Variables Impacting Lymph Node Recovery in Colectomy Resection Specimens Removed for Colorectal Adenocarcinoma

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Abstract: *Background*: Recent data suggest that a higher number of nodes evaluated in colectomy specimens for colorectal adenocarcinoma is associated with increased survival. Recommendations mandate the harvesting of at least 12 nodes in colectomy specimens for adequate assessment. Recent studies argue that the above association is complex and is uncontrolled for a variety of variables.

Objective: The study's objective is to evaluate several factors that impact the harvesting of lymph nodes in colectomy specimen.

Patients: We reviewed 306 colectomy specimens from 2 academic medical centers, 177 from Kansas University Medical Center (KUMC) and 129 from the Kansas City Veterans Affairs Medical Center (VAMC) from 2000 to 2007.

Design: Factors evaluated included tumor size, grade, stage, site, number of positive nodes and length of colectomy segment removed. We compared the number of nodes removed at the 2 institutions and whether individual surgeons had an impact on the number of harvested nodes.

Results: Harvesting at least 12 nodes is correlated with larger tumor size, higher grade and stage and specimens longer than 21 cm. More nodes were harvested from the right colon (mean=13 nodes), followed by descending (12 nodes), transverse and rectosigmoid (10 nodes each). Number of positive nodes correlated with tumor grade, but not with tumor site, size, linear length of specimen or whether 12 nodes were harvested.

Cases from the VAMC were more likely to harvest 12 nodes compared to KUMC. It was noted that 2 of 10 surgeons at the VAMC performed 76% of all surgeries. There were 21 surgeons at KUMC; none performed more than 12% of the cases.

Conclusion: Number of harvested nodes is related to other prognostically significant parameters primarily related to tumor biology. The potential impact of surgeon's experience and the type of surgery performed needs further evaluation.

Keywords: Lymph node recovery, colectomy specimens, colorectal adenocarcinoma.

INTRODUCTION

Total number of lymph nodes (LNs) harvested in colectomy specimens for colorectal adenocarcinoma, serves an intricate role in determining adequacy of tumor resection and prognostication. Recent data suggest that a higher number of LNs evaluated in colectomy specimens is associated with better survival, regardless of the pathologic findings [1-3]. Multiple studies suggest that at least 12 harvested LNs in a colectomy specimen are required for accurate correlation with survival [4-7]. Unfortunately this criterion is only achieved in a minority of colon cancer operations [8, 9]. While some investigators are advocating strict adherence of the surgeons to the fundamental principles of colon cancer surgeries, others are calling on the pathologists to be more aggressive in their search for those LNs. As a result of this debate, concerns have been raised about the adequacy of surgical resection and the thoroughness of the pathologic examination.

At present the American College of Surgeons, the American Society of Clinical Oncology and others are advocating the harvesting of at least 12 LNs in colectomy specimens for adequate assessment [4, 10]. Unfortunately, the number of LNs harvested is not only being used as a benchmark for both surgeons and pathologists, but is also proposed to be used as a basis for payment strategies to surgeons and institutions by insurance companies. However, the reality is that the Commission on Cancer of the American College of Surgeons has not made any final recommendations as of yet. In addition, recent published studies contradict the prognostic value of LN adequacy and argue that any association is more complex and is influenced by a variety of confounding variables [11, 12].

The objective of this study is to evaluate the impact of several key confounding tumoral and non tumoral factors on harvesting $\geq$ 12 LNs per colectomy specimen acquired from

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patients with colorectal adenocarcinoma from two institutions.

MATERIALS AND METHODS

Three hundred and six colon cancer colectomy specimens from 2 academic medical centers, including 177 from Kansas University Medical Center (KUMC) and 129 from The Kansas City Veterans Affairs Medical Center (VAMC), with surgery conducted from 2000 to 2007 are included in the study. Factors evaluated included tumor size, grade, stage, tumor location, number of positive LNs, number of harvested LNs, and length of colectomy segment removed. In addition, institutional site (KUMC or VAMC) and the surgeon of record were recorded. All clinical and histologic data were collected from surgical pathology records and recorded in a data base. Data were identified by date of surgery and by surgical pathology specimen number; but no other Protected Health Information (PHI) were collected. This is a retrospective study involving past pathology reports. Patient identification (except as noted above for specimen identification) was removed from all study material. No threat was posed to the patients' health, treatment or privacy. The studies were performed with the approval from the institutional review board at the University of Kansas Medical Center.

Statistical Considerations

Descriptive statistics were employed to characterize various clinical and pathological variables. We reported means, standard deviations, and 95% confidence intervals for parametric variables. Medians and interquartile ranges were used for data that are not normally distributed. Frequencies were reported for categorical variables. Comparisons of numerical values between groups (site, surgeon, etc.) were performed by t-test for normally distributed data or by Mann-Whitney test or Kruskal-Wallis test for non-parametric variables. Comparison between categorical variables was performed by Chi-square test. Multiple linear regressions were used to assess the relationship between number of positive LNs and each of the clinical and pathologic variables collected. Partial correlation coefficients were provided to describe the association of node positivity and each of the factors, while eliminating or controlling for the effect of the remaining variables. Pearson's correlation coefficient was used for normally distributed date; Spearman's correlation coefficient was used if the data were skewed.

RESULTS

The results of our study show several factors impacting the likelihood to harvest at least 12 LNs per colectomy specimen. These factors have been divided into two categories: 1) tumor related factors and 2) procedural or non-tumor related factors.

Tumor Factors

When cases were divided between those that did or did not achieve a yield of at least12 LNs, tumor size, grade and stage were of significant impact. In those specimens where $\geq$12 LNs were identified, median tumor size was 4.5 cm in greatest dimension, compared to 3.2 cm for those specimens where less than 12 LNs were harvested (p value < 0.001, Mann-Whitney test, Fig. **1**). This finding held true whether surgeries were performed at KUMC or at VAMC (data not shown). Table **1** shows that tumor grade influenced the adequacy of LN assessment. Similarly for specimens with tumors of higher stages (T3/T4) the yield of $\geq$12 LNs per specimen was higher. There was a significant positive correlation between tumor grade and stage and yield of $\geq$12 LNs per specimen (p value = 0.035 and p value <0.05, respectively). A higher percentage of cases with $\geq$12 harvested LNs were identified in poorly differentiated tumors as compared to moderately and well differentiated tumors (68% *vs* 50% *vs* 37%, respectively).

Table 1. Relationship Between Tumor Grade and Number of Resected Lymph Nodes in Colorectal Resection Specimen for Adenocarcinoma

Tumor Grade*	Less than 12 Nodes Resected	12 or More Nodes Resected	Total
Well differentiated	12 63%	7 37%	19
Moderately differentiated	121 50%	122 50%	243
Poorly differentiated	14 32%	30 68%	44
Total	**147 48%**	**159 52%**	**306**

*p = 0.035 Chi-Square Test.

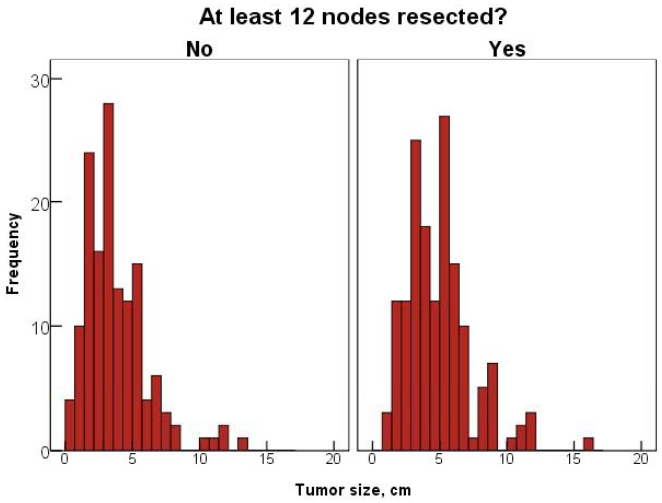

Fig. (1). The influence of tumor size on adequacy of nodal assessment in colorectal adenocarcinoma resection specimens. The likelihood of harvesting 12 or more nodes correlated with larger tumors.

The likelihood of harvesting $\geq$12 LNs was also influenced by tumor location of resection (p<0.001, Kruskal-Wallis test). More LNs were harvested from the right colon (median=13 LNs), followed by descending (12 LNs), transverse and rectosigmoid (10 LNs, each). Tumor located within the right colon had the highest percentages of 12 LNs or more (66%). That was followed by descending colon tumor (61%), then rectosigmoid tumors (41%) and transverse colon tumors (36%) (Table **2**). When we studied the relationship between tumor size and tumor location the

right colon housed the largest tumors (median size 4.5 cm), followed by descending colon (4.0 cm) and rectosigmoid and transverse colon tumors (3.5 cm, each) (Fig. **2**).

Table 2. Relationship Between Tumor Location and Number of Resected Lymph Nodes in Colorectal Resection Specimen for Adenocarcinoma

Location of Resection*	Less than 12Nodes Resected	12 or More Nodes Resected	Total
Cecum/ Ascending Colon	39 34%	75 66%	**114**
Transverse Colon	16 64%	9 36%	**25**
Descending Colon	12 39%	19 61%	**31**
Sigmoid Colon Rectum	80 59%	56 41%	**136**
Total	**147 48%**	**159 52%**	**306**

*p < 0.001 Chi-Square Test.

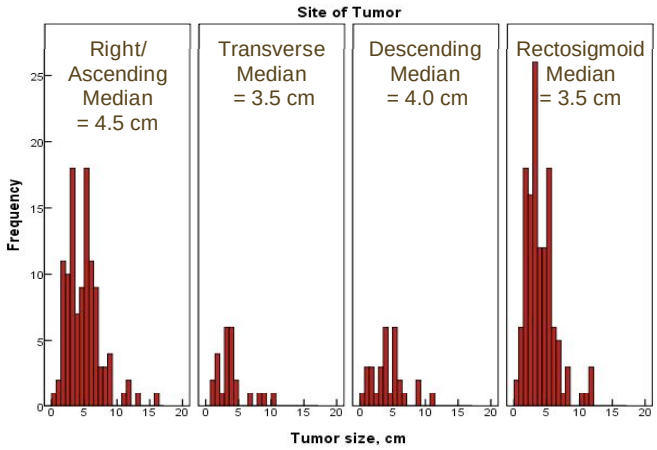

Fig. (2). Their isa relationship between tumor size and location for colorectal adenocarcinoma in colectomy specimens. Significantly larger tumors were located in the right colon (p = 0.021 Kruskal-Wallis Test).

Although the number of positive nodes and whether there was nodal involvement correlated with tumor grade (p<0.001, Kruskal-Wallis test; p=0.004, Chi-square test), there was no statistically significant correlation of whether or not at least 12 LNs were harvested with number of positive nodes, evidence of nodal involvement, tumor site or linear length of specimen. Table **3** demonstrates the lack of relationship between at least 12 LNs harvested and the ability to detect nodal involvement.

Procedural and Non Tumor Related Factors

There was no impact of institutional site on the relationship between our ability to harvest 12 or more LNs and tumor location. The highest percentages of cases with 12 LNs or more continued to be from right colon tumors, with the same sequence at both institutions. However there was a significant difference between the 2 institutions as far as the number of nodes collected. Surgeries performed at the VAMC were more likely to yield 12 LNs or more /specimens (Table **4**, p < 0.001). Institutional differences were not related to tumor location, as there was no significant difference between tumors resected from the different sites per institutions (Table **5**).

Table 3. No Relationship Between 12 or More Harvested Lymph Nodes and Evidence of Nodal Metastasis in Colorectal Specimens for Adenocarcinoma

Evidence of Nodal Involvement*	Less than 12 Nodes Resected	12 or More Nodes Resected	Total
No	93 50%	94 50%	187
Yes	54 45%	65 55%	119
Total	**147 48%**	**159 52%**	**306**

*p = 0.27 Fishers Exact Test.

Table 4. Influence of Institutional Site on Whether 12 or More Lymph Nodes Are Harvested in Colectomy Specimen for Colorectal Adenocarcinoma

Institutional Site of Surgery	Less than 12 Nodes Resected	12 or More Nodes Resected	Total
KUMC	101 57%	76 43%	177
VAMC	46 36%	83 64%	129
Total	**147 48%**	**159* 52%**	**306**

* p < 0.001 Chi-Square Test.

Table 5. Relationship Between Tumor Location and Institutional Site on Whether 12 or More Lymph Nodes Are Harvested in Colectomy Specimen for Colorectal Adenocarcinoma

Location of Resection*	KUMC	VAMC	Total
Cecum/Ascending Colon	71 40%	43 33%	**114 37%**
Transverse Colon	17 10%	8 6%	**25 8%**
Descending Colon	14 8%	17 13%	**31 10%**
Sigmoid Colon Rectum	75 42%	61 47%	**136 44%**
Total	**147**	**129**	**306**

*p = 0.22 Ch-Square Test.

We attempted to investigate factors impacting institutional difference on why more cases at the VAMC yielded 12 or more LNs as compared to KUMC, despite having the same individuals (pathology residents) grossly evaluating specimens at both institutions. We correlated surgeons experience in performing colectomies for tumor resections. Our results show that surgeons that had performed 10 or more colectomy

procedures were more likely to have obtained specimens with at least 12 LNs (Table **6**). It was noted, that 2 of 10 surgeons at the VAMC performed 76% of surgeons. In contrast, there were 21 surgeons at KUMC; none performed more than 12% of the cases.

Table 6. Influence of Number of Surgical Procedures Performed by Surgeons Annually on whether 12 or More Lymph Nodes are Harvested in Colectomy Specimen for Colorectal Adenocarcinoma

Number of Cases*	Less than 12 Nodes Resected	12 or More Nodes Resected	Total
<10	39 63%	23 37%	**62**
≥ 10	108 44%	136 56%	**244**
Total	**147** **48%**	**159*** **52%**	**306**

*p = 0.006 Fishers Exact Test.

Another factor that seemed to influence adequacy of LN assessment is the length of the resected segment of colon. While resected specimens 22 cm or longer yielded a slightly higher number of LNs (median of 12) than did segments less than 22 cm (median of 11), this was only marginally statistically significant (p=0.032, Mann-Whitney test). However, for the more critical question of whether at least 12 LNs were harvested, there was no statistically significant difference based on segment length (adequacy of 55% *vs* 48%, p=0.25, Chi-square test).

Finally, there was evidence that surgery date had an impact on number of harvested LNs. The likelihood of harvesting 12 nodes or more/specimen was significantly higher in surgeries performed in 2005 or later as compared to those performed prior to 2005 (Fig. **3**). Again this observation was consistently noted in both institutions.

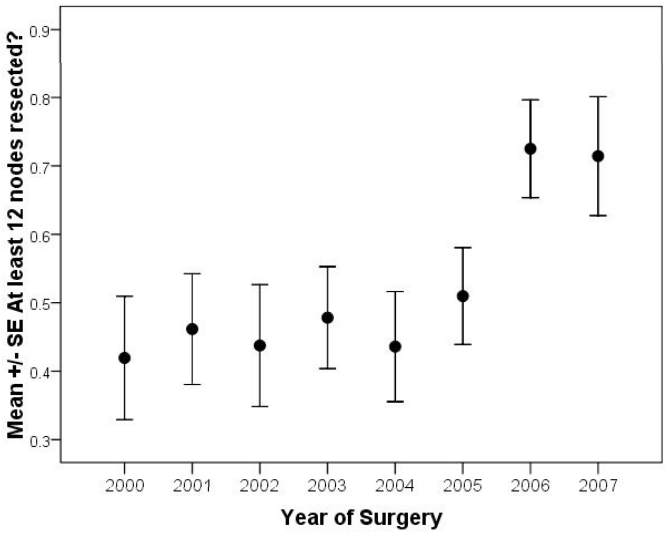

Fig. (3). A graph that shows the influence of surgery date on the number of harvested nodes in colectomy specimen for colorectal adenocarcinoma. Surgeries performed after 2005 were more likely to include 12 or more nodes per specimen (p = 0.002 Chi-Square Test), an observation that consistently noted in both institutions (KUMC p = 0.015, VAMC p = 0.036).

DISCUSSION

The results of our study suggest that the number of harvested LNs is not a straight forward process, but is related to several prognostically significant tumoral and non-tumoral parameters. The likelihood of harvesting 12 or more LNs is correlated with larger, higher grade and higher stage tumors. When tumor location is taken into account, more LNs were recovered form the right colon, followed by the descending, transverse, and lastly the rectosigmoid regions. Larger tumors were identified in the right colon and decreased in size in respect to the tumor location. It is yet to be determined if this effect is due to correlation or causation. These findings were consistent between institutions, even though the yield of at least 12 LNs differed between the two institutions.

Although the finding of node positivity correlated with tumor grade and stage, there was no significant correlation with whether 12 or more LNs were harvested with respect to tumor size, site or linear length of specimen. Our results are in total agreement with similar recent studies suggesting that tumor location, tumor grade [13], stage [14-16] and size is significantly impacting the number of identifiable LNs [17]. Shen *et al.* have recently reported that number of harvested LNs is most significantly associated with tumor location (right sided *vs* left sided cancer), patient age and length of resected specimen [12].

It is interesting to note that since this benchmark has been utilized, the percentage of colectomy specimen that has yielded 12 or more LNs has increased over time. However, this number is still surprisingly low. In a recent study by Moug *et al*, inadequate LN retrieval, as defined by NCI, occurred in approximately 50% of the cases [18]. Similarly researchers using the National Cancer Data Base, have determined that only 17.5% of hospitals met or exceeded the benchmark rate of 75% compliance with the 12-LN measure [8]. Fig. (**3**) shows that the likelihood of harvesting 12 LNs or more per specimen improved with time, an observation that was consistently noted in both institutions. This was probably due to the increased diligence of pathologists and their supporting staff over time.

One of the strengths of our study is that the data are obtained from 2 different institutions (VAMC and KUMC) where the same group of individuals (pathology residents) performed gross evaluation of colectomy specimens at both institutions. This was unique in the study as it allowed us to evaluate other confounding factors in a more objective and direct way, excluding the potential impact of prosector's skills and techniques.

The potential relevance of other confounding factors such as host response, patient's age and the use of various techniques to facilitate identification of nodes was also reported by others with mixed results.

Non-tumor factors that appear to have an impact on number of nodes harvested are surgery date, institution site, surgeons' experience and/or technique as well as segmental resection length. Although it is interesting that those surgeons at the VAMC were more likely to have performed

more than 10 surgeries over the 8 years evaluated, the potential impact of the surgeon's experience and the type of surgery performed need further evaluation. This was the most compelling factor when comparing the VAMC to KUMC. Several studies have suggested the potential impact of surgeons training and surgical techniques on lymph node harvesting [14, 15, 19-23]. It has been known that surgeons with more training and/or experience in colorectal procedures were more successful in obtaining adequate resections. Barbas el al, have recently shown that advanced fellowship training is associated with increasing number of lymph nodes analyzed [22]. If surgeons, pathologists and insurance companies wish to utilize the number of LNs harvested to determine adequacy of resection, these other variables must be factored into the equation.

Experience in adequately resected pericolonic mesenteric tissue and accompanying lymph nodes have been shown to be of prognostic significance [14, 15, 20-23]. Although we don't argue the numerous studies suggesting a better prognosis for patients in whom more nodes are examined, caution is advised when assessing the correlation between survival and number of LNs in colectomy specimens for colorectal cancer. Circumstances differ significantly for each patient, as well as each cancer surgery. The number of LNs assessed depends on multiple factors including, the surgeon, the pathologist, and the particular anatomy of the patient, (e.g. correlating number of LNs with survival does not hold for rectal cancer or any other scenario in which preoperative radiation or chemotherapy may destroy the nodes [24]). In a recent study by Wong *et al*, the authors retrospectively reviewed the 1995-2005 national Surveillance, Epidemiology, and End Results (SEER)-Medicare database, representing one fourth of the United States, for colon cancer colectomy LN examination rates in comparison to 5-year survival. Their analysis showed that higher numbers of identifiable nodes didn't correlate with higher rates of node-positive disease nor did it affect patient survival [25]. Similarly, Kim *et al.* have demonstrated that additional lymph node examination from mesenteric tissue surrounding colorectal cancer in resection specimens was of no added clinical or pathologic relevance [26].

In conclusion, our results that the harvesting of at least 12 LNs in colectomy specimens for colorectal cancer is complex and the impact of various tumoral and non tumoral confounding factors should be taken into consideration before generalizing its use in guiding treatment or reimbursement. Creating simple solutions for quality improvements, especially when not based on sound evidence, such as setting quality benchmarks for number of nodes evaluated, although attractive to policy makers and payers, could lead to failure in achieving the desired improvement in patient outcomes. In fact it could be very disruptive to efforts aiming at developing effective strategies to solve the underlying problems.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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