Hepato-Gastroenterology

Lymph Node Ratio May Predict Relapse Free Survival and Overall Survival in Patients with Stage II & III Colorectal Carcinoma

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ABSTRACT

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Background/Aims: Lymph node ratio (LNR) defined as the number of lymph nodes (LNs) involved with metastases divided by number of LNs examined, has been shown to be an independent prognostic factor in breast, stomach and various other solid tumors. Its significance as a prognostic determinant in colorectal cancer (CRC) is still under investigation. This study investigated the prognostic value of LNR in patients with resected CRC. **Patients & Methods**: We retrospectively examined 145 patients with stage II & III CRC diagnosed and treated at a single institution during 9 years period. Patients were grouped according to LNR in three groups. Group 1; LNR < 0.05, Group 2; LNR= 0.05-0.19 & Group 3 > 0.19. Chi square, life table analysis and multivariate Cox regression were used for statistical analysis. **Results:** On multivariate analysis, number of involved LNs (NILN) (HR=1.15, 95% CI 1.055-1.245; P =0.001) and pathological T stage (P =0.002) were statistically significant predictors of relapse free survival (RFS). LNR as a continuous variable (but not as a categorical variable) was statistically significant predictor of RFS (P =0.02). LNR was also a statistically significant predictor of overall survival (OS) (P=0.02). **Conclusion:** LNR may predict RFS and OS in patients with resected stage II & III CRC. Studies with larger cohorts and longer follow up are needed to further examine and validate the prognostic value of LNR.

Keywords: Colon cancer – Rectal cancer – Lymph node metastasis

INTRODUCTION

Colorectal carcinoma (CRC) is the second most common malignancy diagnosed in Kingdom of Saudi Arabia (KSA) (1). Approximately 60% of patients present with localized disease. Five year overall survival is 44% for CRC in Saudi population which is improving over time with the use of modern surgical techniques, radiation treatment, systemic therapy and supportive treatment (1).

Surgical resection is the mainstay of treatment for early stage (stage I, II and III) CRC. Pathological stage of disease is the most important determinant of long term outcome. Five year survival rate for resected stage I (T1-2, N0) is 93%, stage II (T3-4, N0) is 72-85%, and for stage III (LN positive disease) is reported to be 44-83% (2,3).

Beside pathological stage, other factors considered to have prognostic significance include presence of vascular invasion, residual tumor and pre op CEA (4). Prognostic factors for which the significance is not validated yet include tumor grade, circumferential margin positivity, mismatch repair deficiency, 18q deletions and perineural invasion (5-10).

Pathological involvement of LNs and the number of involved nodes are strong predictors of outcome. Therefore AJCC seventh edition has further sub classified stage III disease according to the number of LN involved (N1: 1-3 regional LN involved, N2 : 4 or more than 4 LN involved) (11). In addition to the number of LNs involved, recent data suggest that lymph node ratio (LNR) may potentially predict outcome (12, 13). To our knowledge, there are no published reports investigating the prognostic effect of LNR in patients with CRC from the Middle East. This study represents a single institution experience in the Middle East including patients with stage II and III CRC undergone curative surgery.

PATIENTS & METHODS

From April 2000 to August 2009, 246 consecutive patients with CRC were treated at our institution. 101 cases with stage I & IV were excluded. 145 patients with stage II-III are the subject of this report. Data of all patients were collected retrospectively from paper and electronic records. LNR was calculated for patients with stage II & III disease. LNR was defined as the number of positive LNs divided by the total number of LNs examined. Patients were grouped according to LNR into 3 groups (Group 1; LNR < 0.05, Group 2; LNR=0.05-0.19 & Group 3 > 0.19). This LNR grouping has been adopted and modified from the study published by Berger et al (12). Chi square was used to test the differences

in frequencies of relapse and death between groups. Life table analysis was used to calculate 2 year RFS and OS. Forward stepwise multivariate Cox proportional hazards regression was used to assess predictors of outcome. Covariates considered in this analysis were age, gender, number of involved LNs (NILN), LNR, T stage and use of adjuvant chemotherapy.

RESULTS

Among 145 patients, 76 (52%) had stage II and 69 (48%) had stage III disease. Eighty eight (61%) were males and 57 (39%) females. Median age was 55 (25-90) years. Seventy (48%) had colonic cancer and 75 (52%) had rectal/recto-sigmoid cancer. Patients received fluoropyrimidine based adjuvant chemotherapy as per institutional policy. In addition, patients with rectal/recto-sigmoid cancer received neo-adjuvant or adjuvant radiotherapy as indicated. Patient's characteristics are shown in table.1.

TABLE 1. Patients' characteristics.

Characteristic	Number (%)
Gender	
Male	88 (61)
Female	57 (39)
Median Age (years)	55 (25-90)
Site of initial disease	
Colon	70 (48)
Rectal/Recto-sigmoid	75 (52)
AJCC Stage	
Stage II	76 (52)
Stage III	69 (48)
T Stage	
T2	18 (12)
T3	108 (75)
T4	19 (13)
Adjuvant chemotherapy	
Yes	73 (50)
No	69 (48)
Missing	3 (2)
Neo-adjuvant Radiation (± chemotherapy)	
Yes	16 (11)
No	129 (89)
Adjuvant Radiation	
Yes	23 (16)
No	120 (83)
Missing	2 (1)

Median number of LNs examined was 11 (1-53) and the mean was 13.7. There were 78 (54%) patients in group 1; (LNR < 0.05), 31 (21%) in group 2; (LNR=0.05-0.19) and 36 (25%) in group 3; (LNR > 0.19) (Table.2).

TABLE 2. Pathological status of lymph nodes and lymph node ratio.

Number of LNs examined	
Median (range)	11 (1-53)
Mean	13.7
Number of involved LNs	
Median (range)	0 (0-15)
Mean	1.5
LNR	
Median (range)	0 (0-1)
Mean	0.16
LNR groups	
Group 1: LNR < 0.05	78 (54%)
Group 2: LNR 0.05-0.19	31 (21%)
Group 3: LNR > 0.19	36 (25%)

After a median duration of follow up of 19 (1-96) months, 49/145 (34%) relapsed. In LNR groups 1, 2 & 3; 28%, 39% & 43% relapsed respectively (Chi square; P=0.26). Two years RFS for groups 1, 2 & 3 were 73%, 65% & 52% respectively (Log rank; P=0.26).

On multivariate analysis, age, gender, and use of adjuvant chemotherapy were not significant predictors of RFS (Table 3). LNR as a continuous variable (but not as categorical variable) was statistically significant predictor of RFS (P =0.02). NILN (HR=1.15, 95% CI 1.055-1.245; P =0.001) and T stage (P =0.002) were also statistically significant predictors of RFS.

TABLE 3. Results of stepwise multivariate Cox proportional hazards regression for relapse free survival.

Covariate	Hazard ratio (Exponent)	95% CI	P value
Age	1.004	0.98-1.02	0.77
Sex	1.10	0.59-2.03	0.76
NILN	1.15	1.06-1.25	0.001
LNR			0.46
Group 2 vs. Group 1	1.5	0.70-3.20	0.30
Group 3 vs. Group 1	0.94	0.37-2.43	0.91
T stage			0.002
T3 vs. T2	1.67	0.50-5.52	0.40
T4 vs. T2	5.26	1.45-19.00	0.01
Adjuvant chemotherapy No vs. Yes	1.54	0.72-3.29	0.26

Fourteen out of 145 patients died. In LNR groups 1, 2 & 3; 5%, 10% & 19% of patients died respectively (Chi square; P=0.05). Two years OS for groups 1, 2 & 3 were 97%, 95% & 90% respectively (Log rank; P=0.24).

On multivariate analysis, age, gender, T stage and use of adjuvant chemotherapy were not significant predictors of OS. NILN (HR=1.11, 95% CI 1.01-1.22; P =0.036) and LNR as a categorical variable (but not as continuous variable) were statistically significant predictor of OS (Table 4).

TABLE 4. Results of stepwise multivariate Cox proportional hazards regression for overall survival.

Covariate	Hazard ratio (Exponent)	95% CI	P value
Age	1.01	0.99-1.03	0.16
Sex	0.89	0.61-1.30	0.57
NILN	1.11	1.01-1.22	0.036
LNR			0.02
Group 2 vs. Group 1	0.36	0.08-1.61	0.18
Group 3 vs. Group 1	0.17	0.04-0.82	0.03
T stage			0.73
T3 vs. T2	1.21	0.66-2.22	0.53
T4 vs. T2	1.36	0.64-2.90	0.43
Adjuvant chemotherapy No vs. Yes	1.41	0.90-2.21	0.13

DISCUSSION

It is very well established that number of Lymph nodes involved in CRC is one of the strongest prognostic factors. Also number of LN harvested turn out to be a very strong determinant of outcome for various tumor sites (14). LNR takes into account both the number of LN harvested and number of LN involved. LNR can be an independent prognostic factor regardless the number of LN harvested and the number of LN involved in a given situation.

Studies addressing the importance of LNR as prognostic factor vary widely in sample size and cut-off points for LNR. In a multivariate analysis, Berger et al (12) analyzed data from intergroup trial 0089 of adjuvant chemotherapy for stage II and III colon cancer. Multivariate analysis showed that LNR (LNR quartiles : <0.05, 0.05-0.19, 0.2-0.39 and 0.4-1.0) was a significant prognostic factor for OS, DFS and Cancer specific survival in patients with 10 or more LNs removed. This study is the biggest study published so far addressing the prognostic value of LNR in 3411 patients with CRC. For this reason we adopted similar LNR grouping cut offs. Our patients in group 1 and 2 had LNR of <0.05 and 0.05-0.19 respectively. However, due to small sample size in our study, patients with LNR > 0.19 were placed in one group (group III). In our analysis we included patients with stage II and III CRC as was performed by other investigators (12,15).

On multivariate analysis, we found that NILN and T stage were statistically significant predictors of RFS (P = 0.001 and 0.002 respectively) as it has been found in the study by Berger et al. However, in our population LNR groups as a continuous variable but not as a categorical variable was a significant predictor of RFS. This finding may be explained by small sample size. Nevertheless, there was a trend showing as LNR increases as categorical variable, the relapse rate increases and 2 years RFS decreases. In addition, LNR was also a significant predictor for OS (P =0.02) on multivariate analysis.

Other studies addressed LNR in patients with only stage III colon cancer. Lee HY et al reviewed 201 patients with stage III colon cancer. Cases were divided into 3 LNR groups (0.01–0.11, 0.12–0.24 and 0.25–0.92). The 5-year DFS according to this stratification was 83.6%, 61.1%, and 20% respectively (13). Derwinger K. et al reviewed 265 patients with resected stage III colon cancer. Four groups were analyzed based on LNR: ≤0.125, 0.126-0.266, 0.267-0.450 and ≥0.451. The 3 year disease free survival was 80% and 29% in LNR group 1 and 4 respectively. In Cox proportional hazard analysis the risk ratio between LNR groups 1–2 was 1.8, LNR groups 2–3: 1.4 and groups 3–4: 2.0 (16).

Galizia G et al reviewed 145 patients with resected stage III colon cancer. Receiver operating characteristic curve identified 0.1818 as the best LNR cut off to predict outcome. 5 year survival was 24.9% and 71.8% for LNR > 0.1818 and ≤ 0.1818 respectively. LNR (HR + 43.44; P < 0.0001) was the only covariate able to predict long term disease free survival (17). Adopting similar cut off of 0.1818 for our patients (group A; n= 108: LNR ≤ 0.1818 and group B; n = 37: LNR > 0.1818) and analyzing patients with stage II and III together, we found that median survival for both groups was not reached but was statistically significantly longer in group A than in group B (P= 0.037). Two year survival rates for groups A and B were 97% and 87 % respectively (Fig. 1).

RFS was not reached and for group A and it was 44 months for group B (P=0.24). RFS for groups A and B were 70% and 54 % respectively (Fig. 2).

FIGURE 1. Overall survival of stage II and III patients with LNR cutoff of 0.1818.

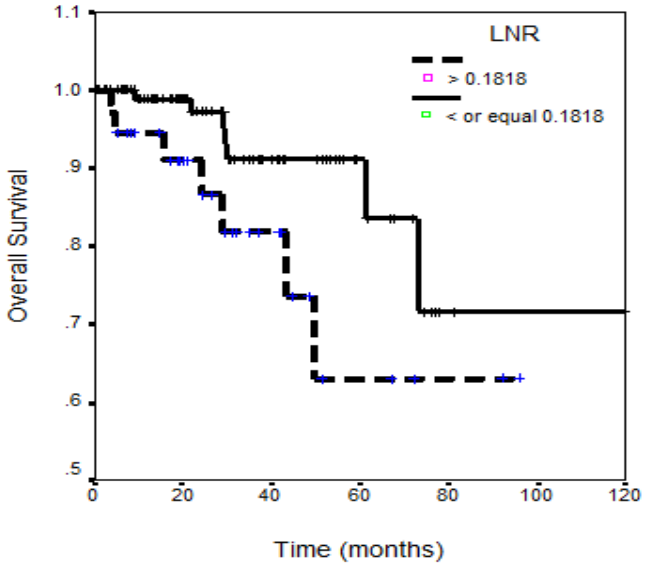
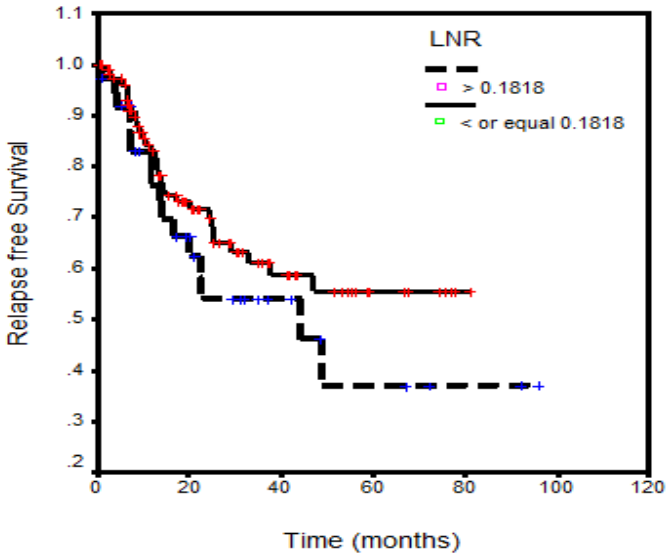


FIGURE 1. Relapse free survival of stage II and III patients with LNR cutoff of 0.1818.



Despite the relatively small size of our study and short duration of follow up, our results are consistent with findings from other larger studies. In addition and to the best of our knowledge this is the only study investigating the prognostic significance of LNR in Middle Eastern patients with CRC. However LNR should not be considered a substitute for an adequate LN dissection. Current standards recommend a minimum of 12 LNs to be harvested and examined to obtain an accurate assessment of LN involvement (18). Studies addressing the importance of LNR as prognostic factor vary widely in sample size and cut-off points for LNR. The cut-off points for LNR in grouping patients or for recommending adjuvant chemotherapy has yet to be established. For all these reasons the potential advantage of LNR in staging or prognosticating CRC patients should be investigated in large cohort of patients prospectively.

CONCLUSION

In our study population, LNR appears to be a predictor of RFS and OS in Middle Eastern patients with stage II and III CRC. Further studies with larger cohorts and longer follow up are needed to further examine the prognostic value of LNR.

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