

Factors Influencing Lymph Node Retrieval in Colorectal Adenocarcinoma

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ABSTRACT

Background: Retrieval and examination of an adequate number of lymph nodes is an essential part of the correct staging of colorectal adenocarcinoma. The surgeon, pathologist, and factors inherent to patient and tumor affect lymph node yield. This study aims to evaluate the influence of patient and tumor characteristics upon lymph node retrieval by analyzing the mean number of lymph nodes and to assess whether these variables are specifically associated with adequate lymph node sampling.

Methods: A retrospective study on colectomy specimens of colorectal adenocarcinoma was performed in the Department of Pathology, Patan Academy of Health Sciences, Nepal from April 2011 to October 2019. Variables including age, gender, anatomical location, tumor size, grade, lymphovascular invasion, perineural invasion, length of the surgical specimen, T stage, N stage, and AJCC stage were analyzed to determine their impact on the number of lymph nodes retrieved. The variables were also analyzed to determine their influence on adequate lymph node retrieval.

Results: Gender, age, maximum tumor size, grade, lymphovascular invasion, perineural invasion, T stage, N stage, and AJCC stage showed no statistically significant association. Right-sided adenocarcinoma yielded a notably greater number of lymph nodes with a higher probability of adequate lymph node sampling. Significantly more lymph nodes were retrieved in longer surgical specimens.

Conclusions: Right-sided location and longer surgical specimens were associated with higher lymph node retrieval in colorectal adenocarcinoma.

Keywords: Adenocarcinoma; colorectal; lymph node retrieval; staging

INTRODUCTION

Colorectal cancer is the third most common cancer worldwide.¹ The incidence is predicted to increase in developing regions.² Examination of an adequate number of lymph nodes is an essential part of the correct staging of colorectal adenocarcinoma.³

The status of regional lymph nodes is the single most powerful prognostic factor in the absence of metastasis.⁴ An increased survival has been noted in patients who had a higher number of lymph nodes evaluated.^{5,6} The possible explanation behind this alliance could be that a more extensive lymph node examination curtails the risk of understaging, leading to adequate management and further improved survival.⁶

International guidelines propose an examination of a minimum number of 12 lymph nodes to ensure adequate sampling.^{7,8} Despite this recommendation, inadequate

lymph node evaluation is common as reported by several studies.⁹⁻¹² Variables that influence lymph node harvest includes the surgeon, the pathologist, and factors inherent to the patient and tumor.¹³

METHODS

This retrospective study was performed in the Department of Pathology at Patan Academy of Health Sciences, Patan Hospital, Lalitpur, Nepal on 87 colectomy specimens of colorectal adenocarcinoma received between April 2011 and October 2019. Patients with malignancies other than adenocarcinoma and patients who had appendiceal carcinoma were excluded from the study. All the relevant data, including descriptive statistics of the patients, were retrieved from the archived reports and entered in an excel table. The variables considered in the study included patient data (age, gender) and tumor characteristics (anatomical location of the tumor, tumor size, grade, lymphovascular invasion,

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perineural invasion, length of the surgical specimen, T category, N category, and AJCC stage). Tumor location was classified as right-sided (caecum to splenic flexure), left-sided (splenic flexure to rectosigmoid junction), and rectum. Tumor grade, T stage, N stage, and AJCC stage were defined according to the WHO guidelines. There were two cases of signet ring cell carcinoma and eight mucinous carcinomas which were graded as poorly differentiated. For each category, the mean number of lymph nodes retrieved as well as the proportion of patients with adequate (defined as the retrieval of ≥ 12 lymph nodes) and inadequate lymph nodes examined was calculated.

We then assessed statistical associations between patient and tumor characteristics and the number of lymph nodes retrieved. Analysis of the data was performed using SPSS version 17.0. Bivariate analysis of the number of lymph nodes retrieved with five study variables (gender, lymphovascular invasion, perineural invasion, T stage, AJCC stage) was done using the Chi-squared test. Multivariate analysis of three study variables (tumor location, grade, N stage) was done using the Analysis of Variance (ANOVA). Further post hoc comparisons were run for the statistically significant variables. The correlation between the number of lymph nodes and three continuous variables (age, tumor size, and length of the surgical specimen) was tested using Pearson's correlation coefficient. We furthermore assessed

whether these variables (excluding the continuous variables) were specifically associated with the rate of adequate lymph node sampling. The threshold for significance was set at 5%.

RESULTS

Of the 87 patients, 46 (53%) were male and 41 (47%) were female with a mean age of 57 (range 21-89) years. Of the cancers, 41 (47%) were right-sided, 23 (26.5%) left-sided and 23 (26.5%) rectal. Adequate lymph node sampling according to existing guidelines (≥ 12) was achieved in 29 (33.3%) patients.

Bivariate analysis of gender, lymphovascular invasion, perineural invasion, T category, and AJCC stage performed with a mean number of lymph nodes as well as categories of <12 Vs ≥ 12 lymph nodes showed no statistically significant association (Table 1). However, in multivariate analysis, a significant association ($p=0.010$) was found between the mean number of examined lymph nodes and tumor location, notably, a higher number of lymph nodes in right-sided adenocarcinoma. Right-sided location was also associated with a higher probability of adequate lymph node sampling ($p=0.024$) (Table 2, 3). Tumor grade, N category, tumor size, and age were not significantly associated with the number of lymph nodes retrieved. However, significantly more lymph nodes were retrieved in longer surgical specimens (Table 2, 4).

Table 1. Bivariate analysis of study variables with total lymph node count.

No.	Variables		No. of Pts	No. of lymph nodes		Mean LN	95% CI for means difference		p-value
				<12	≥ 12		p value	Lower	
1	Gender	Male	46	30	16	9.8	0.874	-2.801	3.290
		Female	41	28	13	10.04			
2	Lymphovascular invasion	Present	20	15	5	8.85	-4.99	2.21	0.445
		Absent	67	43	24	10.23			
3	Perineural invasion	Present	15	9	6	11	-2.71	5.32	0.52
		Absent	72	49	23	9.69			
4	T stage	T1 & T2	19	13	6	8.94	- 7.153	0.615	0.09
		T3 & T4	68	45	23	10.19			
5	AJCC stage	I & II	57	39	18	8.84	-6.25	0.002	0.05
		III & IV	30	19	11	11.96			

Table 2. Multivariate analysis of study variables with total lymph node count.

No.	Variables	No. of Pts	No. of lymph nodes			Mean LN	F statistic	p-value
			<12	≥12	p value			
1	Tumor location	Rt. colon	41	22	19	12.29	4.909	0.010
		Lt. colon	23	16	7	8.39		
		Rectum	23	20	3	7.21		
2	Tumor grade (differentiation)	Well	20	10	10	10.65	0.284	0.754
		Moderate	44	29	15	10.04		
		Poor	23	19	4	9.04		
3	N classification	0	57	39	18	8.84	1.960	0.147
		1	18	12	6	12.11		
		2	12	7	5	11.75		

Table 3. Post hoc comparisons of the statistically significant variable (tumor location) obtained after multivariate analysis using ANOVA.

Site (mean LN)	Comparator (mean LN)	Mean difference of LN	95% CI of the mean diff.		p-value
			Lower	Upper	
Right colon (12.29)	Left colon (8.39)	3.901	0.380	7.420	0.030
	Rectum (7.21)	5.075	1.56	8.59	0.005
Left colon (8.39)	Rectum (7.21)	1.174	-2.81	5.16	0.559

Table 4. Correlation of total lymph nodes retrieved with continuous variables.

Correlation of lymph nodes with	Pearson's correlation coefficient (R)	p-value
Age	- 0.198	0.066
Tumor size	0.068	0.531
Length of specimen	0.384	<0.001

DISCUSSION

Adequate lymph node evaluation is essential for the proper staging of colorectal adenocarcinoma. The number of sampled lymph nodes has been discussed as a marker of quality of surgical therapy and pathological work-up as well as an independent prognostic marker guiding therapeutic decisions.^{14,15}

At the World Congress of Gastroenterology in Sydney, twelve was established as the minimum standard of lymph nodes to be examined since this number would allow for a correct diagnosis of N0 in 90% of cases^{7,14,16,17} In our study, adequate lymph node sampling according to existing guidelines (≥12 lymph nodes) was achieved in 29 (33.3%) patients. Several large population-based studies showed adequate lymph node evaluation in 27-40% of their patients.¹⁰⁻¹² These findings suggest that despite existing guidelines, substandard lymph node evaluation is common.

Lymph node yield is affected by numerous factors inherent to patient and tumor as well as related to surgical and histopathological practice.¹³ In our study, notably, a higher number of lymph nodes was retrieved in right-sided colon cancer. Right-sided location was also associated with a higher rate of adequate (≥12) lymph node sampling. Similar findings have been reported by numerous other studies.^{9,10,18,19} A study conducted by Baxter et al found that patients with right-sided colon cancer were twice as likely to receive adequate lymph node evaluation compared to those with left-sided or rectal cancers.¹⁰ The greater length of the mesenteric root and a higher immune response associated with microsatellite instability have been discussed as possible causes.^{13,20,21} Numerous studies including ours shows that the longer the surgical specimen, the higher the number of retrieved lymph nodes. This stands to reason as a longer colon segment will come with more lymph nodes containing mesocolon resulting in a higher yield.^{18,19} Stracci et al reported longer specimens in males, younger patients, non-screening detected tumors, tumors with a high pathological stage, and right-sided tumors. Laparoscopic surgery resulted in shorter surgical specimens.¹⁸ We found no significant statistical association between lymph node yield with gender, age, lymphovascular invasion, perineural invasion, T stage, N category, AJCC stage, tumor size, and grade. However, on the literature review, among the factors inherent to patients, younger patients^{9,10,18,22} and female gender^{17,23}

were associated with higher lymph node yield. With regards to tumor characteristics, a higher yield was observed with greater tumor size^{9,17,19,22,24}, presence of lymphovascular invasion⁹, advanced stage^{19,24,25} and increasing grade²⁵. Some studies have found the operating surgeon^{9,16,22,26} and the pathologist^{16,22,26} grossing the specimen to be two vital “modifiable factors” affecting lymph node retrieval.

The limitations of the present study include its relatively smaller sample size and retrospective nature. Due to the unavailability of data, the impact on lymph node yield of other significant factors, like operating surgeon and pathologist performing grossing could not be analyzed.

CONCLUSIONS

Right-sided location and longer surgical specimens were associated with higher lymph node retrieval in colorectal adenocarcinoma.

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