



AperTO - Archivio Istituzionale Open Access dell'Università di Torino

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

This is the author's manuscript	
Original Citation:	
Availability:	
This version is available http://hdl.handle.net/2318/128596	since
Published version:	
DOI:10.1007/s00464-012-2694-5	
Terms of use:	
Open Access	
Any one can free by access the full taxt of works meeds available as	

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



## UNIVERSITÀ DEGLI STUDI DI TORINO

The final publication is available at Springer via <u>http://link.springer.com/article/10.1007%2Fs00464-012-2694-5</u>

DOI :10.1007/s00464-012-2694-5

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

Marco Ettore Allaix<sup>1</sup>-, Alberto Arezzo<sup>1</sup>, Paola Cassoni<sup>2</sup>, Massimiliano Mistrangelo<sup>1</sup>, Giuseppe Giraudo<sup>1</sup> and Mario Morino<sup>1</sup>-

(1)

Digestive, Colorectal, Oncologic and Minimally Invasive Surgery, Department of Surgical Sciences, University of Torino, Corso A. M. Dogliotti 14, 10126 Turin, Italy

(2)

Department of Medical Sciences, University of Torino, Turin, Italy

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  $\leq 1$  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  $\geq$ 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  $P \le 0.200$  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)
Ι	41 (26.0)
Ш	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 (%)]	
Ι	48 (30.4)
П	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  $\leq 1$  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  $\leq 1 \text{ cm}$  (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  $\leq 1 \text{ cm}$  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

		Univariate analysis		Multivariate analysis	
	N = 129	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 harv	vested				
≥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					

		Univariate analysis		Multivariate analysis	
	N = 129	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 infi	ltrate				
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 le	akage				
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	
Ν	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		
М					
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 har	vested				
≥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 inf	iltrate				
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 le	akage				
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	y				
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 har	vested				
≥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 inf	iltrate				
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 le	akage				
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





Overall survival according to lymph node ratio (LNR); P < 0.001, Log rank test Survival (%)



#### 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 LN examined [26-28], which, in turn, varies depending on several other factors, including patient-related variables (age, gender, body mass index), tumorrelated 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.

References

1.

MacFarlane JK, Ryall RDH, Heald RJ (1993) Mesorectal excision for rectal cancer. Lancet 341:457–460

2.

Heald RJ, Moran BJ, Ryall RDH, Sexton R, MacFarlane JK (1998) The Basingstoke experience of total mesorectal excision, 1978–1997. Arch Surg 133:894–899 3.

Huang MJ, Liang JL, Wang H, Kang L, Deng YH, Wang JP (2011) Laparoscopic-assisted versus open surgery for rectal cancer: a meta-analysis of randomized controlled trials on oncologic adequacy of resection and long-term oncologic outcomes. Int J Colorectal Dis 26:415–421 4.

Morino M, Parini U, Giraudo G, Salval M, Brachet Contul R, Garrone C (2003) Laparoscopic total mesorectal excision: a consecutive series of 100 patients. Ann Surg 237:335–342

5.

Schwenk W, Haase O, Neudecker J, Müller JM (2005) Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev (3):CD003145 6.

Bonjer HJ, Hop WC, Nelson H, Sargent DJ, Lacy AM, Castells A, Guillou PJ, Thorpe H, Brown J, Delgado S, Kuhrij E, Haglind E, Påhlman L, Transatlantic Laparoscopically Assisted vs Open Colectomy Trials Study Group (2007) Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. Arch Surg 142:298–303

7.

Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer J (2008) Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. Cancer Treat Rev 34:498–504

8.

Breukink S, Pierie JP, Wiggers T (2006) Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev CD005200. doi:<u>10.1002/14651858.CD005200.pub2</u>9.

Poon JTC, Law WL (2009) Laparoscopic resection for rectal cancer: a review. Ann Surg Oncol 16:3038–3047

10.

Staudacher C, Di PS, Tamburini A, Vignali A, Orsenigo E (2007) Total mesorectal excision (TME) with laparoscopic approach: 226 consecutive cases. Surg Oncol 16:S113–S116

11.

Pugliese R, Di Lernia S, Sansonna F, Maggioni D, Ferrari GC, Magistro C, Costanzi A, De Carli S, Artale S, Pugliese F (2009) Laparoscopic resection for rectal adenocarcinoma. Eur J Surg Oncol 35:497–503

12.

Ng KH, Ng DC, Cheung HY, Wong JC, Yau KK, Chung CC, Li MK (2009) Laparoscopic resection for rectal cancers: lessons learned from 579 cases. Ann Surg 249:82–86 13.

Morino M, Allaix ME, Giraudo G, Corno F, Garrone C (2005) Laparoscopic versus open surgery for extraperitoneal rectal cancer: a prospective comparative study. Surg Endosc 19:1460–1467 14.

Bretagnol F, Lelong B, Laurent C, Moutardier V, Rullier A, Monges G, Delpero JR, Rullier E (2005) The oncological safety of laparoscopic total mesorectal excision with sphincter preservation for rectal carcinoma. Surg Endosc 19:892–896

15. Strahl

Strohlein MA, Grutzner KU, Jauch KW, Heiss MM (2008) Comparison of laparoscopic vs open access surgery in patients with rectal cancer: a prospective analysis. Dis Colon Rectum 51:385–391 16.

Araujo SE, da Silva eSousa AH Jr, de Campos FG, Habr-Gama A, Dumarco RB, Caravatto PP, Nahas SC, da Silva J, Kiss DR, Gama-Rodrigues JJ (2003) Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial. Rev Hosp Clin Fac Med Sao Paulo 58:133–140 17.

Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, Heath RM, Brown JM, UK MRC CLASICC Trial Group (2007) Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. J Clin Oncol 25:3061– 3068

18.

Braga M, Frasson M, Vignali A, Zuliani W, Capretti G, Di Carlo V (2007) Laparoscopic resection in rectal cancer patients: outcome and cost-benefit analysis. Dis Colon Rectum 50:464–471 19.

Ng SS, Leung KL, Lee JF, Yiu RY, Li JC, Teoh AY (2008) Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. Ann Surg Oncol 15:2418–2425

20.

Lujan J, Valero G, Hernandez Q, Sanchez A, Frutos MD, Parrilla P (2009) Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer. Br J Surg 96:982–989 21.

Ng SS, Leung KL, Lee JF, Yiu RY, Li JC, Hon SS (2009) Long-term morbidity and oncologic outcomes of laparoscopic-assisted anterior resection for upper rectal cancer: ten-year results of a prospective, randomized trial. Dis Colon Rectum 52:558–566 22.

André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 27:3109–3116

23.

Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA (2007) Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 99:433–441 24.

NICE Improving Outcomes in Colorectal Cancer, Manual Update, London: National Institute for Clinical Excellence, May 2004

25.

Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, Miedema B, Ota D, Sargent D, National Cancer Institute Expert Panel (2001) Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 93:583–596

26.

Goldstein NS, Sanford W, Coffey M, Layfield LJ (1996) Lymph node recovery from colorectal resection specimens removed for adenocarcinoma. Trends over time and a recommendation for a minimum number of lymph nodes to be recovered. Am J Clin Pathol 106:209–216 27.

Hernanz F, Revuelta S, Redondo C, Madrazo C, Castillo J, Gomez-Fleitas M (1994) Colorectal adenocarcinoma: quality of the assessment of lymph node metastases. Dis Colon Rectum 37:373–376

28.

Wong JH, Severino R, Honnebier MB, Tom P, Namiki TS (1999) Number of nodes examined and staging accuracy in colorectal carcinoma. J Clin Oncol 17:2896–2900 29.

Evans MD, Barton K, Rees A, Stamatakis JD, Karandikar SS (2008) The impact of surgeon and pathologist on lymph node retrieval in colorectal cancer and its impact on survival for patients with Dukes' stage B disease. Colorectal Dis 10:157–164 30.

Sermier A, Gervaz P, Egger JF, Dao M, Allal AS, Bonet M, Morel P (2006) Lymph node retrieval in abdominoperineal surgical specimen is radiation time-dependent. World J Surg Oncol 4:29 31.

Wichmann MW, Muller C, Meyer G, Strauss T, Hornung HM, Lau-Werner U, Angele MK, Schildberg FW (2002) Effect of preoperative radiochemotherapy on lymph node retrieval after resection of rectal cancer. Arch Surg 137:206–210 32.

Baxter NN, Morris AM, Rothenberger DA, Tepper JE (2005) Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: a population-based analysis. Int J Radiat Oncol Biol Phys 61:426–431

33.

Nagtegaal ID, van de Velde CJ, van der Worp E, Kapiteijn E, Quirke P, van Krieken JH (2002) Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. J Clin Oncol 20:1729–1734 34.

Rullier A, Laurent C, Capdepont M, Vendrely V, Belleannée G, Bioulac-Sage P, Rullier E (2008) Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: number, status, and impact on survival. Am J Surg Pathol 32:45–50

35.

Joseph NE, Sigurdson ER, Hanlon AL, Wang H, Mayer RJ, MacDonald JS, Catalano PJ, Haller DG (2003) Accuracy of determining nodal negativity in colorectal cancer on the basis of the number of nodes retrieved on resection. Ann Surg Oncol 10:213–218

36.

Jakub JW, Russell G, Tillman CL, Lariscy C (2009) Colon cancer and low lymph node count. Who is to blame? Arch Surg 144:1115–1120

37.

Baxter NN, Virnig DJ, Rothenberger DA, Morris AM, Jessurun J, Virnig BA (2005) Lymph node evaluation in colorectal cancer patients: a population-based study. J Natl Cancer Inst 97:219–225 38.

Gelos M, Gelhaus J, Mehnert P, Bonhag G, Sand M, Philippou S, Mann B (2008) Factors influencing lymph node harvest in colorectal surgery. Int J Colorectal Dis 23:53–59 39.

Tepper JE, O'Connell MJ, Niedzwiecki D, Hollis D, Compton C, Benson AB 3rd, Cummings B, Gunderson L, Macdonald JS, Mayer RJ (2001) Impact of number of nodes retrieved on outcome in patients with rectal cancer. J Clin Oncol 19:157–163 40.

Marchet A, Mocellin S, Ambrosi A, Morgagni P, Garcea D, Marrelli D, Roviello F, de Manzoni G, Minicozzi A, Natalini G, De Santis F, Baiocchi L, Coniglio A, Nitti D, Italian Research Group for Gastric Cancer (IRGGC) (2007) The ratio between metastatic and examined lymph nodes (N Ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy: results of an Italian multicentric study in 1853 patients. Ann Surg 245:543–552 41.

Mariette C, Piessen G, Briez N, Triboulet JP (2008) The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in oesophageal cancer regardless of neoadjuvant chemoradiation or lympadenectomy extent. Ann Surg 247:365–371

42.

Ceelen W, Van Nieuwenhove Y, Pattyn P (2010) Prognostic value of the lymph node ratio in stage III colorectal cancer: a systematic review. Ann Surg Oncol 17:2847–2855 43.

Stocchi L, Nelson H, Sargent DJ, O'Connell MJ, Tepper JE, Krook JE, Beart R Jr, North Central Cancer Treatment Group (2001) Impact of surgical and pathologic variables in rectal cancer: a United States Community and Cooperative Group report. J Clin Oncol 19:3895–3902 44.

Edler D, Ohrling K, Hallström M, Karlberg M, Ragnhammar P (2007) The number of analyzed lymph nodes - a prognostic factor in colorectal cancer. Acta Oncol 46:975–981 45.

Peng JJ, Xu Y, Guan ZQ, Zhu J, Wang M, Cai G, Sheng W, Cai S (2008) Prognostic significance of the metastatic lymph node ratio in node-positive rectal cancer. Ann Surg Oncol 15:3118–3123 46.

Rosenberg R, Friederichs J, Schuster T, Gertler R, Maak M, Becker K, Grebner A, Ulm K, Höfler H, Nekarda H, Siewert JR (2008) Prognosis of patients with colorectal cancer is associated with lymph node ratio. A single-center analysis of 3026 patients over a 25-year time period. Ann Surg 248:968–978

47.

Peschaud F, Benoist S, Julié C, Beauchet A, Penna C, Rougier P, Nordlinger B (2008) Prognosis of patients with colorectal cancer is associated with lymph node ratio: a single-center analysis of 3026 patients over a 25-year time period. Ann Surg 248:1067–1073 48.

Kim YS, Kim JH, Yoon SM, Choi EK, Ahn SD, Lee SW, Kim JC, Yu CS, Kim HC, Kim TW, Chang HM (2009) Lymph node ratio as a prognostic factor in patients with stage III rectal cancer treated with total mesorectal excision followed by chemoradiotherapy. Int J Radiat Oncol Biol Phys 74:796–802

49.

Moug SJ, Saldanha JD, McGregor JR, Balsitis M, Diament RH (2009) Positive lymph node retrieval ratio optimises patient staging in colorectal cancer. Br J Cancer 100:1530–1533 50.

Priolli DG, Cardinalli IA, Pereira JA, Alfredo CH, Margarido NF, Martinez CA (2009) Metastatic lymph node ratio as an independent prognostic variable in colorectal cancer: study of 113 patients. Tech Coloproctol 13:113–121

51.

Huh JW, Kim YJ, Kim HR (2012) Distribution of lymph mode metastases is an independent predictor of survival for sigmoid colon and rectal cancer. Ann Surg 255:70–78