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A PROSPECTIVE STUDY FOR EVALUATION OF LYMPH NODES IN PATIENT WITH COLON CANCER UNDERGOING COLON RESECTION

Ashish Kumar Dubey¹, Raghvendra Choubey², P. S. Lubana³

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ABSTRACT: BACKGROUND: Lymph node status is important in staging a colon cancer, the difference between stage I and stage II disease relies on T category and this variable literally represent the number of lymph nodes harvested. Differentiation of stage II & stage III lymph node status is very important & more lymph nodes you find, the better the chances of identifying a positive node and that patient will be correctly staged as stage III. **METHODS:** A prospective study of 30 patients with stage II & stage III Colon cancer patient, who underwent curative resection, having 12 or more lymph nodes harvested from the specimen, were prospectively followed up and analyzed for 5 years. The kaplan-Meier method was performed by Cox proportional hazardsratio model with right censored Colon cancer survival data at a 10% significance level. **RESULTS:** In our study LNP (Number of positive lymph nodes), & LNR (Ratio of positive lymph nodes), predict the overall survival in the patient of all stages. Whereas for the patient of stage II LNT (Total number of lymph nodes) ($p<.261$) had shown to have effect on overall survival. In the patient of stage III, LNR (Ratio of positive lymph nodes), (0.003) & LNP (Number of positive lymph nodes), (.012) were the most prognostic factors but correlation analyses indicated that LNR (Ratio of positive lymph nodes) had the best discriminating capability to predict 5- year survival. **CONCLUSION:** The primary end point of the study was 5-year survival, including overall, disease-free and disease-specific survival. Lymph node involvement is the key factor that determines the stage and prognosis for Colon cancer. Our results demonstrate that LNT (Total number of lymph nodes) is only prognostic for patients with stage II diseases and that LNR (Ratio of positive lymph nodes), LODDS (Log odds of positive lymph nodes), and LNP (Number of positive lymph nodes), are prognostic factors for patients with stage III diseases. **KEYWORDS:** Colon cancer, Survival, Lymph node harvest, outcome.

INTRODUCTION: Colon cancer is the most common gastrointestinal malignancy and the second-leading cause of cancer death in India. Approximately 80% of colon cancer patients present with resectable localized disease and in these patients, nodal metastases have long been recognized as the most important factor predicting long-term survival. How does cancer spread to lymph nodes? Cancer can spread from where it started (the primary site) to other parts of the body.

When cancer cells break away from a tumor, they can travel to other areas of the body through either the bloodstream or the lymph system. If the cells travel through the lymph system, they may end up in the lymph nodes. Cancer cells can also travel in the bloodstream to reach distant organs. Either way, most of the escaped cancer cells die or are killed before they can start growing somewhere else. But one or two might settle in a new area, begin to grow, and form new tumors. This spread of cancer to a new part of the body is called metastasis¹.

In order for cancer cells to spread to new parts of the body, they have to go through several changes. They have to be able to break away from the original tumor and attach to the wall of a lymph

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vessel or blood vessel. Then they must move through the vessel wall to flow with the blood or lymph to a new organ or lymph node. When cancer grows inside lymph nodes, it usually affects the lymph nodes near the tumor itself. These nodes are the ones that have been trying to filter out or kill the cancer cells. (Figure 1).

LYMPH NODE COUNTS AND SURVIVAL: Nodal involvement is an important determinant in the decision to administer adjuvant chemotherapy, and with the demonstration over the last decade of highly effective systemic therapies for colon cancer, it is essential to ensure that all patients who would benefit from such treatment receive counseling concerning to these therapies and have access to them.² Numerous studies have shown an improvement in disease-specific and overall survival when good numbers of lymph nodes are examined for colon cancer³. The improvement in outcomes is probably due to stage migration that allows for increased utilization of adjuvant chemotherapy. (Figure 2).

LYMPH NODE COUNTS AS A QUALITY INDICATOR: As wide-ranging quality improvement efforts emerge throughout the health care system, finding mechanisms for optimizing cancer care through accurate staging and appropriate treatment has become an area of substantial interest to policy makers. Among patients surgically treated for colon cancer, several studies have demonstrated better survival for patients with more lymph nodes evaluated, according to background information in the article. "The proposed mechanism behind this association suggests that a more extensive lymph node evaluation reduces the risk of under staging, in which inadequate assessment may incorrectly identify a patient with node-positive disease as node negative, thus failing to identify appropriate treatment."

Most practice organizations and consensus panels now advocate for the surgical evaluation of 12 or more lymph nodes for acceptable staging of newly diagnosed colon cancer patients. Recently, some studies have questioned the under staging mechanism, suggesting that efforts by payers and professional associations to increase the number of lymph nodes evaluated during colon cancer surgery may have a limited role in improving survival. Several institutional and population-based studies showed a survival benefit associated with increasing numbers of Lymph node examined from Stage II and Stage III Colon cancer patients.

The origin of the database SEER (Surveillance Epidemiology and End Results) versus NCCN (National Comprehensive Cancer Network) also influenced the findings of Lymph node examination on patient's prognosis. In our study, increased numbers of Lymph nodes were examined, increased numbers of Lymph nodes were associated with improvements in overall survival and relapse-free survival for Stage II but not in Stage III patients.⁴ A suboptimal lymph node harvest may erroneously categorise stage III disease as stage II in colon cancer. Despite the importance and implication of adequate node evaluation, population based studies have shown that only between 22% to 37% of cancers have an adequate number of nodes analyzed.

AIMS AND OBJECTIVES: Our Goal was to clarify the ability of lymph node evaluation to predict long term survival across several evaluation types or TNM stages. This study prospectively analyzed the ability of lymph node evaluation to predict long term survival across several evaluation types or TNM stages.

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The results highlight the prognostic role and value of lymph node evaluation in four perspectives as follows:

- Through a correlation study among these five types of evaluation, we noted that LNN (negative number of lymph nodes) highly correlated with LNT (Total number of lymph nodes), and that LODDS (Log odds of positive lymph nodes), highly correlated with LNR (Ratio of positive lymph nodes), (Pearson correlation = 0.97, $p < 0.0001$)
- LNT (Total number of lymph nodes), the difference between stage 1 and stage 2 diseases relies on T category, and this variable literally represent the number of lymph nodes harvested. It is very important and prognostic when the depth of tumor invasion extends beyond the boundary of the muscularis mucosa of the large bowel. In this situation it is reasonable to support the assumption that understating might be considered when stage II patient with T3 and T4 category disease do not have enough lymph nodes to retrieve and examined. By this measure, our results support the benchmark of number of lymph nodes endorsed by NQF as an indicator of cancer care quality.
- The prognostic separation obtained by the LNR (Ratio of positive lymph nodes), was superior to that of the number of lymph nodes examined or the number of positive lymph nodes examined after surgical resection for patients with stage III colon cancer and LNR (Ratio of positive lymph nodes), was significantly predictive of Overall survival for patients with stage III colon cancer.
- And finally, our result from ROC (Receiver Operating Characteristics) analysis demonstrated that the ability to predict 5-year OS (Overall survival), DFS (Disease free survival), DSS (Disease specific survival) for patients with stage III disease was best for LNR (Ratio of positive lymph nodes), followed by LODDS, LNP, LNN, & LNT. LNN (Number of negative lymph nodes) LNT (Total number of lymph nodes), and LODDS (Log odds of positive lymph nodes)

METHODS: The first step in the statistical analysis was correlation among the different evaluation types of lymph node (continuous variable) analyzed with Pearson's test. We then constructed several Cox proportional hazard model according to TNM staging, one model for stage I, one model for stage II, and the remaining model for stage III. The Kaplan-Meier method was used to calculate cumulative survival-All p values were two sided, and the significance level was specified as $p < 0.05$. Also, we used ROC (Receiver Operating Characteristic Curve) analysis to determine the predictability of the continuous variables, LNT, LNP, LNN, LNR, and LODDS with regard to the three types of survival (OS, DFS, DSS).

We used PASW statistics 18 (SPSS) as statistical software for all of Analysis:

- Overall survival (OS) denotes the percentage of patients who are still alive after a specific period of time after colectomy for cancer.
- Disease free survival (DFS) denotes the percentage of patients who have no sign of cancer for a specific period of time after colectomy for cancer.
- Disease Specific Survival (DSS) denotes percentage of patients who have not died from colon cancer of metastasis after a specific period of time after colectomy for Cancer.

Studied variables included:

1. Total number of lymph nodes (LNT),
2. Number of positive lymph nodes (LNP),

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3. Number of negative lymph nodes (LNN),
4. Ratio of positive lymph nodes (LNR), and
5. Log odds of positive lymph nodes (LODDS).

RESULTS: Total 90 newly diagnosed colon cancer patients were registered during period of 5 years. Out of which 30 patients presented with non-metastatic colon cancer disease. Among them 30 patient (male 16(55.2%) & female 13(44.8%)) who had met the inclusion and exclusion criteria were eligible for this study.

CORRELATION ANALYSES / STASTICAL ANALYSIS: The first step in the statistical analysis was correlation among the different evaluation types of lymph node (continuous variable) analyzed with Pearson's test. If there was a correlation, we dropped one of the highly correlated pair.⁵ Then the value of LNT, LNP, LNN, LNR and LODDS ranged from 4 to 15(9.07±5.599), 0 to 4(1.79±2.22), 1 to 15 (7.28±4.644), 0 to 3 (7.28±4.644), -1.49 to. 368 (.587±.523) respectively.

Because LNN had a high correlation with LNT (Pearson correlation coefficient = 0.92, $p < 0.001$) and LODDS had high correlation with LNR (coefficient = 0.769, $p < 0.001$), both variables were excluded from the hazard modeling process. Correlation between LNT & LNR was low (-0.185 $p < 0.338$) but between LNT & LNP was (0.591, $p < 0.001$) & between LNP & LNR was (0.470, $p < 0.010$). (Table no. 1).

		LNT	LNP	LNN	LNR	LODDS
LNT	Pearson Correlation	1	.591**	.922**	-.185	-.074
	Sig. (2-tailed)		.001	.000	.338	.703
	N	29	29	29	29	29
LNP	Pearson Correlation	.591**	1	.234	.470*	.630**
	Sig. (2-tailed)	.001		.222	.010	.000
	N	29	29	29	29	29
LNN	Pearson Correlation	.922**	.234	1	-.448*	-.391*
	Sig. (2-tailed)	.000	.222		.015	.036
	N	29	29	29	29	29
LNR	Pearson Correlation	-.185	.470*	-.448*	1	.769**
	Sig. (2-tailed)	.338	.010	.015		.000
	N	29	29	29	29	29
LODDS	Pearson Correlation	-.074	.630**	-.391*	.769**	1
	Sig. (2-tailed)	.703	.000	.036	.000	
	N	29	29	29	29	29

TABLE 1: CORRELATION ANALYSIS

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

Nevertheless, we still included these three variables in the Cox proportional hazard model to assess their interaction. The mean follow up time for all groups was 27.31±10.35 months. During this time period, a total of 31% of this cohort died (20%, 38.9% and 100% for stage I, stage II & stage III respectively).

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COX-PROPORTIONAL HAZARD MODEL: The result of multivariate Cox proportional hazard⁹ model with regard to overall survival, evaluating the independent of these prognostic factors after controlling for possible confounders.⁶ In our study LNP (Number of positive lymph nodes) & LNR (Ratio of positive lymph nodes) predict the overall survival in the patient of all stages. Whereas for the patient of stage II LNT ($p < .261$) had shown to have effect on overall survival. In the stage III LNR (Ratio of positive lymph nodes) (.003) & LNP (Number of positive lymph nodes) (.012) was significantly associated with overall survival. (Table no. 2).

	Score	Df	Sig.
LNT	1.875	1	.171
LNP	6.384	1	.012
LNR	8.722	1	.003
LODDS	6.578	1	.010
LNN	4.637	1	.031

TABLE 2: Variables not in the Equation^a

Residual Chi Square = 9.893 with 4 df Sig. = .042

³In our study LNR(Ratio of positive lymph nodes)(.003) and LNP(Number of positive lymph nodes) (.012) were the most prognostic factors for patient with stage III disease but correlation analyses for patient with stage III disease indicated that LNR(Ratio of positive lymph nodes) had the best discriminating capability to predict 5- year survival.⁷

RECEIVER OPERATING CHARACTERISTICS CURVE (ROC): Analysis of ROC (Receiver Operating Characteristics Curve) can demonstrate the ability of each lymph node evaluation type (including LNT, LNN, LNP, LNR AND LODDS) to predict 5- year OS (Overall Survival) for stage III patient. The LNT (Total number of lymph nodes) line was the one that followed most closely to the reference line, followed by the LNN (Number of negative lymph nodes) line. The LNR (Ratio of positive lymph nodes) line was nearly superimposed by the LODDS (Log odds of positive lymph nodes) line, and was farthest from the reference line. The LNP (Ratio of positive lymph nodes) line was interposed between the LNR (Ratio of positive lymph nodes line) and the LNN line. (Table 3)

Test Result Variable(s)	Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
LNT	.547	.119	.689	.314	.781
LNP	.872	.081	.002	.712	1.000
LNN	.392	.136	.358	.126	.658
LNR	.906	.078	.001	.753	1.000
LODDS	.875	.100	.001	.680	1.000

TABLE 3: Area Under the Curve

The test result variable(s): LNT, LNP, LNN, LNR, LODDS has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

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- a. Under the nonparametric assumption.
- b. Null hypothesis: true area = 0.5.

The value of AUC(Area under curve) of ROC(Receiver Operating Characteristics Curve) was largest for LNR (0.906, 0.902 & CI 95%-0.75321 & 0.753-1.000 for 3 year OS & DFS respectively) followed by LODDS (0.875 & 0.875 CI -95%-.68021 & 0.680-1.00 for 5 year OS & DFS respectively), and LNP (0.872 & 0.872 CI- 95%0.712-1&0.712-1.00 for 5 year OS (Overall Survival) & DFS (Disease specific survival) respectively. The lowest AUC (Area under curve) among the five lymph node evaluation was LNT (0.547 & 0.547 CI -95%-0.314-0.781 & 0.314-0.781 for 5 years, OS (Overall Survival), & DFS (Disease specific survival) respectively.

CONCLUSION: Multiple prognostic factors have been identified, that affect the survival of patients with colon cancer. The presence of lymph node involvement is undoubtedly the most important prognostic factor and has long been recognized. Dukes¹¹ in 1932 recognized the importance of nodal status and incorporated this factor into his staging system for rectal cancer. In 1939, Simpson and Mayo^[7] applied Dukes' staging system to patients with colon cancer. All subsequent staging systems for colon cancer, including the current tumor-node-metastasis system, have continued to recognize the impact of involved lymph nodes. The adverse effect of lymph node involvement on survival has led to the routine use of adjuvant chemotherapy for those patients found to have regional metastases.⁸

However, the relationship between the number of lymph nodes removed or analyzed and patient survival has not been previously studied. Our study reveals that the number of lymph nodes analyzed is a significant variable that affects survival in both node-negative and node-positive patients. Regardless of the number of positive nodes, survival improved as more nodes were removed. If a patient was classified as node-negative, survival was also affected positively with an increase in the number of nodes analyzed. As information pertaining to regional lymph nodes has become the focus of our study of colon cancer care, a comparison evaluating the independent prognostic significance of lymph node evaluations found very important.⁹

In the present study using Cox proportional hazard³ model and ROC analysis, we compared the ability of five type of lymph node evaluation to predict 5-year survival after potentially curative RO colonic resection for adenocarcinoma of colon.¹⁰ Multivariate analyses were performed separately on the node-negative and node-positive groups to ascertain the effect of lymph node removal. In our study multivariate regression model results for the node-negative and node-positive patients, respectively. In the lymph node-positive group, age, T stage, tumor grade, tumor differentiation, the number of positive lymph nodes, and the total number of nodes recovered were highly significant predictors of survival. Lymph node involvement is the key factor that determines the stage and prognosis for Colon cancer.

Nevertheless Lymph node positivity alone does not identify all patients with a poor prognosis, as 20 to 40% of patients with Stage II (LN-negative) disease die of their cancers. Our results demonstrate that LNT (Total number of lymph nodes) is only prognostic for patients with stage II disease, and that LNR (Ratio of positive lymph nodes), LODDS (Log odds of positive lymph nodes) and LNP (Ratio of positive lymph nodes) are prognostic factors for patients with stage III disease.

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- We also note that LODDS (Log odds of positive lymph nodes) was highly correlated with LNR (Ratio of positive lymph nodes) and that both of these factors possess discriminating capability to predict 5-year survival.
- The basic Patho-surgical principle reminds us that the lymph nodes play an integral part in the staging and grading of colon cancer.
- Data reminds us how important it is to treat each colon cancer survivor as an individual - there is not one "mold" that fits each person.
- ³Regardless of age, patients who had 12 or more nodes examined had better survival than those with less than 12 nodes examined. The elderly accounts for nearly half of the patients with colon cancer. Older patients undergo inadequate lymph node evaluation more frequently than younger patients do. Improving lymph node evaluation will result in more accurate pathologic staging for the elderly.¹¹
- The results of this study were striking. It should support efforts ongoing by some medical professional societies and expert panels to consider a minimum number of lymph nodes examined during the surgery practice. Organizations and consensus panels currently support the surgical evaluation of 12 or more lymph nodes for acceptable staging of newly diagnosed colon cancer patients.

Among patients surgically treated for colon cancer, several studies have demonstrated better survival for patients with more lymph nodes evaluated.

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Fig. 1: Mechanism showing cancer spread to lymph node

Fig. 2: Types of Lymph Nodes Around Colon

Fig. 3: Receiver Operating Curve

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AUTHORS:

1. Ashish Kumar Dubey
2. Raghvendra Choubey
3. P. S. Lubana

PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Department of Surgery, Bundelkhand Medical College, Saugor, M. P.
2. Assistant Professor, Department of Orthopaedics, Bundelkhand Medical College, Saugor, M. P.
3. Associate Professor, Department of Surgery, MGMC & My Hospital, Indore, M. P.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Ashish Kumar Dubey,
Flat No. 2, Type-V,
Bundelkhand Medical College,
Saugor, Madhya Pradesh.
Email: drashish15184@gmail.com

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