RESEARCH ARTICLE

Lymph Node Ratio is an Independent Prognostic Factor in Node Positive Rectal Cancer Patients Treated with Preoperative Chemoradiotherapy Followed by Curative Resection

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Abstract

Background: The lymph node ratio (LNR) has been shown to be an important prognostic factor for colorectal cancer. However, studies focusing on the prognostic impact of LNR in rectal cancer patients who received neoadjuvant chemoradiotherapy (CRT) followed by curative resection have been limited. The aim of this study was to investigate LNR in rectal cancer patients who received neoadjuvant chemoradiotherapy (CRT) followed by curative resection. Materials and Methods: A total of 131 consecutive rectal cancer patients who underwent neoadjuvant CRT and total mesorectal excision were included in this study. Patients were divided into two groups according to the LNR (≤0.2 [n=86], >0.2 [n=45]) to evaluate the prognostic effect on overall survival (OS) and disease-free survival (DFS). Results: The median number of retrieved and metastatic lymph node (LN) was 14 (range 1-48) and 2 (range 1-10), respectively. The median LNR was 0.154 (range 0.04-1.0). In multivariate analysis, LNR was shown to be an independent prognostic factor for both overall survival (hazard ratio[HR]= 3.778; 95% confidence interval [CI] 1.741-8.198; p=0.001) and disease-free survival (HR=3.637; 95%CI 1.838-7.195; p<0.001). Increased LNR was significantly associated with worse OS and DFS in patients with <12 harvested LNs, and as well as in those ≥12 harvested LNs (p<0.05). In addition, LNR had a prognostic impact on both OS and DFS in patients with N1 staging (p<0.001). Conclusions: LNR is an independent prognostic factor in ypN-positive rectal cancer patients, both in patients with <12 harvested LNs, and as well as in those ≥12 harvested LNs. LNR provides better prognostic value than pN staging. Therefore, it should be used as an additional prognostic indicator in ypN-positive rectal cancer patients.

Keywords: Lymph lode ratio - rectal cancer - prognosis - preoperative chemoradiation

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Introduction

The number of metastatic lymph nodes (LNs) has been demonstrated to be one of the most important prognostic factors in colorectal cancer (Greene et al., 2002). However, the number of metastatic LNs is not only related to the severity of disease, but also depends on the number of retrieved LNs. For this reason, lymph node ratio (LNR; number of metastatic LNs/number of harvested LNs) has been studied in colorectal cancer to complement the current staging system for more precise prediction of patient prognosis (Peschaud et al., 2008; Rosenberg et al., 2008; Kim et al., 2009; Moug et al., 2009). These studies have found that, LNR is not only an important prognostic indicator, but also a more accurate stratification system than the current metastatic lymph node number-based staging system in colorectal cancer (Peschaud et al., 2008; Rosenberg et al., 2008; Kim et al., 2009; Moug et al., 2009).

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is the current standard of care for patients with T3 or T4 tumors and/or positive lymph nodes (Kapiteijn et al., 2001; Sauer et al., 2004). However, some studies have demonstrated that the number of harvested LNs is significantly decreased in rectal cancer patients received preoperative CRT (Rullier et al., 2008; Doll et al., 2009; Wang et al., 2009). The number of harvested LNs in rectal cancer patients treated with preoperative CRT is frequently fewer than 12, as recommend by the American Joint Committee on Cancer (AJCC) and the National Cancer Institute (Goldstein et al., 1996). Therefore, LNR, which takes both the number of positive LNs and harvested LNs into consideration, may serve as a better prognostic indicator in rectal cancer patients received preoperative CRT. The aim of this study is to evaluate the impact of LNR on prognosis in ypN-positive rectal cancer patients.

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Materials and Methods

We performed a retrospective review of a prospectively entered database, from January 1999 to December 2011, a total of 140 consecutive patients with primary rectal cancer treated with preoperative CRT followed by curative resection were pathologically diagnosed with node-positive (ypN-positive) rectal cancer at our institution. Nine patients were excluded from this study (five were lost to follow-up, one was died of postoperative complication, three refused to receive postoperative chemotherapy). The remaining 131 patients were included in the analysis.

All the patients underwent digital rectal examination, colonoscopy, abdominal and pelvic computed tomography (CT), and chest X-ray for clinical staging. Transrectal ultrasonography was performed in 102 (77.9%) patients, and 118 (90.1%) patients received pelvic magnetic resonance imaging for preoperative staging. Preoperative CRT was delivered to patients who had a clinical stage of T3 or T4 and/or positive lymph nodes.

The details on radiotherapy have been previously published (Jin et al., 2006). In brief, a total dose of 50 Gy was delivered in 2.0-Gy daily fractions to the pelvic area. Preoperative chemotherapy was initiated on the first day of radiotherapy. Capecitabine was administered concurrently with radiotherapy at a dose of 1, 600 mg/m2/day for 35 days

After preoperative CRT, all patients underwent curative resection, and TME principle was followed for every patient. The median interval between preoperative CRT and surgery was 7 weeks (range 6-8 weeks).

Postoperative specimens were examined by at least two pathologists specialized in colorectal cancer. When less than 12 lymph nodes were found, re-examination was performed by a third pathologist. The pathologic stage of the tumor was determined according to the American Joint Committee on Cancer (seventh Edition) staging system.

About 3 to 6 weeks after completing the surgery, all the patients received postoperative chemotherapy. Two different chemotherapy regimens were used: (1) capecitabine, and (2) oxaliplatin, leucovorin, and 5-fluorouracil.

After hospital discharge, patients were suggested to visit the doctors every 3 month within first 2 years and every 6 month thereafter. During each follow-up, patients received a series of evaluations, including digital rectal examination, complete blood count, liver function test, and carcinoembryonic antigen (CEA) level test. Abdominal and pelvic computed tomography (CT), and chest X-ray were conducted every 6 months after surgery. Colonoscopy was performed per year after surgery.

Statistical analysis

Continuous variables are expressed as median and range, and were analyzed with the Student's t-test, while categorical ones are expressed as numbers with percentages, and were analyzed by chi-square test or Fisher's exact test when appropriate. Overall survival (OS) was defined from the date of operation to the date of death. Disease-free survival (DFS) was defined as the time from operation to local recurrence, metastasis, or death. Kaplan-Meier method was used to analyze survival of patients, and comparisons were analyzed by log-rank test. Cox's proportional hazards model was used for multivariate analysis, adjusted hazard ratios (HRs) and their 95%CIs were calculated. All statistical tests were two-sided, and a P value of less than 0.05 was considered statistically significant. Data were analyzed by Statistical Package for the Social Science (SPSS) 18.0 for Windows (SPSS Inc. Chicago, IL, USA).

Results

Patient characteristics

The clinicopathological characteristics of the patients are detailed in Table 1. The median age of patients was 56 years (range 26-86 years). Eighty-two (62.6%) patients underwent low anterior resection (LAR), 44 (33.6%) patients underwent abdominoperineal resection (APR), 5 (3.8%) patients underwent Hartmann's operation. The median harvested and metastatic lymph node numbers were 14 (range 1-48) and 2 (range 1-10). Less than 12 LNs were harvested in 43 (32.8%) patients. The median LNR was 0.154 (range 0.04-1.0), and the median follow-up was 49 months (range 6-103 months).

According to LNR of patient, patients were divided into two groups (≤ 0.2[n=86], >0.2[n=45]). With increased LNR, both ypT and ypN stage increased (p<0.01). The proportion of patients whose harvested LNs <12 was

Table 1. Comparison of Clinicopathological Characteristics of Patients accrording to Lymph Node Ratio (LNR)

Characteristics	Total (n=131)	LNR		*P* value
		≤ 0.2 (n=86)	0.2 (n=45)	
Age (median, years)	56 (26-86)	55 (26-83)	57 (36-86)	0.261
Sex (%)				0.977
Male	73 (55.7)	48 (55.8)	25 (55.6)	
Female	58 (44.3)	38 (44.2)	20 (44.4)	
Tumor location (%)				0.794
Mid (5-10cm)	95 (72.5)	63 (73.3)	32 (71.1)	
Low (0-5cm)	36 (27.5)	23 (26.7)	13 (28.9)	
Preoperative CEA (%)				0.786
≤5 ng/ml	72 (55.0)	48 (55.8)	24 (53.3)	
>5 ng/ml	59 (45.0)	38 (44.2)	21 (46.7)	
Type of surgery (%)				0.964
LAR	82 (62.6)	54 (62.8)	28 (62.2)	
APR	44 (33.6)	29 (33.7)	15 (33.3)	
Hartmann's operation	5 (3.8)	3 (3.5)	2 (4.4)	
ypT stage (%)				0.002
ypT0-2	77 (58.8)	59 (68.6)	18 (40.0)	
ypT3-4	54 (41.2)	27 (31.4)	27 (60.6)	
ypN stage (%)				<0.001
ypN1	90 (68.7)	70 (81.4)	20 (44.4)	
ypN2	41 (31.3)	16 (18.6)	25 (55.6)	
No. of harvested LNs (%)				0.005
<12	43 (32.8)	21 (24.4)	22 (48.9)	
≥12	88 (67.2)	65 (75.6)	23 (51.1)	
CRM (%)				0.626
Negative	124 (94.7)	82 (95.3)	42 (93.3)	
Positive	7 (5.3)	4 (4.7)	3 (6.7)	
Tumor differentiation (%)				0.527
Well	26 (19.8)	15 (17.4)	11 (24.4)	
Moderate	73 (55.7)	48 (55.8)	25 (55.6)	
Poor	32 (24.4)	23 (26.7)	9 (20.0)	

CEA, carcinoembryonic antigen; LAR, low anterior resection; APR, abdominoperineal resection; LN, lymph node; CRM, circumferential resection margin

significantly higher in high LNR group (48.9% *vs* 24.4%, p=0.005). Other clinicopathologic characteristics, such as age, sex, tumor location, were not significantly different between two groups.

Prognostic factor for survival

In univariate analysis (Table 2), LNR, ypT stage, and ypN stage were significantly associated with OS and DFS. Other clinicopathologic characteristics, such as age, gender, and type of surgery, were not significantly associated with OS or DFS. In multivariate analysis (Table 3), LNR was identified as an independent prognostic factor for both OS (HR=3.778; 95%CI 1.741-8.198; p=0.001) and DFS (HR=3.637; 95%CI 1.838-7.195; p<0.001). ypN stage was also demonstrated to be an independent prognostic factor for OS (HR=2.264; 95%CI 1.097-4.673; p=0.027)and DFS (HR=2.223; 95%CI 1.157-4.310; p=0.017).

Table 2. Table 2 Univariate Analysis of the Effect of Covariates on Overall and Disease-Free Survival

Characteristics	Overall survival 5-year (%)	P value	Disease-free survival 5-year (%)	P value
Age (years)		0.377		0.299
≤56	67.5		57.1	
<56	76.2		65.7	
Sex		0.45		0.858
Male	73		61.5	
Female	69.8		60.9	
Tumor location		0.628		0.17
Mid (5-10cm)	74.9		66.3	
Low (0-5cm)	63		48.8	
Preoperative CEA		0.24		0.19
≤5 ng/ml	75.8		66	
<5 ng/ml	66.1		55	
Type of surgery (%)		0.474		0.223
LAR	78.1		66.8	
APR	60.4		53.7	
Hartmann's operation	60		30	
ypT stage (%)		0.021		0.01
ypT0-2	81.4		70.6	
ypT3-4	59.5		49.5	
ypN stage (%)		<0.001		<0.001
ypN1	82.5		75.6	
ypN2	52.8		34.1	
No. of harvested LNs (%)		0.85		0.828
<12	69.8		60.4	
≥12	70		61.9	
CRM (%)		0.182		0.542
Negative	73.2		61.7	
Positive	45.7		57.1	
Tumor differentiation		0.638		0.621
Well	66.5		57.4	
Moderate	71.4		61.8	
Poor	76.1		64.4	
LNR		<0.001		<0.001
≤0.2	86.2		78.9	
<0.2	47.8		30	

CEA, carcinoembryonic antigen; LAR, low anterior resection; APR, abdominoperineal resection; LN, lymph node; CRM, circumferential resection margin; LNR, lymph node ratio

Subgroup analysis according to number of harvested LNs and ypN classification

As we found LNR was an independent prognostic factor for OS and DFS, we next evaluated the prognostic value of LNR in different subgroups (Table 4). Firstly, the prognostic impact of LNR was analyzed according to the number of harvested LNs. Increased LNR was significantly associated with worse OS and DFS in patients with <12 harvested LNs, and as well as in those≥12 harvested LNs (p<0.05). In order to find out whether LNR had a prognostic impact in each ypN classification, we performed a subgroup analysis based on LNR in patients with ypN1 and ypN2 stages, respectively. In the ypN1 subgroup, increased LNR was significantly associated with reduced OS and DFS rates (p<0.001). In the ypN2 subgroup, increased LNR also associated with worse OS and DFS, but the difference did not reach statistically significant (p>0.05). According to LNR, patients in ypN1

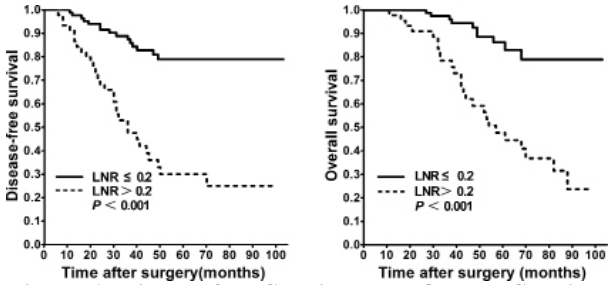

Figure 1. Disease-free Survival and Overall Survival According to Lymph Node Ratio (LNR)

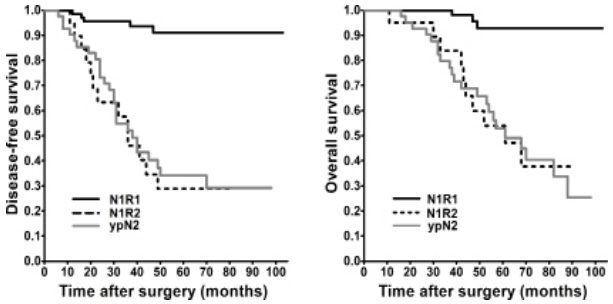

Figure 2. Comparison of overall survival (OS) and Disease-free Survival (DFS) According to N1G1, N1G2, and ypN2. ypN1 patients with an LNR>0.2 (N1R2) had a significantly worse 5-year OS (53.9% vs 92.9%; P<0.001) and DFS (28.8% vs 91.1%; P<0.001) than ypN1 patients with an LNR≤0.2 (N1R1). Patients in N1R2 group had similar 5-year OS (53.9% vs 52.8%; P=0.930) and DFS (28.8% vs 34.1%; P=0.738) rates to ypN2 group

Table 3. Multivariate Analysis of The Effect of Covariates on Overall and Disease-Free Survival

Characteristics	Overall survival			Disease-free survival		
	HR	95%CI	*P* value	HR	95%CI	*P* value
ypN stage (N2/N1)	2.264	1.097-4.673	0.027	2.223	1.157-4.310	0.017
LNR:>0.2	3.778	1.741-8.198	0.001	3.637	1.838-7.195	<0.001

*HR, hazard ratio; CI, confidence interval; LNR, lymph node ratio

Table 4. Subgroup Analysis of the Effect of Covariates on Survival according to the Number of Harvested Lymph Nodes and ypN Stage

Characteristics	No. of patients	Overall survival				Disease-free survival			
		5-year (%)	HR	95%CI	*P* value	5-year (%)	HR	95%CI	*P* value
No. of harvested LNs < 12					0.03				0.005
LNR≤0.2	21	90.9	1			95.2	1		
LNR>0.2	22	53.3	9.755	1.253-75.966		31	18.151	2.382-138.286	
No. of harvested LNs ≥ 12					<0.001				<0.001
LNR≤0.2	65	84.6	1			73.7	1		
LNR>0.2	23	41.6	4.838	2.080-11.253		28.3	4.232	2.032-8.816	
ypN1					<0.001				<0.001
LNR≤0.2	70	92.9	1			91.1	1		
LNR>0.2	20	53.9	11.189	3.076-40.704		28.8	12.12	4.305-34.121	
ypN2					0.289				0.541
LNR≤0.2	16	66.5	1			37.5	1		
LNR>0.2	25	42.4	1.635	0.659-4.059		31.2	1.281	0.580-2.830	

LN, lymph node; LNR, lymph node ratio; HR, hazard ratio; CI, confidence interval

group could be divided into two groups (N1R1 *vs* N1R2). Patients in N1R2 group had similar 5-year OS (53.9% *vs* 52.8%; p=0.930) and DFS (28.8% *vs* 34.1%; p=0.738) rates to ypN2 group (Figure 2).

Discussion

Preoperative CRT followed by total mesorectal excision is now standard treatment for rectal cancer patients with T3 or T4 tumors and/or positive lymph nodes (Kapiteijn et al., 2001; Sauer et al., 2004; Lee et al., 2013). Adequate examination of the regional lymph node plays a vital role in the prediction of patient prognosis, as lymph node involvement after preoperative CRT is the most important prognostic factor in these patients (Kim et al., 2006; Chang et al., 2009). According to current TNM staging system, at least 12 LNs are needed for accurate nodal staging. Many factors influence the number of lymph nodes retrieved, including tumor (size, stage) (Baxter et al., 2005), and the patient (age, sex) (Thorn et al., 2004; Gao et al., 2013), and neoadjuvant CRT (Rullier et al., 2008; Doll et al., 2009; Wang et al., 2009). Recent studies demonstrated that the total number of retrieved LNs was decreased due to preoperative chemoradiation, probably because of lymph node atrophy, fibrosis and lymphocyte depletion caused by radiotherapy or/and chemotherapy, and the number of harvested LNs was frequently less than12, despite the maintenance of vigorous surgical standards (Rullier et al., 2008; Doll et al., 2009; Wang et al., 2009; Lee et al., 2012). Lee et al. (2012) found that <12 LNs were harvested in 30.5% patients after preoperative CRT. Similarly, we found that <12 LNs were retrieved in 32.8% patients.

In the 7th AJCC staging system, nodal staging system for colorectal cancer is solely based on the number of metastatic lymph nodes. In order to complement the current staging system for more precise prediction of patient prognosis, LNR, incorporating both the number of harvested LNs and positive LNs in one prognostic value, has shown to be an important prognostic indicator for colorectal cancer patients received postoperative adjuvant treatment (Peschaud et al., 2008; Rosenberg et al., 2008; Kim et al., 2009; Moug et al., 2009). However, studies of prognostic value of LNR in rectal cancer patients treated with preoperative CRT are limited.

In the current study, we investigated the prognostic value of LNR in 131 rectal cancer patients treated with preoperative CRT followed by curative resection. In multivariate analysis, LNR showed to be an independent prognostic factor for both OS and DFS. In subgroup analysis, LNR was also significantly associated with OS and DFS in patients with <12 harvested LNs, and as well as in those≥12 harvested LNs. Moreover, LNR had a prognostic impact on both OS and DFS in patients with N1 stage. Subgroups of the ypN1 stage divided by the cut-off value 0.2 of LNR showed a different prognosis. ypN1 patients with an LNR>0.2 had a significantly worse 5-year OS (53.9% *vs* 92.9%; p<0.001) and DFS (28.8% *vs* 91.1%; p<0.001) than ypN1 patients with an LNR≤0.2. Although previous studies indicate that lymph node involvement after preoperative CRT is the most important prognostic factor (Kim et al., 2006; Chang et al., 2009), our results demonstrated the limitations of the currently used ypN staging system, which, in fact, was not originally designed to stratify patients after neoadjuvant CRT. Our results showed that LNR could stratify patient prognosis more accurately than pN staging. The superior stratification power of LNR over ypN stage might be due to the fact that patient grouping by LNR is less influenced by the total number of harvested LNs than patient grouping by ypN stage.

There are several limitations in our study. Because this study was not prospectively designed, it is subject to potential bias. The cutoff value of LNR is different from other studies (Kang et al., 2011; Klos et al., 2011; La et al., 2013; Madbouly et al., 2013; Nadoshan et al., 2013). In fact, the cutoff value varies among different studies, ranged from 0.07 to 0.6 (Madbouly et al., 2013). However, all of these studies find that LNR is a powerful predictor of outcome and sometimes even more powerful than nodal status. In accordance with our study, Nadoshan et al. (2013) demonstrated that LNR >0.2 was a significant prognostic factor for survival in patients with stage III rectal cancer undergoing pre-operative chemoradiotherapy. Nevertheless, Madbouly et al. (2013) showed that a cutoff value of 0.375 was determined to be

the most accurate predictive point. These different cutoff values could be explained by the disproportion of patient grouping according to ypN stage, LNR, and mean number of LNs retrieved. The inconsistent cutoff value of LNR remains one of the limitations of validation in clinical practice. Prospective studies are needed to define the LNR cutoff value that will optimize patient prognosis in stage III rectal cancer.

In conclusion, LNR is an independent prognostic factor for OS and DFS in ypN-positive rectal cancer patients, both in patients with <12 harvested LNs, and as well as in those≥12 harvested LNs. In addition, LNR has a prognostic impact on both OS and DFS in patients with N1 staging. LNR provides better prognostic value than pN staging. Therefore, LNR should be used as an additional prognostic indicator in ypN-positive rectal cancer patients.

References

Baxter NN, Virnig DJ, Rothenberger DA, et al (2005). Lymph node evaluation in colorectal cancer patients: a population-based study. *J Natl Cancer Inst*, **97**, 219-25.

Chang GJ, Rodriguez-Bigas MA, Eng C, Skibber JM (2009). Lymph node status after neoadjuvant radiotherapy for rectal cancer is a biologic predictor of outcome. *Cancer*, **115**, 5432-40.

Doll D, Gertler R, Maak M, et al (2009). Reduced lymph node yield in rectal carcinoma specimen after neoadjuvant radiochemotherapy has no prognostic relevance. *World J Surg*, **33**, 340-7.

Gao C, Li JT, Fang L, Wen SW, Zhang L, Zhao HC (2013). Pre-operative predictive factors for intra-operative pathological lymph node metastasis in rectal cancers. *Asian Pac J Cancer Prev*, **14**, 6293-9.

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**, 209-16.

Greene FL, Stewart AK, Norton HJ (2002). A new TNM staging strategy for node-positive (stage III) colon cancer: an analysis of 50, 042 patients. *Ann Surg*, **236**, 416-21.

Jin J, Li YX, Liu YP, et al (2006). A phase I study of concurrent radiotherapy and capecitabine as adjuvant treatment for operable rectal cancer. *Int J Radiat Oncol Biol Phys*, **64**, 725-9.

Kang J, Hur H, Min BS, Lee KY, Kim NK (2011). Prognostic impact of the lymph node ratio in rectal cancer patients who underwent preoperative chemoradiation. *J Surg Oncol*, **104**, 53-8.

Kapiteijn E, Marijnen CA, Nagtegaal ID, et al (2001). Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*, **34**, 638-46.

Kim NK, Baik SH, Seong JS, et al (2006). Oncologic outcomes after neoadjuvant chemoradiation followed by curative resection with tumor-specific mesorectal excision for fixed locally advanced rectal cancer:Impact of postirradiated pathologic downstaging on local recurrence and survival. *Ann Surg*, **244**, 1024-30.

Kim YW, Kim NK, Min BS, et al (2009). The influence of the number of retrieved lymph nodes on staging and survival in patients with stage II and III rectal cancer undergoing tumor-specific mesorectal excision. *Ann Surg*, **249**, 965-72.

Klos CL, Bordeianou LG, Sylla P, Chang Y, Berger DL (2011). The prognostic value of lymph node ratio after neoadjuvant chemoradiation and rectal cancer surgery. *Dis Colon Rectum*, **54**, 171-5.

La Torre M, Mazzuca F, Ferri M, et al (2013). The importance of lymph node retrieval and lymph node ratio following preoperative chemoradiation of rectal cancer. *Colorectal Dis*, **5**, 382-8.

Lee SD, Kim TH, Kim DY, et al (2012). Lymph node ratio is an independent prognostic factor in patients with rectal cancer treated with preoperative chemoradiotherapy and curative resection. *Eur J Surg Oncol*, **38**, 478-83.

Lee WC, Yusof MM, Lau FN, Phua VC (2013). Preoperative long course chemoirradiation in a developing country for rectal carcinoma: Kuala Lumpur hospital experience. *Asian Pac J Cancer Prev*, **14**, 3941-4.

Madbouly KM, Abbas KS, Hussein AM (2013). Metastatic lymph node ratio in stage III rectal carcinoma is a valuable prognostic factor even with less than 12 lymph nodes retrieved: a prospective study. *Am J Surg*, [Epub ahead of print].

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**, 1530-3.

Nadoshan JJ, Omranipour R, Beiki O, et al (2013). Prognostic value of lymph node ratios in node positive rectal cancer treated with preoperative chemoradiation. *Asian Pac J Cancer Prev*, **14**, 3769-72.

Peschaud F, Benoist S, Julie C, et al (2008). The ratio of metastatic to examined lymph nodes is a powerful independent prognostic factor in rectal cancer. *Ann Surg*, **248**, 1067-73.

Rosenberg R, Friederichs J, Schuster T, et al (2008). Prognosis of patients with colorectal cancer is associated with lymph node ratio: a single-center analysis of 3, 026 patients over a 25-year time period. *Ann Surg*, **248**, 968-78.

Rullier A, Laurent C, Capdepont M, et al (2008). Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma:number, status, and impact on survival. *Am J Surg Pathol*, **32**, 45-50.

Sauer R, Becker H, Hohenberger W, et al (2004). Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*, **351**, 1731-40.

Thorn CC, Woodcock NP, Scott N, et al (2004). What factors affect lymph node yield in surgery for rectal cancer? *Colorectal Dis*, **6**, 356-61.

Wang H, Safar B, Wexner S, et al (2009). Lymph node harvest after proctectomy for invasive rectal adenocarcinoma following neoadjuvant therapy: does the same standard apply? *Dis Colon Rectum*, **52**, 549-57.