

RESEARCH ARTICLE

Prognostic Value of Lymph Node Ratios in Node Positive Rectal Cancer Treated with Preoperative Chemoradiation

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Abstract

Background: To investigate the impact of the lymph node ratio (LNR) on the prognosis of patients with locally advanced rectal cancer undergoing pre-operative chemoradiation. **Methods:** Clinicopathologic and follow up data of 128 patients with stage III rectal cancer who underwent curative resection from 1996 to 2007 were reviewed. The patients were divided into two groups according to the lymph node ratio: LNR ≤ 0.2 (n=28), and >0.2 (n=100). Kaplan-Meier and the Cox proportional hazard regression models were used to evaluate the prognostic effects according to LNR. **Results:** Median numbers of lymph nodes examined and lymph nodes involved by tumour were 10.3 (range 2-28) and 5.8 (range 1-25), respectively, and the median LNR was 0.5 (range, 0-1.6). The 5-year survival rate significantly differed by LNR (≤ 0.2 , 69%; >0.2 , 19%; Log-rank p value < 0.001). LNR was also a significant prognostic factor of survival adjusted for age, sex, post-operative chemotherapy, total number of examined lymph nodes, metastasis and local recurrence (≤ 0.2 , HR=1; >0.2 , HR=4.8, 95% CI=2.1-11.1) and a significant predictor of local recurrence and distant metastasis during follow-up independently of total number of examined lymph node. **Conclusions:** Total number of examined lymph nodes and LNR were significant prognostic factors for survival in patients with stage III rectal cancer undergoing pre-operative chemoradiotherapy.

Keywords: Node ratio - rectal cancer - prognosis - preoperative chemoradiation

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Introduction

Lymph nodes involvement is an important factor that has a significant effect on the prognosis of colorectal cancer patients (Elder et al., 2007; Simunovic et al., 2009; Kotake et al., 2012). According to the guidelines for colorectal cancer from the AJCC/UICC, a minimum of twelve lymph nodes must be retrieved and examined for accurate staging (Edge et al., 2010). Currently, to perform surgical staging of the colorectal cancer, the total number of resected lymph nodes will consider which might be varying substantially depending on the surgical situations (Shimomura et al., 2011). In addition to adequate surgical resection and precise pathologic examination several factors influence the number of lymph nodes retrieved after curative resection. One of these factors is preoperative chemoradiation therapy which is now standard treatment for locally advanced rectal cancers patients. These neoadjuvant therapies result in a significant decrease in the number and size of retrieved lymph nodes (Wichmann et al., 2002; Baxter et al., 2005) Therefore cases of insufficient retrieved lymph nodes are not infrequent among locally advanced rectal cancer patients who need an additional prognostic index for their adjuvant treatment decisions.

Recent studies showed LNR which means the ratio of involved to the total resected lymph nodes is a better prognosis predictor than pathological node (pN) classification in node positive colorectal cancer patients and sometimes it has been found as an important predictive factor of mortality and recurrence (Rosenberg et al., 2008; 2010; Ainsworth et al., 2010; Qiu et al., 2011; Tong et al., 2011). So the aim of the this study was to investigate the impact of LNR on prognosis, recurrence and survival of locally advanced rectal cancers patients in the presence of preoperative chemoradiation effect on the number of retrieved lymph nodes.

Materials and Methods

One hundred twenty eight cases of stage III rectal cancer undergoing a radical resection after preoperative chemoradiation over 11 years in Cancer Institute of Iran were included. Patients who had complete pathologic response after preoperative chemoradiation and patients who had no retrieved lymph node in proctectomy specimens were excluded.

All patients had undergone radical resection 4-6 weeks after neoadjuvant chemoradiation. During the study, the concurrent chemotherapy regime has changed

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from the continuous infusion of 5-fluorouracil (5-FU) in days 1-4 and 29-33 of radiotherapy in the first 5 years of study to oral capecitabine 825mg/m twice daily as the radiosensitizer for all duration of radiotherapy. The radiotherapy course included 45 GY in 25 fraction over 33 days.

Cancer research center of Cancer Institute of Iran approved this study on march 2011. No ethical consideration was applied to this study.

Recorded clinicopathologic features included age and gender of the patients, the tumours depths and differentiation, the number of harvested lymph nodes, the number of involved lymph nodes and the LNR. The LNR was defined as the number of metastatic lymph nodes (LNs) divided by the number of LNs retrieved.

The LNR was divided in two groups (≤ 0.2 and > 0.2) concerning the mean and median in the sample.

Follow up data were available in all patients. Follow-up was performed through tumor marker every two month for the first year, every four month for the second year, and at six month interval for the next three years. Chest xray and abdominal and pelvic ultrasonography was performed every six month and abdominal and pelvic computed tomography was performed annually. Colonoscopy was done in the first yr of follow up and if negative three years later and five years thereafter. Follow up was done from the time of diagnosis until death, recurrence and metastasis. Local recurrence and metastasis was confirmed histologically. Cause of death was registered for patients who died during follow-up.

The statistical analysis was made using statistical package for social science (SPSS Inc., Chicago, IL, USA, version 20). Survival curve was prepared by Kaplan-Meier analysis. Log-rank method and Cox proportional hazard ratio were used for univariate and multivariate analysis of prognostic factors. P value < 0.05 was considered significant.

Results

We studied 128 patients including 61 women (48%) and 67 men (52%). Patients had ages between 16 and 85 years with mean of 49 years. All patients had rectal adenocarcinoma and in 35 patients (27.3%) including 21 male and 14 female tumors was located in rectosigmoid junction. The tumors were well differentiated in 37%, medium differentiated in 40%, un-differentiated in 13% and mucinous in 10%.

Mean number of total examined lymph nodes was 10.3 ranging from 2 and 28. Mean number of involved lymph nodes was 5.8 ranging from 1 to 25. Only in 39 patients 12 or more than 12 lymph nodes were harvested and in 61 patients the number of harvested lymph nodes was 7-11. In the remaining 28 patients less than 7 lymph nodes were detected by pathologic examination. Fifty percent of patients received adjuvant chemotherapy. Mean duration of follow up was 39 months (range 1-156).

During follow-up 64 (50%) of patients showed systemic metastasis and 58 (45%) showed local recurrence and 79 (62%) died. There were no difference between men and women regarding metastasis (31 female, 33 male, p

value: 0.586), recurrence (25 female, 33 male, p value: 0.35) and death (38 female, 41 male, P value: 0.80).

We found seven times higher risk of local recurrence among patients with LNR more than 0.2 compared with patients with LNR less than or equal to 0.2 (54 versus 4, respectively) (Table 1, 2 and Figure 1). Risk of metastasis was similar between two groups by LNR, while risk of death was 7 times higher among patients with LNR more than 0.2 compared with patients with LNR less than or equal to 0.2 (72 versus 7, respectively) (Figure 2 and 3).

To determine the effect of LNR on the prognosis, the five year survival rate by LNR was estimated. That with a LNR of less than or equal to 0.2 was significantly higher than that of the group with a LNR greater than 0.2-69% for $LNR \leq 0.2$ and 19% for $LNR > 0.2$.

Table 1. Variables Analysis According to LNR

		Lymph Node Ratio		Total	P-value
		≤ 0.2	> 0.2		
No of patients		28	100	128	
Sex	Female	10 (36%)	51 (51%)	61 (48%)	0.2
	Male	18 (64%)	49 (49%)	67 (52%)	
Histologic grade	Differentiated	13 (47%)	34 (34%)	47 (37%)	0.31
	Medium	7 (25%)	44 (44%)	51 (40%)	
	Mucinous	4 (14%)	9 (9%)	13 (10%)	
Tumor location	Un-diff	4 (14%)	13 (13%)	17 (13%)	0.11
	Rectosigmoid	11 (39%)	24 (24%)	35 (27%)	
Post-Operative Chemotherapy	Rectum	17 (61%)	76 (76%)	93 (73%)	0.61
	Yes	15 (54%)	48 (48%)	63 (49%)	
Metastasis	No	13 (46%)	52 (52%)	65 (51%)	0.09
	Yes	10 (36%)	54 (54%)	64 (50%)	
Recurrence	No	18 (64%)	46 (46%)	64 (50%)	< 0.001
	Yes	4 (14%)	54 (54%)	58 (45%)	
Death	No	24 (86%)	46 (46%)	70 (55%)	< 0.001
	Yes	7 (25%)	72 (73%)	80 (62%)	
		21 (75%)	27 (27%)	48 (38%)	

Table 2. Overall Survival, Local Recurrence and Distant Metastasis According to Prognostic Factors

	Overall survival HR (95%CI)	Local Recurrence HR (95%CI)	Distant Metastasis HR (95%CI)
Sex: Male vs. Female	1.2(0.7-1.9)	1.6(0.9-2.8)	0.9(0.5-1.5)
Age: 35-54 vs. < 35	1.3(0.7-2.5)	1.8(0.8-3.8)	1.0(0.5-1.9)
55+ vs. < 35	1.2(0.6-2.4)	1.4(0.6-3.1)	1.1(0.5-2.3)
Post-Operative Chemotherapy:			
Yes vs. No	1.0(0.6-1.5)	1.2(0.7-2.0)	1.5(0.9-2.5)
Total lymph node examined:			
7-11 vs. < 7	2.8(1.3-6.2)	1.7(0.8-3.4)	3.4(1.4-8.2)
≥ 12 vs. < 7	4.5(1.9-10.6)	1.8(0.8-4.1)	6.7(2.7-16.7)
LNR: > 0.2 vs. ≤ 0.2	5.0(2.1-11.6)	8.4(2.9-24.0)	2.6(1.3-5.4)

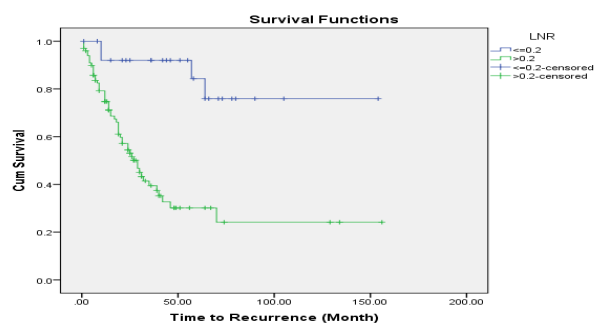


Figure 1. Disease Free Survival (Time to local Recurrence). Curve in stage III rectal cancer patients according to metastatic lymph node ratio (2 group: $LNR \leq 0.2$, > 0.2)

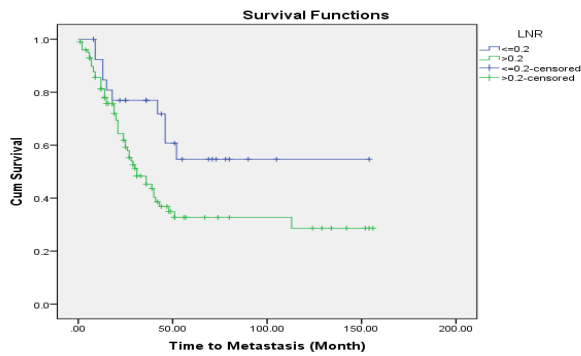


Figure 2. Disease Free Survival (Time to distant Metastases). Curve in stage III rectal cancer patients according to metastatic lymph node ratio (2 group: $LNR \leq 0.2$, > 0.2)

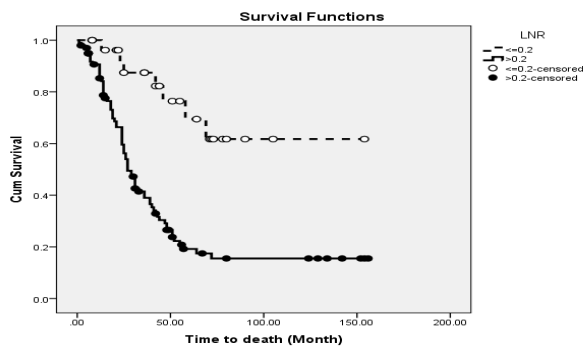


Figure 3. Five Years Survival Curve in Stage III. Rectal cancer patients according to metastatic lymph node ratio (2 Group: $LNR \leq 0.2$, > 0.2)

Discussion

In the current study we evaluate the prognostic impact of the LNR in patients with node positive rectal cancer who received preoperative chemoradiation therapy. Although nodal involvement is one of the most powerful prognostic factor in colorectal cancer, recently, the LNR was identified as an independent prognostic factor in these patients. In this study we found LNR as an accurate predictor of outcome of colorectal cancer patients who had inadequate number of harvested lymph nodes caused by preoperative chemoradiation. Five year survival was 69% for $LNR < 0.2$ and 19% for $LNR > 0.2$. Also LNR was a significant predictor of local recurrence and distant metastasis in our locally advanced rectal cancer patients.

Many studies (Nagtegaal et al., 2002; Wichmann et al., 2002; Baxter et al., 2005; Sermier et al., 2006; Rullier et al., 2008; Mekenkamp et al., 2009) have reported a significant decrease in the number of lymph nodes retrieved from patients with locally advanced rectal cancer who received preoperative chemoradiation, probably because lymph node atrophy, fibrosis and lymphocyte depletion (Marks et al., 2010). A study (Bakter et al., 2005) based on the surveillance, Epidemiology and End Result (SEER) registry showed that only 19% of patients with stage III rectal cancer had at least 12 retrieved lymph nodes after preoperative chemoradiation therapy. So LNR can improve the clinical decision for adjuvant treatment of these patients.

Previous study that evaluated the association between LNR and prognosis in patients with rectal cancer after preoperative chemoradiation reported various cutoff point

for LNR chosen by various methods, but all of them found it as a powerful predictor of outcome and sometimes even more powerful than nodal status (Chin et al., 2009; Manilich et al., 2011; Tong et al., 2011).

Peng et al. (2008) demonstrated for the first time the relationship between LNR s and survival rate in rectal cancer patients. The mean LNR was 0.34. LNR was an independent risk factor for local recurrence rate and disease free survival and overall survival in their study.

Similar to other studies, our study show the risk of local recurrence was 7 times higher in $LNR \geq 0.2$ than $LNR < 0.2$. Only in a study by shin on 190 rectal cancer patients LNR was not a predictive factor for local recurrence.

Ceelen et al. (2010) reviewed 16 studies including 33,984 patients with stage III colon or rectal cancer conducted from 1975 to 2009. The prognostic value obtained by the LNR was superior to that of number of positive nodes. In seven studies, the total number of positive nodes was no longer an independent prognostic indicator when LNR was included in the regression model. Four studies reported that the number of positive nodes was a statistically significant predictor of outcome but with a lower significance than LNR.

In a study by Kang et al. (2011) a total of 75 patients diagnosed as node positive after preoperative chemoradiation therapy followed by curative resection were enrolled. Patients were categorized into two group based on their median LNR which was 0.143. Patients with lower LNR had better overall survival. There was no difference between the survival rate of patients with higher LNR and also N2 patients.

In a study (Huh et al., 2010) on 514 colorectal cancer with proven lymph node metastasis patients were categorized into four group on the basis of quartiles: LNR1 (< 0.09), LNR2 (0.09-0.18), LNR3 (> 0.18 and < 0.34) and LN4 (≥ 0.34) with a median follow-up period of 48.5 months, the 5-year overall survival rates of patients with LNR1, LNR2, LNR3, LNR4 were 79, 72, 62 and 55% respectively and the 5-year disease-free survival rates were 73, 67, 54 and 42% respectively. LNR remained statistically significant both in patients with < 12 and with > 12 nodes retrieved. Similarly Lee et al. (2012) evaluate prognostic effect of LNR in 154 node positive rectal cancer and found prognostic impact of LNR (< 0.15 , 0.16-0.3 and > 0.3) on DFS and OS of patients with less than 12 harvested lymph nodes as well as more than 12 harvested lymph nodes.

Park et al. (2011) in a study on 186 stage III colorectal cancer patients had selected cutoff point of LNR as 0.07 because there was significant survival difference at that LNR. Five year survival of N1 patients (less than 4 nodes) was lower in the group of $LNR > 0.07$. Ainsworth et al. (2012) have shown a LNR of > 0.25 is prognostically significant for overall survival and disease free survival.

Several studies (Peschaud et al., 2008; Kim et al., 2009; Priolli et al., 2009; Dekker et al., 2010; Rosenberg et al., 2010; Thomas et al., 2012) had chosen different cutoff points by different parameters such as quartiles, median value and arbitrary values. The cutoff points for LNR were proposed in many studies but the optimal level need to be determined. In our study the cutoff point was 0.2 according

to mean and median of the sample, which is not approved as the optimal threshold for LNR. Also our study is a retrospective study with limited number of patients with a non uniform protocol for preoperative chemoradiation and also adjuvant chemotherapy. So the potential impact of LNR on outcome and prognosis of locally advanced rectal cancer patients treated by preoperative chemoradiation need to be investigated in large prospective studies with an optimal level of cutoff point.

In conclusion, LNR may help to determine the prognosis of colorectal cancers when the accurate staging in patients with fewer than 12 lymph nodes is not possible.

Acknowledgements

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