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The Impact of Neoadjuvant Chemotherapy on Lymph Node Harvest and Lymph Node Size in Colorectal Carcinoma

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1. Abstract

1.1. Background: Adequate staging of colorectal tumors in part depends on obtaining a sufficient number of lymph nodes. The minimum number of lymph nodes required is twelve. A number of factors are known to impact node harvests including, carcinoma grade and size as well as patient age. The impact of neoadjuvant chemotherapy on mode harvest is unclear.

1.2. Materials and Methods: We compared the number of lymph nodes and the size of lymph nodes in 30 patients not treated by neoadjuvant chemotherapy to those treated by neoadjuvant chemotherapy (39 patients). Number of nodes obtained was also correlated with patient age, pretherapy stage, patient gender, site of carcinoma, outcome, presence of positive nodes, and grade of carcinoma. The relationship between the presence of positive nodes and outcome was also tested. Statistical analysis was performed using the T-test.

1.3. Results: Treated cases had slightly fewer lymph nodes than untreated cases. Treated cases had an average of 19.9 nodes while untreated cases had an average of 24.4 nodes (p=0.03). Lymph nodes from treated cases were smaller than nodes from untreated cases (mean 2.8mm vs 3.3mm) (p=0.02). Eight patients in the treated group had fewer than ten nodes obtained while the untreated group had node harvests always above 12 nodes. Increasing patient age correlated slightly with decreasing number of nodes(p=0.10) but no correlation between node number and the other variables was seen.

1.4. Conclusions: Lymph node dissections from treated patients harvested fewer and on average smaller lymph nodes than those from untreated patients. This difference supports that some patients in the treated cohort may be under staged because too few lymph nodes are obtained during nodal dissections.

2. Introduction

The number of lymph nodes obtained from colorectal cancer resection specimens is known to correlate with appropriate staging and clinical outcome [1-5]. Studies have demonstrated that a minimum of twelve lymph nodes should be obtained from colorectal cancer resection specimens for accurate staging and prognostication [1-5]. The total number of lymph nodes examined appears to impact the recognition of positive lymph nodes and hence the assigned P-stage. When insufficient numbers of lymph nodes are obtained from colorectal specimens, staging may be inappropriately low and result in unreliable patient prognostication based on stage [1-5]. Thus the acquisition of a sufficient number of lymph nodes is imperative for accurate staging and determination of patient prognosis. A number of factors have been shown to govern the number of lymph nodes obtained from a colorectal resection specimen [6]. Poorly differentiated carcinomas and those with a high T-stage are associated with a higher number of lymph nodes obtained at time of specimen examination. Length of resection specimen also impacts total number of nodes obtained. Shorter lengths of colonic resection specimen may be associated with fewer nodes obtained by dissection of the specimen. The location of the carcinoma in the colon or rectum also may impact the number of lymph nodes obtained [7-10]. Studies have

shown that a smaller number of lymph nodes are obtainable from sigmoid colon and rectum specimens. Patient age appears to impact the number of lymph nodes obtainable from resection specimens [11]. Other factors may also impact the number of lymph nodes obtained from colorectal tumor resection specimens. Potentially, pre-operative neoadjuvant chemotherapy might reduce the total number of lymph nodes obtainable. It may also impact the size of lymph nodes found. Currently neoadjuvant chemotherapy is given to patients with a variety of high grade and or high stage cancers including those of the breast, rectum, and gastroesophageal junction carcinomas. A study performed by White, et al [12] found that neoadjuvant chemotherapy did not reduce the node harvest at the time of axillary dissection. Some studies have shown that neoadjuvant chemotherapy reduces the number of lymph nodes harvested in colorectal carcinoma [13-18]. Herein, we report a study on the impact of neoadjuvant chemotherapy for colorectal adenocarcinoma on nodal harvest.

3. Materials and Methods

This study underwent Institutional Review Board review at the University of Missouri and was found to be exempt. The study is also in compliance with the Helsinki Accord. The records of the Department of Pathology, Surgical Pathology section were searched for all colon and rectum resections for adenocarcinoma for the years 2014 to 2019. Sixty-nine cases of resection specimens were obtained. Thirty-nine of these had received pre-operative neoadjuvant therapy while thirty had not been treated pre-operatively. These sixty-nine cases formed the basis for this study.

The glass slides from each case were retrieved from the Pathology files and were reviewed for total number of lymph nodes obtained from the nodal dissections. The size of the lymph nodes obtained was also recorded for each case. Correlation was performed for numbers of nodes harvested and size of lymph nodes obtained for those cases with and without pre-operative neoadjuvant chemotherapy.

Differences in the number of lymph nodes harvested from treated and untreated specimens were analyzed using the T-test for both a non-directional hypothesis and for a directional hypothesis.

Differences in the number of lymph nodes harvested were statistically analyzed with the variables: patient age, gender, site of carcinoma, pretherapy stage, patient outcome (dead of disease, alive with disease, alive with no evidence of disease), presence of positive nodes and grade of carcinoma.

Statistical analysis of differences in nodal size between the treated and untreated group was performed by first examining the data of outliers using the Tukey Test. We performed analyses on the original data set and, on the data, set from which outliers had been removed (refined data set). We used a t-test to determine if differences existed in lymph node size between the treated and untreated groups.

4. Results

A total of sixty-nine cases (30 untreated and 39 treated) met the search criteria and formed the basis for the study. Impact of Neoadjuvant Chemotherapy on the Number of Nodes: Treated cases had slightly (21%) fewer lymph nodes than untreated cases (Figure 1) On average, treated cases had 19.9 nodes and untreated cases had 24.4 nodes. This difference (4.6 nodes per case) has borderline statistically. significance (p=0.055) for a non-directional hypothesis but is statistically significant (p=0.03) for a directional hypothesis. For the present study, the directional hypothesis was that untreated cases would have a greater number of lymph nodes than treated cases.

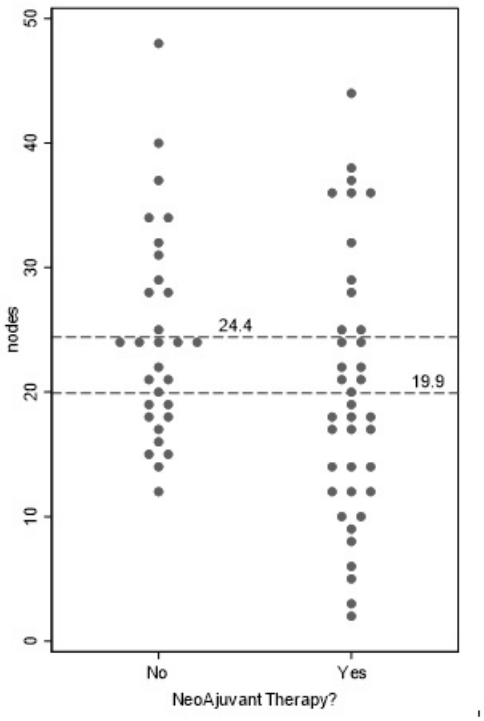

Figure 1: Distribution of Number of Nodes per Case. Left panel: did not receive neoadjuvant chemotherapy. Right panel received neoadjuvant chemotherapy. The figure shows distributions of the refined data (i.e. after removal of outliers). The dashed lines indicate the mean number of nodes in each group.

4.1. Identification of Size Outliers

We plotted the distribution of node size by case in the original data set (Figure 2). This distribution revealed two outliers. In the untreated group, case 28 had an abnormally large distribution of nodes. This case had 37 nodes of which ranged from 2mm to 45 mm. Thirty-six of 37 nodes in case 28 were larger than the median size (2.5 mm) of the remaining population of nodes. This case was classified as an outlier and removed. In the untreated group, there was one large node (30 mm) which was twice as large as the next largest node and approximately 13 times larger than the median node size (2.2 mm) of the untreated group. This node was removed. Thus, the refined groups were formed by removing case 28 from the untreated group and the single large node from the treated group. The refined groups were only used for analysis of node size. No outliers were identified with respect to the number of nodes.

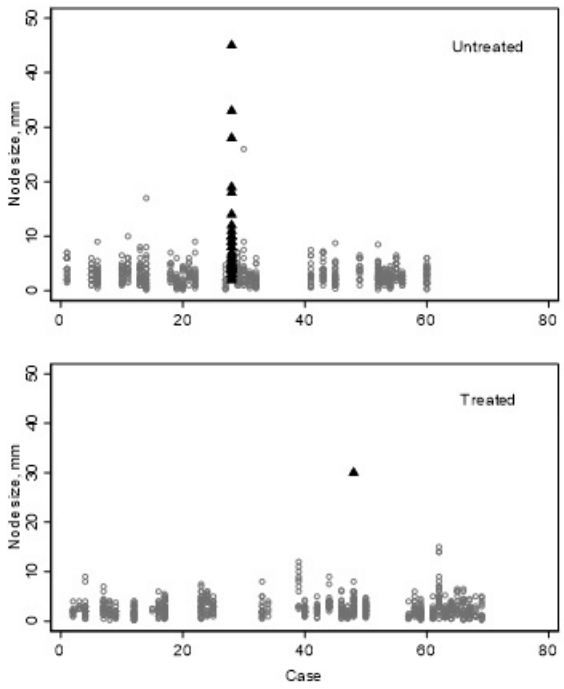

Figure 2: Distribution of node sizes by case. Upper panel: did not receive neoadjuvant chemotherapy. Lower panel received neoadjuvant chemotherapy. Potential outliers are indicated by solid triangles. Case 28 was identified as an outliner in the untreated group. A single node (size = 30, case 48) was identified as an outlier in the treated group.

4.2. Impact of Neoadjuvant Chemotherapy on the Size of Nodes

Analysis of the refined cohorts (i.e., outliers removed) showed that the average node size of untreated nodes was slightly larger (difference = 0.23 mm, t_1334 = 2.4, p = 0.02). The distribution of node sizes was skewed to the right in both groups (Figure 3, Table 1). Comparison of the node size distributions of the original cohorts (i.e., outliers included) also showed that the average node size was larger in the untreated cohort (difference = 0.58 mm, t_1373 = 4.0, p=0.0001). Thus, including the outliers increased the size of the untreated group relative to the treated group.

Metastatic Deposits: Because cases containing metastatic deposits might have larger or more findable nodes than cases without metastases, the sets of data for treated and untreated cases were compared for numbers of lymph nodes with metastatic deposits. Twenty-one of 733 nodes (2.9%) in the untreated group and 31 of 775 nodes (4.0%) in the treated group were positive for metastatic deposits. The difference in proportions was not statistically significant (z=1.2, p = 0.24).

Of the other variables tested only patient age demonstrated any correlation with number of lymph nodes harvested. There was a slight correlation between increasing age and reduction in lymph nodes harvested (p=0.10). There was no correlation between the other variable and number of harvested lymph nodes. Specifically, there was no relationship between number of lymph nodes harvested and patient outcome. Also, no relationship could be demonstrated between the number of lymph nodes harvested and the presence of positive nodes. Finally, there was no relationship between the presence of a positive node and the presence or absence of neoadjuvant chemotherapy.

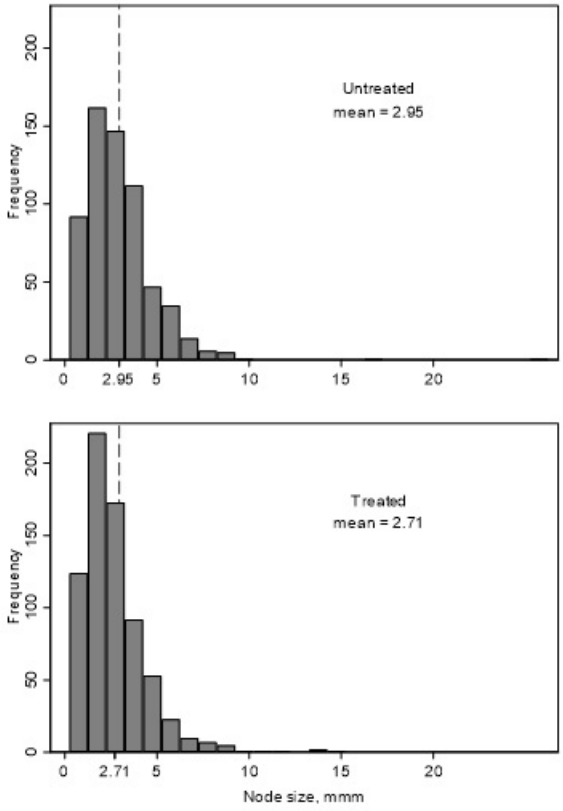

Figure 3: Size Distribution of Lymph Nodes. Upper panel: did not receive neoadjuvant chemotherapy. Lower panel received neoadjuvant chemotherapy. Distributions are for the refined cohorts (i.e., outliers removed).

Table 1: Node Size Distribution. The table shows a five-point summary of the distribution of node sizes. The treated cohort received neoadjuvant chemotherapy. Summaries are provided for the original (outliers included) and refined (outliers excluded) cohorts.

Cohort	Outliers	Node size, mm					
		Minimum	25th pct	Median	Mean	75th pct	Maximum
Treated	Excluded	0.25	1.5	2.2	2.8	3.5	15
Untreated	Excluded	0.25	1.8	2.5	3.3	4.0	26
Treated	Included	0.25	1.5	2.2	2.7	3.5	30
Untreated	Included	0.25	2.0	2.8	3.0	4.0	45

5. Discussion

The size of lymph node harvests is an important component for the appropriate staging of patients with colorectal carcinomas [1-5]. Studies have demonstrated that a minimum of twelve lymph nodes is required for appropriate staging [1-5]. A number of factors may impact the number of lymph nodes obtainable from resections specimens and include patient age, location of carcinoma and grade of carcinoma [5-11]. Pre-operative neoadjuvant therapy may also represent a factor influencing the number of lymph nodes obtainable at time of dissection.

The impact of neoadjuvant chemotherapy on lymph node harvests from the axilla of women treated with neoadjuvant chemotherapy for breast cancer has been well studied [19-22]. Data from these studies is conflicting. Some authors had reported that patients receiving neoadjuvant therapy have substantially fewer lymph nodes present in dissections than those patients not receiving neoadjuvant chemotherapy. Other studies, particularly that by White, et al [6] indicate that lymph nodal harvests are not impacted by neoadjuvant chemotherapy [1]. Because fewer studies have been reported for colorectal carcinoma resection specimen lymph node harvests, we studied the relationship between pre-operative chemotherapy and node number in sixty-nine cases (thirty-nine receiving neoadjuvant therapy and thirty without pre-operative chemotherapy). Data associated with radio chemotherapy for colorectal carcinoma indicates a reduction in node harvests but often no impact on prognosis [13-18].

Our study of 39 patients treated by neoadjuvant chemotherapy for colorectal carcinoma and 30 untreated with neoadjuvant chemotherapy revealed small statistically significant difference in numbers of lymph nodes harvested from resected specimens. All cases in the untreated group yielded twelve or more lymph nodes per specimen. Harvests from patients not undergoing pre-operative neoadjuvant chemotherapy invariably had twelve or more lymph nodes available for assessment fulfilling the minimum requirements for lymph node harvest deemed to be necessary for accurate staging. In patients with neoadjuvant chemotherapy, eight patients were associated with lymph node harvests containing an insufficient number of lymph nodes for accurate staging and prognostication. The difference in mean number of lymph nodes from treated and untreated case was statistically significant. Treated cases had a mean number of lymph nodes of 19.9 while untreated cases had a mean number of lymph nodes of 24.4. This difference occurred despite diligent searches for lymph nodes often following clearing techniques and multiple individuals performing node searches on cases with less than fifteen nodes obtained at time of initial harvest.

A potential explanation for this difference in number of lymph nodes obtained, may be that lymph nodes in patients receiving neoadjuvant chemotherapy are smaller than those in specimens obtained from patients not receiving neoadjuvant chemotherapy. Potentially, some of the missed nodes in treated specimens were so small that they went unnoticed at time of dissection. We found that the mean lymph node size in untreated patients was 2.95 mm while the mean lymph node size in patients undergoing neoadjuvant chemotherapy was 2.71mm. Thus, a difference of 0.23mm existed between the two groups. A simple T-test demonstrated that this difference between the treated and untreated study populations was statistically significant ($p=0.02$). While differences in nodal size were not great, the difference was significant and suggests that a greater percentage of lymph nodes in the treated group may fall below the size clinically detectable on gross examination.

We were concerned that including outliers might distort the analysis; however, excluding outliers can also create distortions. For that reason, we performed our analysis of lymph node size with datasets that included and excluded outliers. Both analyses supported the conclusion that untreated lymph nodes are larger, on average, than treated lymph nodes. The outliers led to a larger difference in effect. We were also concerned that the frequency of metastatic deposits could influence lymph node size. We found no significant difference in the proportion of nodes with metastatic deposits in the treated and untreated groups.

Our study did not demonstrate significant associations between node harvest size and patient gender or patient prognosis. Additionally, there was no relationship between the number of nodes obtained and the presence of positive lymph nodes, the site of the carcinoma, the pretherapy stage or the grade of the carcinoma.

A number of studies including the present report have documented a reduction in the number of lymph nodes harvested from colorectal specimens following neoadjuvant therapy. [12-18], [23-26] Estimates suggest that the nodal count may be reduced by approximately four lymph nodes [25]. The prognostic impact of this reduction is less clear. While Tan et al [23] felt that the dissection of at least twelve lymph nodes after neoadjuvant therapy did improve overall survival statistics, Miller et al [24] questioned the need for a minimum of twelve lymph nodes for adequate evaluation of patient prognosis. Mechers supported the need for identification of at least twelve lymph nodes [25] Doll et al [16] found that the reduction in lymph nodes following neoadjuvant therapy had no impact on prognosis. Our findings are similar. Neoadjuvant therapy did reduce the number of lymph nodes harvested but this did not impact the number of nodes with metastatic disease or the patient's prognosis. Given this data, it appears reasonable to set a lower limit for the number of nodes required for proper evaluation in the setting of neoadjuvant therapy.

From our data, it appears that patients undergoing neoadjuvant chemotherapy have a higher likelihood of having nodal dissections containing fewer lymph nodes than is believed to be optimal for staging and prognostication of patient outcome based on stage. In our study, specimens with fewer than fifteen lymph nodes underwent multiple attempts at nodal harvest to obtain at least fifteen lymph nodes

per specimen. Despite these repeated efforts to obtain the optimally minimal number of lymph nodes, patients with neoadjuvant chemotherapy had a sub-optimal number of lymph nodes obtained in eight of thirty-nine cases (20%). This indicates that some patients with neoadjuvant chemotherapy may be under staged due to an insufficient number of lymph nodes being obtained at nodal harvest and occasional small but positive lymph nodes being overlooked. Some studies of breast axillary dissections, have revealed similar findings. Additional studies will be necessary to determine the extent to which neoadjuvant chemotherapy for colorectal carcinoma results in under staging of patients.

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