 22.2 % (35/158). The reoperation rate was 7.6 % (12/158). The 30-day mortality rate was 0.6 % (1/158).
Table 1
Baseline characteristics

	Laparoscopic TME (n = 158)
Gender	
Male [n (%)]	94 (59.5)
Age (years)	
Median (range)	68 (28–90)
ASA status [n (%)]	

	Laparoscopic TME (n = 158)
I	41 (26.0)
II	83 (52.5)
III	34 (21.5)
Type of surgical procedure [n (%)]	
Anterior resection	126 (79.7)
Abdominoperineal resection	32 (20.3)
Conversion to open surgery [n (%)]	21 (13.3)
Locally advanced neoplasm	12 (7.6)
Difficult exposure	5 (3.1)
Difficult in transecting the distal rectum	2 (1.3)
Obesity	2 (1.3)
Postoperative complications [n (%)]	35 (22.2)
Anastomotic leakage	17 (12.5)
Wound infection	7 (4.4)
Prolonged ileus	6 (3.8)
Urinary tract infection	3 (1.9)
Pulmonary infection	2 (1.3)
Postoperative mortality [n (%)]	1 (0.6)
Intestinal infarction	1
Tumor grading [n (%)]	
G1	52 (32.9)
G2	78 (49.4)
G3	28 (17.7)
Tumor staging [n (%)]	
I	48 (30.4)
II	38 (24.1)
III	50 (31.6)
IV	22 (13.9)
Distal margin [n (%)]	
≤1 cm	30 (24.1)
>1 cm	128 (75.9)
Circumferential margin [n (%)]	
Positive	0 (0)
Negative	158 (100)
Number of lymph nodes harvested (n)	
Median (range)	12 (3–25)
Peritumoral lymphocytic infiltrate [n (%)]	

	Laparoscopic TME (n = 158)
Negative	68 (43)
Positive	90 (57)
Lymphovascular invasion [n (%)]	
Negative	85 (53.8)
Positive	73 (46.2)
Neoadjuvant chemoradiotherapy [n (%)]	35 (22.2)
Adjuvant treatment [n (%)]	
Chemotherapy	72 (48)
Chemoradiotherapy	16 (10.7)

TME total mesorectal excision

Anatomopathological results

The clearance of the distal margin was ≤1 cm in 30 (18.9 %) cases, with no distal margin tumor infiltration. All circumferential margins were clear. The rectal cancer stages, according to the 7th AJCC TNM staging system, for the 158 patients were stage I in 48 patients, stage II in 38, stage III in 50, and stage IV in 22. The median number of LN harvested was 12 (range = 3–25). The proportion of specimens with fewer than 12 examined LN was significantly higher in the group of 35 patients who underwent neoadjuvant CRT (77.1 vs. 40.7 %; $p < 0.001$). Furthermore, the median number of LN harvested was lower in stage I–II patients (n = 10.5) than in stage III patients (n = 11) ($p = 0.079$). Among the stage III patients, there was a higher percentage of pN2 in the group with more than 12 LN in the surgical specimen (40 vs. 20 %; $p = 0.100$). LN metastases were distributed among the stage I–III patients as follows: 86 patients were in the LND0 group, 35 in LND1, 13 in LND2, and 2 in LND3.

Long-term results

The median follow-up period was 122 months (range = 60–180). Seven (4.4 %) patients were lost to follow-up (4 stage I and 3 stage II). A total of 72 (48 %) patients received adjuvant chemotherapy and 16 (10.7 %) adjuvant CRT. The local recurrence rate was 8 % (12/150) at a median time of 24.5 months (range = 10–56).

The distribution of stages was similar between the group of patients with local recurrence (LR group) and the group of patients who did not experience a local recurrence (non-LR group): stage I: 25 % (n = 3) versus 29.7 % (n = 41), $p = 0.989$; stage II: 33.3 % (n = 4) versus 22.5 % (n = 31), $p = 0.618$; stage III: 33.3 % (n = 4) versus 33.3 % (n = 46), $p = 0.750$; stage IV: 8.4 % (n = 1) versus 14.5 % (n = 20), $p = 0.876$. A significantly higher rate of patients with fewer than 12 LN was found in the LR group than in the non-LR group (83.3 vs. 42.2 %, $p = 0.014$). Both groups did not differ in terms of use of neoadjuvant CRT (33.3 vs. 21 %, $p = 0.532$).

Distant metastases developed in 23 (17.8 %) stage I–III patients. The port-site metastases rate was 1.3 % (2/150), involving a stage IV patient 17 months after surgery and a stage III patient 28 months after surgery.

The 5-year overall survival rate was 69.8 % and the disease-free survival rate was 60.5 %. The 5-year overall survival rate was 92.3 % for stage I patients, 85.6 % for stage II, and 63.1 % for stage III; no patient with stage IV disease was alive at 41 months after surgery ($p < 0.001$). The 5-year

disease-free survival rate was 86.5 % for stage I patients, 75.6 % for stage II, and 48.4 % for stage III; no patient with stage IV was disease-free at 41 months after surgery ($p < 0.001$).

Excluding the stage IV patients, univariate analysis showed that for the risk of local recurrence (Table 2), tumor grade ($p = 0.006$), lymphovascular invasion ($p = 0.010$), distal surgical margins ≤1 cm ($p = 0.018$), and number of LN harvested ($p = 0.050$) were all statistically significant, while pT stage and neoadjuvant CRT showed a statistical trend ($p = 0.111$ and $p = 0.085$, respectively). Multivariate analysis indicated distal surgical margins ≤1 cm as an independent predictor of local recurrence ($p = 0.028$), while the number of LN harvested ($p = 0.087$), tumor grade ($p = 0.052$), and pT stage ($p = 0.100$) had a statistical trend.

Table 2

Univariate and multivariate analyses of risk factors for local recurrence after laparoscopic total mesorectal excision

	N = 129	**Univariate analysis**		**Multivariate analysis**	
		Hazard ratio (95% CI)	**P†**	**Hazard ratio (95% CI)**	**P†**
Age (years)					
>68	57	1			
≤68	72	0.647 (0.187–2.237)	0.491		
Gender					
Female	55	1			
Male	74	1.358 (0.377–4.889)	0.639		
Type of surgical procedure					
Abdominoperineal resection	27	1			
Anterior resection	102	1.149 (0.233–5.670)	0.865		
Conversion to open surgery					
No	115	1			
Yes	14	1.981 (0.383–10.258)	0.415		
pT stage					
T1–T2	57	1		1	
T3	72	3.600 (0.745–17.390)	0.111	4.753 (0.629–35.913)	0.100
Tumor grade					
G1-2	103	1		1	
G3	26	6.346 (1.695–23.760)	0.006	6.197 (0.981–39.155)	0.052
Number of lymph nodes harvested					
≥12	61	1		1	
<12	68	4.853 (1.001–23.533)	0.050	4.202 (0.986–31.739)	0.087
Lymph node ratio					
0	79	1			
0.01–0.25	26	1.411 (0.248–3.505)	0.676		
>0.25	24	2.057 (0.548–7.725)	0.277		
Lymph node distribution					

	N = 129	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P†	Hazard ratio (95% CI)	P†
0	86	1			
1	35	1.136 (0.823–1.415)	0.453		
2 + 3	15	1.028 (0.323–1.721)	0.301		
Peritumoral lymphocytic infiltrate					
Present	75	1			
Poor/absent	54	2.080 (0.365–11.865)	0.410		
Lymphovascular invasion					
Absent	69	1		1	
Present	60	5.775 (1.533–21.758)	0.010	2.931 (0.509–16.888)	0.229
Distal surgical margin (cm)					
>1	99	1		1	
≤1	30	4.650 (1.307–16.538)	0.018	6.586 (1.222–21.442)	0.028
Postoperative anastomotic leakage					
No	119	1			
Yes	10	1.222 (0.140–10.652)	0.856		
Neoadjuvant treatment					
No	96	1		1	
Yes	33	3.206 (0.851–12.086)	0.085	2.698 (0.454–16.018)	0.275
Adjuvant treatment					
No	41	1			
Yes	88	2.141 (0.541–8.472)	0.278		

95% CI 95% confidence interval

†Stepwise logistic regression analysis

At univariate analysis, the factors associated with a poorer disease-free survival and overall survival (Table 3, 4) were age, pT stage, tumor grade, number of LN harvested, LNR, lymphovascular invasion, peritumoral lymphocytic infiltrate, and postoperative treatment. Both 5-year disease-free survival and overall survival significantly decreased with increasing LNR ($p < 0.001$) (Figs. 1, 2). At multivariate analysis, tumor grade ($p = 0.007$), LNR > 0.25 ($p = 0.015$), and lymphovascular invasion ($p = 0.046$) were significant predictors of poorer disease-free survival (Table 3), while pT stage ($p = 0.088$), number of LN harvested ($p = 0.174$), and peritumoral lymphocytic infiltrate ($p = 0.168$) showed a statistical trend. For overall survival, the only independent factors were LNR >0.25 ($p = 0.031$) and lymphovascular invasion ($p = 0.040$), while tumor grade showed a statistical trend ($p = 0.091$) (Table 4).

Table 3

Univariate and multivariate analyses of risk factors for disease-free survival after laparoscopic total mesorectal excision

		Univariate analysis		Multivariate analysis	
	N = 129	Hazard ratio (95% CI)	P†	Hazard ratio (95% CI)	P†

		Univariate analysis		Multivariate analysis	
	N = 129	**Hazard ratio (95% CI)**	**P†**	**Hazard ratio (95% CI)**	**P†**
Age (years)					
>68	57	1		1	
≤68	72	2.039 (0.917–4.535)	0.081	1.452 (0.238–8.871)	0.686
Gender					
Female	55	1			
Male	74	0.991 (0.459–2.137)	0.981		
Type of surgical procedure					
Abdominoperineal resection	27	1			
Anterior resection	102	0.568 (0.230–1.404)	0.221		
Conversion to open surgery					
No	115	1			
Yes	14	2.056 (0.661–6.402)	0.213		
M					
T1–T2	57	1		1	
T3	72	4.578 (1.825–11.484)	0.001	4.122 (0.775–23.198)	0.088
Tumor grade					
G1-2	103	1		1	
G3	26	16.917 (4.986–27.392)	<0.001	15.565 (5.655–32.329)	0.007
Number of lymph nodes harvested					
≥12	61	1		1	
<12	68	2.277 (1.020–5.083)	0.045	2.533 (0.613–10.468)	0.174
Lymph node ratio					
0	79	1		1	
0.01–0.25	26	3.173 (1.181–8.528)	0.0280	2.856 (0.988–9.112)	0.063
>0.25	24	7.108 (2.599–19.436)	<0.001	6.523 (2.347–20.010)	0.015
Lymph node distribution					
0	86	1			
1	35	1.536 (0.823–2.415)	0.453		
2 + 3	15	2.088 (0.897–3.721)	0.301		
Peritumoral lymphocytic infiltrate					
Present	75	1		1	
Poor/absent	54	2.582 (0.957–6.967)	0.061	1.279 (0.146–1.696)	0.168
Lymphovascular invasion					
Absent	69	1		1	
Present	60	7.500 (2.726–20.636)	<0.001	2.247 (1.166–8.922)	0.046

		Univariate analysis		Multivariate analysis	
	N = 129	**Hazard ratio (95% CI)**	**P†**	**Hazard ratio (95% CI)**	**P†**
Distal surgical margin (cm)					
>1	99	1			
≤1	30	0.865 (0.345–2.167)	0.757		
Postoperative anastomotic leakage					
No	119	1			
Yes	10	1.758 (0.466–6.626)	0.405		
Neoadjuvant treatment					
No	96	1		1	
Yes	33	1.978 (0.763–5.128)	0.161	1.849 (0.313–10.928)	0.556
Adjuvant treatment					
No	41	1		1	
Yes	88	7.771 (2.782–21.707)	<0.001	4.225 (0.706–25.282)	0.109

95% CI 95% confidence interval
†Stepwise logistic regression analysis

Table 4
Univariate and multivariate analyses of risk factors for overall survival after laparoscopic total mesorectal excision

		Univariate analysis		Multivariate analysis	
	N = 129	**Hazard ratio (95% CI)**	**P†**	**Hazard ratio (95% CI)**	**P†**
Age (years)					
>68	57	1		1	
≤68	72	3.333 (1.239–8.971)	0.017	2.004 (0.187–8.510)	0.696
Gender					
Female	55	1			
Male	74	0.856 (0.361–2.029)	0.723		
Type of surgical procedure					
Abdominoperineal resection	27	1		1	
Anterior resection	102	0.373 (0.143–0.976)	0.045	0.513 (0.052–5.088)	0.568
Conversion to open surgery					
No	115	1			
Yes	14	1.103 (0.284–4.278)	0.888		
pT stage					
T1–T2	57	1		1	
T3	72	3.883 (1.359–11.094)	0.011	2.129 (0.183–24.806)	0.546
Tumor grade					

		Univariate analysis		Multivariate analysis	
	N = 129	**Hazard ratio (95% CI)**	**P†**	**Hazard ratio (95% CI)**	**P†**
G1-2	103	1		1	
G3	26	7.750 (2.574–23.336)	<0.001	8.116 (0.718–34.698)	0.091
Number of lymph nodes harvested					
≥12	61	1		1	
<12	68	2.295 (0.915–5.757)	0.077	1.740 (0.274–11.071)	0.557
Lymph node ratio					
0	79	1		1	
0.01–≤0.25	26	3.789 (1.184–12.123)	0.039	3.061 (0.929–12.251)	0.085
>0.25	24	10.286 (3.375–31.353)	<0.001	9.178 (1.288–30.258).	0.031
Lymph node distribution					
0	86	1			
1	35	1.986 (0.912–2.915)	0.298		
2 + 3	15	2.874 (0.822–3.166)	0.211		
Peritumoral lymphocytic infiltrate					
Present	75	1		1	
Poor/absent	54	4.857 (1.285–18.355)	0.020	1.536 (0.659–5.580)	0.696
Lymphovascular invasion					
Absent	69	1		1	
Present	60	31.571 (6.400–55.745)	<0.001	7.580 (1.100–52.235)	0.040
Distal surgical margin (cm)					
>1	99	1			
≤1	30	0.531 (0.167–1.686)	0.283		
Postoperative anastomotic leakage					
No	119	1			
Yes	10	1.807 (0.434–7.529)	0.416		
Neoadjuvant treatment					
No	96	1			
Yes	33	1.650 (0.574–4.746)	0.353		
Adjuvant treatment					
No	41	1		1	
Yes	88	7.967 (2.253–28.174)	<0.001	7.904 (0.274–25.327)	0.228

95% CI 95% confidence interval
†Stepwise logistic regression analysis

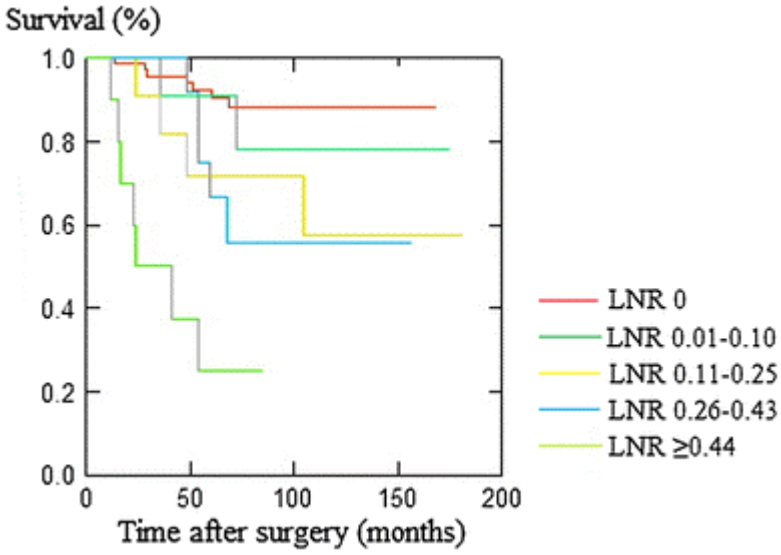

Fig. 1
Overall survival according to lymph node ratio (LNR); P < 0.001, Log rank test

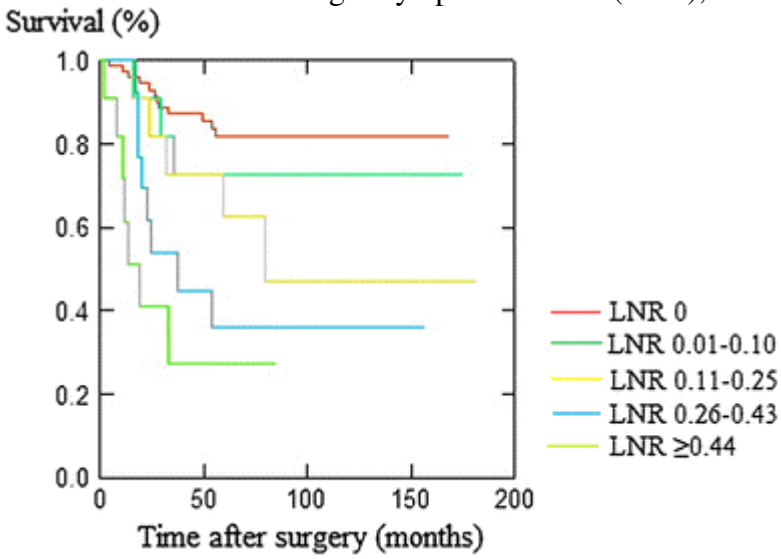

Fig. 2
Disease-free survival according to lymph node ratio (LNR); P < 0.001, Log rank test

Univariate and multivariate analyses were also carried out for the 69 stage I–III patients in whom fewer than 12 LN were examined. Even in the analysis of this subgroup, the LNR >0.25 confirmed its prognostic role for both disease-free survival (p = 0.004 and p = 0.144 at univariate and multivariate analyses, respectively) and overall survival (p = 0.001 and p = 0.155, respectively).

No statistically significant differences were observed for 5-year disease-free survival and overall survival rates between the 19 stage II patients with fewer than 12 LN and the 50 stage III patients (p = 0.245 and p = 0.563, respectively).

Discussion

Evidence-based data support the use of laparoscopic surgery for colon cancer [*5–7*], whereas data on laparoscopic TME with or without a sphincter-saving procedure are limited [*8*, *9*]. Evidence comes mainly from several case series [*4*, *10–12*], comparative nonrandomized studies [*13–15*], or randomized clinical trials (RCTs) [*16–21*] with a limited number of patients or a relatively short follow-up period.

A recent meta-analysis by Huang et al. [*3*] to assess the oncologic adequacy of resection and the oncologic outcomes after laparoscopic versus open surgery for rectal cancer showed that laparoscopic surgery is comparable to open surgery in terms of anatomopathological findings and the local recurrence rate, although no data about the prognostic role of lymphadenectomy were given. To our best knowledge, no clinical trials have analyzed the risk factors for local recurrence, disease-free survival, and overall survival after laparoscopic TME for extraperitoneal rectal cancer over a 5-year minimum follow-up period.

Among the pathological variables associated with oncologic outcome, the number of LN examined in the specimen plays a key role. Accurate pathological staging of colorectal cancer is essential in stage I–III patients in order to select those who might benefit from adjuvant treatment, and it relies on the identification of lymph node metastases [*22*]. A systematic review by Chang et al. [*23*] showed that survival improved as the number of examined LN increased in patients with stage II and III colon cancer. The National Institute of Clinical Excellence (NICE) Colorectal Cancer Guidance and the American Joint Committee on Cancer (AJCC) have recommended that a median of 12 LN should be examined in patients operated on with curative intent-to-treat colorectal cancer [*24*, *25*]. Nevertheless, the number of metastatic LN is related not only to the depth of tumor wall invasion, but also on the number of LN examined [*26–28*], which, in turn, varies depending on several other factors, including patient-related variables (age, gender, body mass index), tumor-related variables (size, stage, and grade), the surgeon, and the pathologist [*29*].

Preoperative CRT leads to a significantly reduced number of LN for examination in the tumor specimen [*30–34*]. It is associated with lymphocyte depletion in the LN and with tissue fibrosis, which makes the LN smaller and more difficult to be identified. We have observed that the proportion of specimens with fewer than 12 examined LN was significantly higher in the group of patients who had neoadjuvant CRT (77.1 vs. 40.7 %; $p < 0.001$). In addition, a higher rate of patients with fewer than 12 LN was found in the group of patients who experienced a local recurrence. Because of the increasing use of neoadjuvant CRT in clinical practice, we believe that the LN status in patients who undergo preoperative treatment should be considered with caution.

Several studies on open surgery have demonstrated that tumor stage is related to the number of LN and vice versa [*35–38*]. A higher number of LN retrieved in the surgical specimen increases the probability of metastatic LN; therefore, patients with stage III rectal cancer might have a higher average number of LN examined than do stage I–II patients [*28*, *39*]. In our study, we observed that the median number of LN harvested was lower in stage I–II patients than in stage III patients ($p = 0.079$). Furthermore, among the stage III patients, there was a higher percentage of pN2 in the group of patients with more than 12 LN in the surgical specimen ($p = 0.100$).

The metastatic LNR, which was initially proposed for patients with esophageal and gastric cancer [*40*, *41*], is expected to yield a more reliable prognosis. Several recent studies have investigated the role of the LNR in colorectal cancer; however, few reported on rectal cancer and none on laparoscopic resection. Ceelen et al. [*42*], in a systematic review of the prognostic value of the LNR in stage III colorectal cancer, stated that it is a stronger prognostic factor than the number of LN for both colon and rectal cancer patients. All identified studies about rectal cancer [*43–50*] showed that the LNR is an independent predictor of overall survival and disease-free survival. In particular, Rosenberg et al. [*46*] in 1,263 rectal cancer patients over a 25-year time period and Peschaud et al. [*47*] in 307 patients with high, mid, or low rectal cancer reported LNR as an independent prognostic factor, even when fewer than 12 LN were examined. Nevertheless, several limitations apply to the interpretation of the results of these studies: most did not separately analyze intra- and extraperitoneal rectal cancer patients [*43*, *46*, *47*], and some included only upper rectal cancer patients [*50*], had a median follow-up period of less than 5 years [*45*, *47–50*], did not report data regarding the surgical technique used [*43*, *49*], or included patients operated on before the introduction of TME [*43*, *46*]. Moreover, different cutoff values for LNR were proposed based mainly on quartiles classification rather than a single value.

To the best of our knowledge, this is the first prospective study to evaluate the role of lymphadenectomy and LNR as prognostic factors after laparoscopic TME for extraperitoneal rectal cancer over a median follow-up period of 122 months. In line with other studies [*44*], our univariate and multivariate analyses showed that a cutoff of 12 LN retrieved in the specimen is a prognostic factor for patients with rectal cancer. We observed a statistical trend toward a higher risk of local recurrence and a worse disease-free survival among patients with fewer than 12 LN harvested. Furthermore, no statistically significant differences were observed in terms of 5-year disease-free survival and overall survival rates between stage II patients with fewer than 12 LN and stage III patients ($p = 0.245$ and $p = 0.563$, respectively), confirming that a minimum of 12 LN may be mandatory to correctly identify node-negative cancers.

At univariate analysis, both 5-year disease-free survival and overall survival significantly decreased with increasing LNR. At multivariate analysis, LNR >0.25 was an independent factor for worse disease-free ($p = 0.015$) and overall survival ($p = 0.031$). The univariate and multivariate analyses carried out for the 69 stage I–III patients with fewer than 12 LN harvested confirmed the prognostic role of the LNR for both disease-free survival ($p = 0.004$ at univariate analysis and $p = 0.144$ at multivariate analysis) and overall survival ($p = 0.001$ and $p = 0.145$, respectively). Our results compare favorably with those reported by Rosenberg et al. [*46*] and Peschaud et al. [*47*], which demonstrated that the LNR they identified was of prognostic relevance independent of the number of resected LN.

Finally, Huh et al. [*51*] recently reported LND as an independent predictor of survival in 1,205 consecutive patients who underwent potentially curative surgery for sigmoid colon or rectal cancer with high ligation of the inferior mesenteric artery. In our series, LND did not show a statistically significant role.

In conclusion, our prospective study highlights the prognostic role of the LNR cutoff value of 0.25 in patients who underwent laparoscopic TME for extraperitoneal rectal cancer, over a long follow-up period. Further prospective large trials are needed to define the LNR cutoff to be used with the TNM staging system and the prognostic significance of LND.

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