Challenging the Feasibility and Clinical Significance of Current Guidelines on Lymph Node Examination in Rectal Cancer in the Era of Neoadjuvant Therapy

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ABSTRACT

Purpose

We sought to examine the feasibility and clinical significance of current guidelines on nodal assessment in patients with rectal cancer (RC) treated with neoadjuvant radiation.

Methods

All patients with RC treated with curative surgery from 1991 to 2003 were included. Number of lymph nodes (LNs) assessed was compared between patients who received neoadjuvant therapy and surgery (NEO) and patients who underwent surgery alone (SURG). Impact of node retrieval on node positivity and disease-specific survival (DSS) in NEO patients was assessed.

Results

In total, 708 patients were identified, of whom 429 (61%) were in the NEO group. These patients had significantly fewer nodes assessed than SURG patients (unadjusted mean, 10.8 v 15.5; adjusted mean difference, -5.0 nodes; $P < .001$). In the NEO group, 63% of patients had fewer than 12 nodes retrieved ($P < .001$ v SURG). The proportion of patients diagnosed with node-positive disease in the NEO group was significantly and monotonically associated with the number of lymph nodes retrieved, with no plateau in the relationship. Fewer nodes retrieved was not associated with inferior DSS.

Conclusion

In a tertiary cancer center, the 12-LN threshold was not relevant and often not achievable in patients with RC treated with neoadjuvant therapy. Lower LN count after neoadjuvant treatment was not associated with understaging or inferior survival. Although we support the critical importance of careful pathologic examination and adequate nodal staging, we challenge the relevance of LN count both in clinical practice and as a quality indicator in RC.

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INTRODUCTION

Accurate determination of tumor depth and nodal status are crucial to accomplish adequate staging of colorectal cancer. To ensure adequate nodal staging, current guidelines recommend that a minimum of 12 to 14 lymph nodes be assessed in colorectal cancer,¹⁻⁵ with some groups suggesting that even more nodes may be beneficial.⁶ These guidelines are based on several lines of evidence that have suggested that an inadequate number of nodes assessed may result in understaging,⁷⁻⁹ with attendant prognostic and possibly therapeutic impacts. In addition, studies have consistently shown that increased nodal harvest is associated with improvement in survival.¹⁰ Indeed, these data have led to the recommendation and adoption of the 12-node minimum as a quality measure by various organizations and payer groups.^{10,11}

The cause-effect nature of this relationship is, however, questionable.¹² More importantly, the data underpinning the guideline and its use as a quality measure are based entirely on patients with colon cancer, with the results being extrapolated to rectal cancer. However, significant differences between the two diseases could threaten the validity of this extrapolation, the most relevant of which is the use of neoadjuvant radiation and chemoradiotherapy in patients with rectal cancer,¹ which is not usually an issue in colon cancer. In this study, we sought to determine the feasibility and clinical relevance of meeting the 12-node guideline in patients with rectal cancer treated with neoadjuvant radiation or chemoradiotherapy. Specifically, we examined two hypotheses: first, preoperative radiation would reduce the number of evaluable nodes, and second, a reduction in the number of nodes would not result in

significant understaging. If there were significant understaging, two downstream effects would be manifested: first, the apparent node-positive rate would increase with the number of nodes evaluated to a plateau representing the true node-positive rate, and second, survival of patients would improve as more nodes were examined. To evaluate the second hypothesis, we tested these two downstream effects.

METHODS

Study Population and Design

We conducted a retrospective cohort study using an institutional database. The study was approved by the institutional review board. All patients with rectal cancer treated with curative surgery from 1991 through 2003 at a single tertiary-care cancer center were included in the study. Patients were categorized into two groups: those treated with surgery alone (SURG) and those treated with neoadjuvant therapy (NEO).

Treatment

Preoperative staging was performed using a combination of clinical examination, endorectal ultrasound, and cross-sectional imaging (computed tomography or magnetic resonance imaging). Indications for neoadjuvant treatment included stage II or III tumors based on clinical and radiologic examinations. Long-course external beam chemoradiotherapy was employed in 96% of patients and involved a median total dose of 50.4 Gy delivered in 26 fractions with fluorouracil (FU)-based single-agent chemosensitization. Rectal resection was performed using the principles of total mesorectal excision, with appropriately high ligation of the superior hemorrhoidal vessels or inferior mesenteric artery.¹³ A complete 6-month course of adjuvant FU-based chemotherapy was typically recommended for all patients completing neoadjuvant chemotherapy and curative surgery. During the study period, infusional FU plus leucovorin was the standard adjuvant chemotherapy used.

Pathologic Examination

All mesenteric tissue was manually dissected and examined for nodes. Pathology assistants were used to gross the specimens. Fat-clearing techniques were not used. Routine microscopy was performed by one of five specialized GI pathologists. If fewer than 12 nodes were identified on first examination, a second attempt to locate lymph nodes was performed by the pathologist or pathology assistant with the assistance of the pathologist. This was performed in the standard fashion, with careful palpation and sectioning through fatty tissues. Submission of additional sections of mesorectum was based on the impression of gross examination; any tissue suspicious for being a lymph node was submitted.

Statistical Analysis

The primary outcome was number of nodes assessed. The main independent variable for this analysis was treatment group (SURG v NEO). Secondary outcomes included node-positivity rate and disease-specific survival (DSS). The main independent variable for these analyses was number of nodes assessed. Covariates including patient factors (age, sex), tumor factors (distance from anal verge, differentiation, lymphovascular invasion, clinical and pathologic stage), and type of surgery (low anterior v abdominoperineal resection) were assessed as potential confounding variables.

Baseline patient characteristics were compared between groups using the *t* test or Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. Linear regression was used to compare number of nodes in the two groups. Logistic regression was used to analyze the association between node number and node positivity. Kaplan-Meier survival analysis was used to analyze DSS, with the log-rank test used to compare groups. DSS was defined as time from diagnosis to death as a result of disease. Patients who were alive or died as a result of other causes were censored at date of death or last follow-up. Survival analyses were also stratified based on pathologic nodal status to account for possible interactions between number of nodes and nodal status. This subgroup analysis sought to assess the issue of possible understaging in patients deemed pathologically node negative based on assessment of a

Table 1. Baseline Patient Clinical Characteristics

Characteristic	SURG Group (n = 279)	NEO Group (n = 429)	P
Median age, years	63	59	.0019
Female sex, %	45.8	36.6	.014
Distance from anal verge, cm	7.2	6.3	.0001
Type of surgery, % APR	19.7	13.3	.022
Poor differentiation, %	4.3	6.3	.26
Circumferential margin positive, %	2.68	2.61	1.00
Pathologic stage, %			
ypT0-2	64.5	59.4	.18
ypT3-4	35.5	40.6	.18
ypN+	33.0	21.0	.0009

Abbreviations: APR, abdominoperineal resection; NEO, neoadjuvant therapy; SURG, surgery alone.

reduced number of nodes. Cox proportional hazards models were used to adjust the survival analysis for potential confounders. All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary NC). Two-sided *P* values less than .05 were considered statistically significant.

RESULTS

Patient Characteristics

A total of 708 patients were identified, of whom 429 (61%) received NEO. A vast majority of these patients were treated with neoadjuvant long-course chemoradiotherapy (n = 411; 96%), whereas 18 patients received radiation alone. All 708 patients were treated with complete resection. Descriptive characteristics are compared between the two groups in Table 1.

Impact of Neoadjuvant Treatment on Number of Nodes Assessed

Mean number of nodes retrieved in the SURG group was 15.5 (median, 13). In the NEO group, significantly fewer nodes were assessed, with a mean of 10.8 nodes (median, 10; *P* < .001), translating to a 30.3% reduction in number of nodes assessed (unadjusted mean difference, 4.7 nodes). In the NEO group, there was a marked shift toward fewer nodes (Figs 1A, 1B), with 63% of patients having fewer than 12 nodes assessed (SURG group: 40% of patients; *P* < .001). Mean number of nodes assessed did not significantly change with time. Mean number of positive nodes identified was 1.1 (median, one) in the SURG group and 0.4 (median, one) in the NEO group. Mean number of negative nodes identified and assessed was 14.4 (median, 12) in the SURG group and 10.4 (median, nine) in the NEO group, thereby accounting for 85% of the absolute reduction in total number of nodes identified and assessed (Fig 2). In multivariable analysis, patients in the NEO group had significantly fewer nodes assessed than patients in the SURG group (mean difference, 5.0 nodes; 95% CI, 3.6 to 6.4; *P* < .001). Age (− 0.13 nodes per year; *P* < .01), sex (− 1.6 nodes in men v women; *P* = .025), and pathologic T stage (+ 1.8 nodes for pT3-4 v pT0-2; *P* = .0091) were significantly associated with number of nodes assessed. The extent of proctectomy (abdominoperineal v anterior resection) did not significantly influence number of nodes (*P* = .9). As in the univariate analysis, multivariable analysis

Fig 1. Histogram of number of lymph nodes assessed in (A) the surgery-alone group versus (B) the neoadjuvant therapy group, showing left shift toward fewer nodes in the neoadjuvant therapy group.

showed that a reduction in number of negative nodes assessed accounted for 88% of the reduction in total number of nodes (mean difference, 4.4 nodes; 95% CI, 3.1 to 5.8).

Impact of Number of Nodes Assessed on Node Positivity in NEO Group

The proportion of patients diagnosed with node-positive disease in the NEO group ranged from 10.8% in patients with zero to three nodes assessed to 31.4% in patients with 20 or more nodes assessed. In univariate and multivariable analyses, there was significant association between number of nodes identified and the node-positivity rate, with a 4% increase in the node-positivity rate for each additional node

Fig 2. Absolute reduction in negative and positive lymph nodes in the surgery-alone and neoadjuvant therapy groups.

Fig 3. Relationship between node-positive rate and number of nodes assessed in the neoadjuvant therapy group.

identified (95% CI, 0.3% to 7.6%; $P = .03$). Figure 3 shows the relationship between number of nodes and node-positivity rate. The positive correlation between number of nodes and node positivity was monotonic, with no plateau in the relationship.

Impact of Number of Nodes Assessed on DSS

The 5-year DSS was 89.2%, with no significant association seen based on number of nodes (Fig 4). Factors most strongly associated with DSS were pathologic T stage (hazard ratio [HR] for pT3/4 v pT0-2, 2.1; 95% CI, 1.4 to 3.1; $P < .001$) and pathologic N stage (HR, 2.4; 95% CI, 1.6 to 3.6; $P < .001$). Number of nodes was not significantly associated with DSS (HR, 0.99; 95% CI, 0.96 to 1.01). We then examined the association between DSS and number of nodes specifically in the subgroup of NEO patients with pathologically node-negative disease to assess whether reduction in node count was associated with understaging in this group. There was no significant association between number of nodes assessed and DSS in univariate ($P = .19$) or multivariable analysis (HR, 0.94; 95% CI, 0.88 to 1.01; $P = .09$).

DISCUSSION

Current guidelines recommending that a minimum of 12 lymph nodes be assessed for adequate staging of colorectal cancer are based

Fig 4. Disease-specific survival of patients stratified by number of lymph nodes (LNs) assessed.

on data for colon cancer and have been extrapolated for use in rectal cancer. In this study, we examined the impact of neoadjuvant radiation on node retrieval in rectal cancer and the resulting clinical implications. We found that neoadjuvant radiation treatment results in significantly fewer nodes assessed and specifically impairs the ability to assess 12 nodes. Indeed, 12 nodes were only assessed in 37% of patient cases. Importantly, however, we found that this reduction in nodes did not result in significant understaging and was not correlated with patient outcome.

Overall, an average of five fewer nodes were assessable in the group treated with neoadjuvant radiation compared with the SURG group. Although there was a greater relative reduction in number of positive nodes than in number of negative nodes, this reflects the effect of neoadjuvant chemoradiotherapy on downstaging nodes. In absolute terms, over 85% of the reduction in total number of nodes assessed resulted from a reduction in negative nodes. This distinction is important when considering nodal assessment guidelines, which are based on assessing a specified total number of nodes to reduce sampling error. However, the inability to identify 12 total nodes in a majority of patients is mostly the result of an inability to identify negative nodes in the radiated specimen, which cannot affect the ability to assess for node positivity. This reduction in negative nodes possibly results from radiation-induced lymphocyte destruction and stromal fibrosis, which may render lymph nodes difficult to detect.^{14,15}

It is generally posited that assessing an adequate number of nodes is important to prevent understaging, with different thresholds proposed for different diseases.^{1-4,16} These fixed thresholds presume that the influence of number of nodes on staging accuracy is purely an issue of sampling error. However, in addition to showing here that neoadjuvant treatment can have a profound effect on the number of evaluable nodes, previous work from our group and others has shown that variables related to tumor biology are consistently associated with number of nodes, presumably as a result of tumor-host interactions.¹⁷⁻²² In colon cancer, Gonen et al²³ suggested that the number of nodes required to be assessed is a function of the T stage of the tumor. In T1 patients, assessment of only four nodes can yield 95% accuracy for nodal status. In addition, factors related to surgical resection (extent of mesenteric resection, specimen length) and pathologic assessment process (use of pathology assistants, specialist histopathologists) can affect the number of nodes assessed.^{17,18,22,24}

Given the numerous factors that can influence node retrieval, it is important to assess the clinical impact of a reduced number of nodes to determine staging accuracy in the post-treatment setting. This is difficult, because the true node-positive rate is unknown, and therefore, there is no comparator for the observed node-positive rate. However, if understaging were a significant issue, two phenomena would be expected. First, as more nodes were assessed, the likelihood of missing node-positive disease would progressively decrease, and thus, the observed node-positive rate would progressively increase to a plateau representing the true node-positive rate. Second, DSS would seem to improve partly because of stage migration. However, we found that the node-positive rate increased monotonically as the number of evaluated nodes increased, without reaching a plateau. Because an understaging mechanism would necessarily result in a plateau, the lack of plateau implies that understaging cannot be the primary driver of this relationship. A more plausible explanation is a biologic one, wherein more aggressive tumors result in both higher

true node-positive rates and an increased number of nodes. We also found that there was no significant relationship between assessment of more nodes and improved survival. These findings imply that patients were accurately staged with respect to nodes after neoadjuvant radiation. Accurate determination of the true nodal status of a patient is important, because it has repeatedly been shown to be one of the strongest prognostic factors in patients with rectal cancer treated with neoadjuvant chemoradiotherapy.²⁵⁻²⁸ Moreover, some authors have questioned the role of routine adjuvant chemotherapy in favorable subsets of patients with rectal cancer,²⁹⁻³¹ a hypothesis that requires confidence in the pathologic nodal status.

Our findings on decreased nodes as a result of radiation are consistent with those of previous studies.^{19-21,32-35} However, some of these studies are population-based^{21,34} or from earlier time periods,^{32,33} in which the uniformity and quality of the surgical and pathologic processes are unclear. To our knowledge, our study is the largest to date conducted in a setting in which standardized surgical and pathologic techniques were used to maximize node retrieval. This is evidenced by the high number of nodes in the control group of this study and in previous reports from our institution on colon cancer.¹⁷

The rigorous approach to node assessment in this study was crucial to minimize the measurement bias that can significantly influence study outcomes. Furthermore, few studies have examined the clinical impact of a decreased number of nodes.^{19,20} In this study, we put forward three complementary lines of evidence suggesting that decreased number of nodes does not have a significant clinical impact. First, although we confirm that neoadjuvant radiation significantly affects the ability to assess 12 nodes, we suggest that this does not increase sampling error or impair the ability to find node-positive disease, because the reduction is largely the result of a loss of negative nodes. Second, we show that the relationship between the number of nodes and node positivity is not consistent with understaging, a finding not previously reported in rectal cancer, to our knowledge. Third, as in the studies by Rullier et al¹⁹ and Ha et al,²⁰ when assessed by experienced pathologists, the reduction in evaluable nodes does not have a significant impact on patient survival.

There are several factors that may contribute to lack of association between number of nodes, staging accuracy, and outcome. First, it is possible that the relationship between number of nodes and node positivity may reach a plateau beyond the limits of our analysis (≥ 20 nodes). This is unlikely, because there are no analogous situations in other disease sites, including colon cancer, that require such a high number of nodes for adequate staging. In addition, the node-positive rate at 20 nodes was 31%, which is higher than in most studies,^{25,36} suggesting that understaging was not at issue here. Finally, from a pragmatic point of view, if the plateau had yet to be reached, guidelines would need to recommend that more than 20 nodes be assessed, a number that is unfeasible. Second, it is possible that we were underpowered to detect small survival differences, especially in subgroup analyses. However, to our knowledge, our sample size is the largest cohort to date with standardized surgery and pathology, and such small differences would be unlikely to be clinically relevant, especially because the cause-effect relationship between number of nodes and survival is questionable at best.¹² Rather, the most likely explanation for the lack of relationship between number of nodes and staging is the predominant effect of radiation on the absolute number of negative nodes, which does not affect staging, and the result of underlying meticulous processes used to identify and analyze mesenteric nodes.

Our results do not support the need for fat-clearing solutions to increase lymph node yield; we found that careful pathologic examination in the absence of these solutions can result in accurate nodal assessment. A further limitation of our study is that it was retrospective. Therefore, it is possible that unmeasured confounders may have influenced the findings. Nevertheless, these variables do not affect the decision to treat with NEO and are not likely to be grossly imbalanced between groups. Our results may also have been subject to selection bias, because patients in the SURG group would tend to have had earlier-stage disease. To minimize the impact of this on our results, multivariable analyses were performed, incorporating several tumor variables (including stage). In this study, the pathologists were not blinded to treatment group. However, because low lymph node yields prompted additional attempts at identifying nodes in the specimen, any measurement bias resulting from the lack of blinding would serve to attenuate the difference in number of nodes between the two groups rather than increase it. One final limitation is that almost all patients in this study were treated with long-course neoadjuvant chemoradiotherapy. Therefore, we were unable to draw any conclusions about differences between various radiotherapy regimens. However, long-course chemoradiotherapy is the de facto standard treatment employed in North America, and thus, our conclusions are applicable to this population.

In conclusion, in this large population of patients with rectal cancer treated at a tertiary-care cancer center, use of neoadjuvant

radiation markedly impaired the ability to assess 12 nodes, as recommended by current guidelines. However, when assessed by expert pathologists, this did not result in significant understaging. Therefore, we question the feasibility and clinical relevance of the 12-lymph node threshold as both a guideline and quality marker in rectal cancer; instead, we favor recommendations based on total mesorectal excision for rectal cancer and sound pathologic processes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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