Lymph Node Evaluation in Colorectal Cancer Patients: A Population-Based Study

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Background: **Adequate lymph node evaluation is required for proper staging of colorectal cancer, and the number of lymph nodes examined is associated with survival. According to current guidelines, the recommended minimum number of lymph nodes examined to ensure adequate sampling is 12. We used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program to determine the proportion of colorectal cancer patients in the United States who receive adequate lymph node evaluation.** ***Methods:*** **For 116 995 adults with colorectal adenocarcinoma, diagnosed from 1988 through 2001, who underwent radical surgery and did not receive neoadjuvant radiation, we evaluated the number of lymph nodes, the likelihood of receiving adequate lymph node evaluation (i.e., at least 12 lymph nodes examined), and the influence of tumor and patient factors on lymph node evaluation. All statistical tests were two-sided.** ***Results:*** **Among all patients, the median number of lymph nodes examined was nine. Only 37% of all patients received adequate lymph node evaluation. The proportion of patients receiving adequate lymph node evaluation increased from 32% in 1988 to 44% in 2001 (P_{trend}<.001, Cochran–Armitage test). Advanced tumor stage was statistically significantly associated with adequate lymph node evaluation (odds ratio [OR] of receiving adequate lymph node evaluation = 2.27, 95% confidence interval [CI] = 2.18 to 2.35). Older patients (≥71 years, OR = 0.45, 95% CI = 0.44 to 0.47) were less likely to receive adequate lymph node evaluation than younger patients, and those with left-sided (OR = 0.45, 95% CI = 0.44 to 0.47) or rectal (OR = 0.52, 95% CI = 0.50 to 0.54) cancers were less likely to receive adequate lymph node evaluation than patients with right-sided cancers. In all analyses, geographic location was an important predictor of adequate lymph node evaluation, which ranged from 33% to 53%, depending on geographic location.** ***Conclusions:*** **In 2001, the majority of patients with colorectal cancer still received inadequate lymph node evaluation. The association of demographic variables, particularly patient age and geographic location, with adequate lymph node evaluation indicates that local surgical and pathology practice patterns may affect adequacy of lymph node evaluation. [J Natl Cancer Inst 2005;97:219–25]**

Colorectal cancer is the second leading cause of cancer death in the United States. Given that 57,000 Americans will die of this disease in 2004 *(1)*, improving the outcome of patients with colorectal cancer is of major importance. In nonmetastatic colorectal cancer, lymph node status is the strongest pathologic predictor of patient outcome. Approximately 68% of patients with no lymph node involvement will survive 5 years, compared with only 40% of those with lymph node metastases *(2)*. Because of the high risk of tumor recurrence, patients with positive lymph nodes are routinely referred for adjuvant therapy *(3)*. In addition, patients with rectal cancer and positive lymph nodes have a higher rate of local recurrence than in patients with negative lymph nodes*(4)*.

Because detection of any positive lymph node is critical for predicting patient outcome, an adequate number of lymph nodes must be examined. In patients with negative lymph nodes, the minimum number of negative lymph nodes necessary for adequate staging is 12 according to both the International Union Against Cancer and the American Joint Committee on Cancer *(5,6)*. The evaluation of at least 12 lymph nodes has been accepted as a standard in rectal cancer treatment by a National Cancer Institute–sponsored panel of experts *(7)*.

Inadequate lymph node sampling has serious implications. It can lead to positive lymph nodes being missed and to patients being inappropriately classified as having lymph node–negative disease *(8,9)*. Such patients may not be given the opportunity to benefit from adjuvant therapy. In addition, inadequate lymph node sampling may result in the failure to remove involved lymph nodes, thus increasing the risk of local recurrence; it may also be a marker of poor-quality surgical or pathologic care, both of which are associated with worse long-term outcome for colorectal cancer patients *(10)*.

The number of lymph nodes sampled has been found to be an important predictor of colorectal cancer outcome, particularly in patients with stage II disease *(11–14)*. For example, Swanson et al. *(11)* used the National Cancer Database to study patients with stage II (T3N0) disease and found that the number of lymph nodes sampled was strongly associated with survival. For patients classified with stage II disease, the 5-year survival rate was 64% when one or two lymph nodes were sampled but 86% when more than 25 nodes were sampled. Other studies *(11,13,14–20)* have consistently shown that the number of lymph nodes examined is important for accurate staging and is prognostic for long-term survival.

Despite the importance of accurate staging, adequacy of operative lymph node retrieval in colorectal cancer patients has not been examined on a broad scale. We present a population-based analysis of lymph node evaluation in the United States.

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Materials and Methods

Data

We used data from the Surveillance, Epidemiology, and End Results[1] (SEER) cancer registry to conduct this study. SEER, a population-based registry sponsored by the National Cancer Institute, collects information on cancer incidence and survival from 11 population-based cancer registries, including approximately 14% of the U.S. population *(2)*. Of the 11 registries, two were added in 1992. Because SEER reports data by registry, our study period includes data from those corresponding 11 distinct geographic locations. The information collected by SEER includes patient characteristics, county of residence, primary tumor site, tumor grade, stage at diagnosis (formal American Joint Committee on Cancer staging has only been available in SEER since 1988), first course of treatment (through completion of the initial treatment plan, including treatment within the first year after diagnosis or until there is evidence either of disease progression or of treatment failure within the first year), timing of radiation, number of lymph nodes evaluated, and follow-up for vital status *(21)*.

Patients

We included patients aged 18 years or older who were diagnosed with localized invasive adenocarcinoma of the colon or rectum from January 1988 through December 2001. For the two registries added in 1992, we included patients diagnosed from January 1992 through December 2001. We excluded patients presenting with in situ or metastatic disease, patients with prior malignancies, patients with malignancies other than adenocarcinoma, and patients who had appendiceal carcinoma. From the 140 921 patients identified, we excluded patients who had cancer of the colon not otherwise localized, patients who did not undergo radical surgical resection, and patients who underwent preoperative radiation. A total of 116,995 patients remained after all exclusions. Because our study used preexisting data with no personal identifiers, it was exempt from review by the University of Minnesota's institutional review board.

Statistical Analysis

We calculated the mean and median number of nodes examined. We then determined the proportion of patients who had no lymph nodes examined and the proportion of patients who had at least 12 lymph nodes examined (defined as adequate lymph node evaluation). We compared patients categorized on the basis of tumor location (right-sided colon cancer [proximal to the splenic flexure], left-sided colon cancer [from the splenic flexure to the rectosigmoid], and rectal cancer), and on the basis of tumor stage (stage I, stage II, and stage III disease). We compared the median number of lymph nodes examined between groups using nonparametric methods, including the Wilcoxon rank-sum test and the Kruskal–Wallis test. We compared the proportion of patients who received an adequate lymph node examination between groups with the chi-square test. We evaluated trends over time by using the Cochran–Armitage trend test on one degree of freedom. We tested for any association between adequate lymph node evaluation and patient age, race/ethnicity, sex, or geographic location; year of diagnosis; or tumor stage, grade, and anatomic site by using logistic regression. We tested for interactions between tumor stage and anatomic site of cancer, tumor stage and race/ethnicity, tumor stage and grade, and sex and anatomic site of cancer. Data were analyzed using SAS version 8e (1999, SAS Institute, Cary, NC). All statistical tests were two-sided.

Results

Of the 116,995 patients (50% male, 50% female) with colorectal cancer who met the eligibility criteria, 42.4% had right-sided colon cancer, 43.2% had left-sided colon cancer, and 14.4% had rectal cancer (Table 1). Most patients (83%) were white, and most patients (82%) had well- or moderately differentiated tumors. Because tumor grade was missing for 7% of the patients, we conducted all multivariable analyses with and without inclusion of tumor grade as a covariate and compared the results for consistency.

The number of lymph nodes examined could be determined for 111 730 (95.5%) patients. The median number of lymph nodes examined for all patients was nine (Fig. 1). No lymph nodes were examined in 6.5% of the patients. When the patients were stratified by tumor stage, no lymph nodes were examined

Table 1. Patient and tumor characteristics

Characteristic	All patients, $N = 116\,995$	Anatomic site of tumor			P value
		Right colon, 49 613	Left colon, 50 536	Rectum, 16 846	
Median patient age, y	71	74	69	68	<.001
Males : Females	50% : 50%	44% : 56%	53% : 47%	58% : 42%	<.001
Patient race/ethnicity*					
White	97 044 (83%)	41 643 (84%)	41 257 (82%)	14 144 (84%)	<.001
Nonwhite	19 676 (17%)	7845 (16%)	9158 (18%)	2673 (16%)	<.001
Tumor stage†					
Stage I	27 323 (25%)	9288 (19.5%)	12 914 (27%)	5121 (33%)	<.001
Stage II	44 771 (40%)	21 652 (45.5%)	18 544 (39%)	4575 (29%)	<.001
Stage III	38 660 (35%)	16 699 (35%)	16 083 (34%)	5878 (38%)	<.001
Tumor Grade‡					
Well or moderately differentiated	89 042 (82%)	35 339 (76%)	40 627 (87%)	13 076 (83%)	<.001
Poorly differentiated	20 031 (18%)	11 149 (24%)	6204 (13%)	2678 (17%)	<.001
Node No. (Median)§	9	11	7	8	

*Race/ethnicity information missing for 275 patients (< 1%).

†Stage information missing for 6241 patients (5%).

‡Grade information missing for 7922 patients (7%).

§Lymph node number missing for 5265 patients (4.5%).

in 9.5% of patients with stage I disease and in 3% of patients with stage II disease. The number of lymph nodes examined differed based on anatomic site in the colon ($P<.001$); more nodes were examined in patients with right-sided colon cancer (median = 11, interquartile range = 7–17; mean = 13) than in those with left-sided colon cancer (median = 7, interquartile range = 4–13; mean = 9) or those with rectal cancer (median = 8, interquartile range = 4–14; mean = 9.5) (Table 2). The number of lymph nodes examined also differed based on tumor stage ($P<.001$); fewer lymph nodes were examined in patients with stage I disease (median = 6, interquartile range = 3–12; mean = 8.4) than in patients with stage II (median = 10, interquartile range = 6–15; mean = 11.6) or stage III (median = 11, interquartile range = 7–16; mean = 12.7) disease.

Only 37% of all patients received adequate lymph node evaluation (i.e., at least 12 lymph nodes examined) (Table 3). Statistically significantly ($P<.001$) higher percentages of patients with stage II (41%) or stage III (46%) disease had adequate lymph node evaluation than patients with stage I disease (25%). The percentage of patients with adequate lymph node evaluation was particularly low for patients with disease at or distal to the splenic flexure: 19% of those with stage I disease, 33% of those with stage II disease, and 40% of those with stage III disease.

We next evaluated whether any patient and tumor factors were associated with adequate lymph node evaluation (Table 3). Irrespective of tumor stage, younger patients were statistically significantly more likely than older patients to receive adequate lymph node evaluation. Overall, 50.5% of patients who were aged 50 years or younger received adequate lymph node evaluation compared with 35% of those aged 70 years or older ($P<.001$). The rate of adequate lymph node evaluation improved over time for all patients, regardless of tumor stage (from 32% in 1988 to 44% in 2001, $P<.001$), and for patients stratified by tumor stage (Fig. 2). Nevertheless, in 2001, only 23% of patients with stage I left-sided colon cancer and only 26% of patients with stage I rectal cancer received adequate lymph node evaluation.

The results of our multivariable analysis are presented in Table 4. After adjusting for confounders, younger patients, patients with right-sided colon cancer, patients with stage II or stage III disease, and patients with poorly differentiated tumors were statistically significantly more likely to receive adequate lymph node evaluation than older patients, those with left-sided cancer, those with stage I disease, or those with well- or moderately well differentiated tumors, respectively ($P<.001$ for all variables). Although the effect of sex was statistically significant, the odds of an adequate lymph node evaluation for women (versus men) was only 1.05—a difference of questionable clinical significance. Indeed, given the large numbers of patients in our analyses, differences that are found to be statistically significant may have little clinical relevance. Race/ethnicity was not associated with adequate lymph node evaluation. In a logistic regression model that included only patients with stage III disease, tumor stage was a predictor of adequate lymph node evaluation: The odds ratio of adequate lymph node evaluation for patients with T3 or T4 (versus T1 or T2) tumors was 1.71 (95% confidence interval [CI] = 1.59 to 1.84, $P<.001$). We repeated the multivariable analyses excluding the two registries that have been in SEER only since 1992 and observed similar results (data not shown).

Because we identified statistically significant interactions between disease stage and race/ethnicity and between disease stage and anatomic site, we conducted separate analyses stratified by stage. Race/ethnicity was not associated with adequate lymph node evaluation for patients with any stage of disease. Among patients with stage I and II disease, those with left-sided cancers were statistically significantly less likely to have an adequate lymph node evaluation than patients with rectal cancer (stage I disease, odds ratio [OR] = 0.70, 95% CI = 0.64 to 0.76]; stage III disease, OR = 0.86, 95% CI = 0.80 to 0.92). For patients with stage II disease, we found no difference in the rate of adequate

Table 2. Median number of lymph nodes evaluated in patients with colorectal cancer identified from the Surveillance, Epidemiology, and End Results database

Characteristic	Median No. of lymph nodes evaluated (interquartile range)			
	All patients	Right colon	Left colon	Rectum
All patients	9 (5–15)	11 (7–17)	7 (4–13)	8 (4–14)
Patient age, y				
≤50	12 (6–18)	15 (10–24)	10 (5–16)	10 (5–17)
51–60	9 (5–15)	12 (8–19)	8 (4–13)	9 (5–14)
61–70	9 (5–14)	11 (7–17)	7 (3–12)	8 (4–13)
≥71	9 (5–14)	10 (6–16)	7 (4–12)	7 (3–12)
Year of diagnosis				
1988 through 1990	8 (4–14)	10 (6–16)	7 (3–12)	7 (3–12)
1991 through 1993	8 (4–14)	11 (6–16)	7 (3–12)	7 (3–13)
1994 through 1996	9 (5–14)	11 (6–17)	7 (4–12)	8 (4–13)
1997 through 1999	10 (5–15)	11 (7–17)	8 (4–13)	8 (4–14)
2000 through 2001	10 (6–16)	12 (7–18)	8 (5–14)	9 (5–14)
Tumor stage				
Stage I	6 (3–12)	9 (5–15)	5 (2–9)	6 (3–11)
Stage II	10 (6–15)	11 (7–17)	8 (5–13)	8 (4–13)
Stage III	11 (7–16)	12 (8–18)	9 (6–15)	10 (6–16)
Patient sex				
Male	9 (5–15)	11 (7–17)	7 (4–13)	8 (4–13)
Female	9 (5–15)	11 (7–17)	8 (4–13)	8 (4–13)
Patient race/ethnicity				
White	9 (5–14)	11 (7–17)	7 (4–12)	8 (4–13)
Nonwhite	10 (5–15)	12 (7–18)	8 (4–13)	9 (4–14)
Tumor grade*				
Well or moderately differentiated	9 (5–14)	11 (7–17)	8 (4–13)	8 (4–13)
Poorly differentiated	10 (6–16)	12 (7–18)	9 (5–14)	9 (5–14)

*Tumor grade determined according standard Surveillance, Epidemiology, and End Results classification *(21)*.

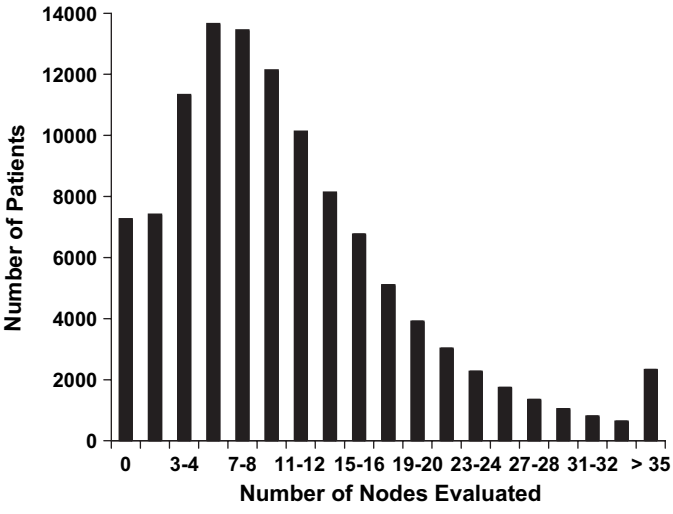

Fig. 1. Number of lymph nodes evaluated per patient in 116995 patients with colorectal cancer identified using the Surveillance, Epidemiology, and End Results database.

Table 3. Rate of adequate lymph node evaluation in all patients with colorectal cancer and in patients stratified by stage of disease*

Characteristic	% of all patients	*P* value† patients with	Rates among patients with stage I disease (*N* = 27 323)	*P* value	Rates among patients with stage II disease (*N* = 44 771)	*P* value	Rates among patients with stage III (*N* = 38 660)	*P* value
Overall Rates	37%		25%		41%		46%	
Patient age, y								
≤50	50.5%	<.001	35%	<.001	56%	<.001	57%	<.001
51–60	40%	<.001	27%	<.001	46%	<.001	48%	<.001
61–70	36%	<.001	23%	<.001	41%	<.001	45%	<.001
≥71	35%	<.001	24.5%	<.001	37%	<.001	43%	<.001
Year of diagnosis								
1988 through 1990	33%	<.001	22%	<.001	37%	<.001	40%	<.001
1991 through 1993	35%	<.001	23%	<.001	38%	<.001	44%	<.001
1994 through 1996	36%	<.001	24%	<.001	40%	<.001	45%	<.001
1997 through 1999	40%	<.001	26%	<.001	43%	<.001	49%	<.001
2000 through 2001	42.5%	<.001	31%	<.001	45%	<.001	52%	<.001
Anatomic site of tumor								
Right colon	47.5%	<.001	38%	<.001	49%	<.001	54%	<.001
Left colon	29%	<.001	17%	<.001	33%	<.001	39%	<.001
Rectum	31%	<.001	23%	<.001	33%	<.001	43%	<.001
Patient sex								
Male	36%	<.001	23%	<.001	40%	.06	45%	<.01
Female	38%	<.001	27%	<.001	41%	.06	47%	<.01
Patient race/ethnicity								
White	37%	<.001	25%	.03	40%	<.001	45%	<.001
Nonwhite	40%	<.001	27%	.03	43%	<.001	50%	<.001
Tumor grade‡								
Well or moderately differentiated	37%	<.001	26%	<.001	40%	<.001	45%	<.001
Poorly differentiated	45%	<.001	29%	<.001	45%	<.001	50%	<.001

*Adequate lymph node evaluation involves evaluating at least 12 lymph nodes.

†The between group comparison of the proportion of patients who received an adequate lymph node examination was determined by the chi-square test.

‡Tumor grade determined according standard Surveillance, Epidemiology, and End Results classification *(21)*.

lymph node evaluation between patients with left-sided cancers and patients with rectal cancers. For patients with all stages of disease, patients with right-sided cancers were twice as likely to have an adequate lymph node evaluation as those with rectal cancers (OR = 1.92, 95% CI = 1.92 to 2.00).

Geographic location of treatment, as recorded by SEER registry, was a statistically significant predictor of adequate lymph node evaluation. We found large, statistically and clinically significant differences between geographic locations in the univariate and multivariable analyses (all *P*<.001). Among registries, the overall percentage of patients with adequate lymph node evaluation ranged from 33% to 53% (Fig. 3). In 2001, the median number of lymph nodes retrieved varied among registries from a median of eight lymph nodes per patient to 14 lymph nodes per patient (*P*<.001); those differences are significant both statistically and clinically.

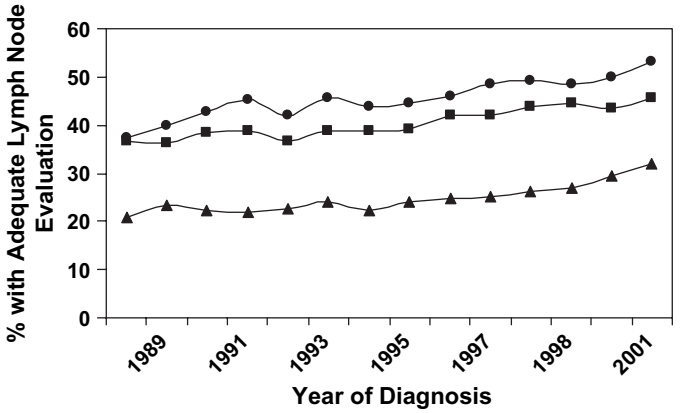

Fig. 2. Percentage of patients with adequate lymph node evaluation (i.e., at least 12 lymph nodes evaluated) by stage of colorectal cancer disease over time. Solid triangles = percentage of patients with stage I disease who had adequate lymph node evaluation; solid squares = percentage of patients with stage II disease who had adequate lymph node evaluation; Solid circles = percentage of patients with stage III disease who had adequate lymph node evaluation.

Discussion

Accurate assessment of lymph node status in patients with nonmetastatic colorectal cancer is clearly essential. Lymph node status is the strongest predictor of long-term outcome in patients with colorectal cancer who do not have metastatic disease. The presence of positive lymph nodes is used to determine the need for adjuvant chemotherapy for patients with colon cancer *(3)* and is associated with increased use of adjuvant radiation and chemotherapy for patients with rectal cancer *(22)*. Inadequate lymph node evaluation is associated with worse outcome in terms of tumor recurrence and patient survival, particularly in patients with stage II colorectal cancer *(11–14)*. The basis for this association is not known, but it likely reflects inaccurate staging and the resulting lack of adjuvant therapy. In fact, some authors go so far as to suggest that patients deemed lymph node negative on the basis of a low number of retrieved lymph nodes should be considered as being at high risk of recurrence and thus as being candidates for adjuvant therapy *(13)*. The retrieval of a low number of lymph nodes is also likely to be an indicator of poor-quality surgical or pathologic care.

Table 4. Multivariable analysis of factors influencing adequate lymph node evaluation in patients with colorectal cancer*

Characteristic	OR	95% CI
Patient age, y†		
≤50	1	Referent
51–60	0.68	0.64 to 0.72
61–70	0.55	0.52 to 0.58
≥71	0.45	0.44 to 0.47
Patient sex†		
Male	1	Referent
Female	1.05	1.02 to 1.08
Anatomic site of tumor†		
Right colon	1	Referent
Left colon	0.45	0.44 to 0.47
Rectum	0.52	0.50 to 0.54
Patient race/ethnicity		
White	1	Referent
Nonwhite	1.00	0.96 to 1.04
Tumor stage†		
I	1	Referent
II	1.86	1.80 to 1.93
III	2.27	2.18 to 2.35
Tumor grade†‡		
Well or moderately differentiated	1	Referent
Poorly differentiated	1.11	1.07 to 1.15

*Adequate lymph node evaluation involves evaluating at least 12 lymph nodes, adjusted for geographic location by registry and diagnosis year. OR = odds ratio of adequate lymph node evaluation; CI = confidence interval.

†$P < .001$ by logistic regression, controlled for other variables.

‡The exclusion of grade from the model did not affect the odds ratio of any other variable. The model including grade is therefore presented.

Despite the importance and implications of adequate lymph node evaluation, we found in a population-based study of more than 100,000 patients with colorectal cancer in the United States who underwent radical surgery with no preoperative radiation that most did not receive adequate lymph node evaluation, particularly those with left-sided colon cancer. In patients with stage II disease, for which evaluation of lymph node status has clear implications for outcome, the median number of lymph nodes evaluated was 10, and even fewer lymph nodes were evaluated in patients with left-sided colon cancer or rectal cancer (median number of lymph nodes evaluated for both sites was eight). Overall, only 41% of patients with stage II disease received adequate lymph node evaluation. Although lymph node retrieval improved over time, even by 2001 less than 50% of patients received adequate lymph node evaluation.

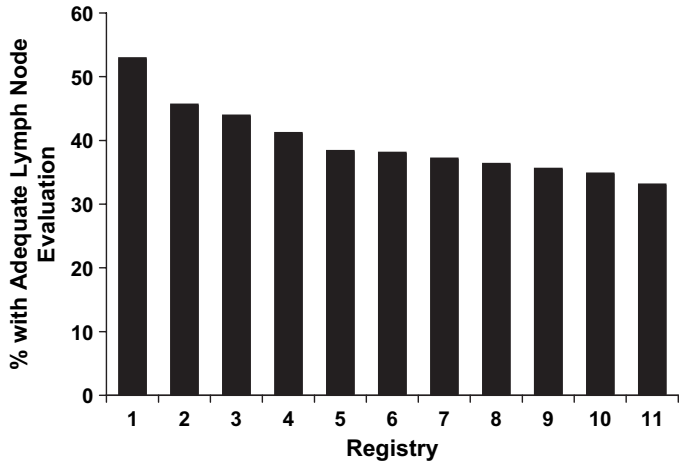

Fig. 3. Percentage of patients with adequate lymph node evaluation (i.e., at least 12 lymph nodes evaluated) for all stages of colorectal cancer by geographic location in the Surveillance, Epidemiology, and End Results registry. This includes only patients diagnosed since 1992 (data for San Jose and Los Angeles available only since 1992). Registry 1 = Hawaii, 2 = Atlanta, 3 = Connecticut, 4 = New Mexico, 5 = Detroit, 6 = Seattle, 7 = San Jose, 8 = Iowa, 9 = Los Angeles, 10 = Utah, 11 = San Francisco–Oakland.

Our findings are similar to those of the National Cancer Database analysis of lymph node evaluation in patients with stage II colon cancer diagnosed from 1985 through 1991 *(11)*. In that analysis, 40% of 31,515 patients with T3N0 disease received adequate lymph node evaluation. The results of two other population-based studies demonstrate even worse lymph node evaluation than was seen in our study. In a Canadian study that used the population-based Ontario Cancer Registry *(23)*, only 27% of 1789 patients diagnosed with stage II disease from 1997 through 2000 had at least 12 nodes evaluated. In a French population-based study *(24),* only 19% of lymph node–negative patients with colorectal cancer received adequate lymph node evaluation during 1990. The consistency of these findings indicates that most patients with colorectal cancer have inadequate lymph node evaluation.

Single-institution studies have demonstrated that higher rates of adequate lymph node evaluation are possible when standard methods of pathologic evaluation are used. Goldstein *(16)* reported the experience at the William Beaumont Hospital (Royal Oak, MI), in which trends in lymph node examination for T3 tumors were evaluated over time. From 1990 through 2000, a mean of 17 lymph nodes (median = 16 lymph nodes) were evaluated per colorectal cancer specimen. By 2000, a mean of 29.5 lymph nodes were evaluated per specimen. It is interesting to note that Goldstein found that the mean number of lymph nodes per specimen statistically significantly increased when pathology assistants rather than pathologists were responsible for retrieving lymph nodes from the gross specimen. Wong et al. *(9)* reported the experience of the Department of Pathology at the Queen's Medical Center (Honolulu, HI) from 1992 through 1996. In almost 200 patients with T2 or T3 colorectal cancers resected for cure, a mean of 17 lymph nodes per patient were evaluated. Therefore, it is possible to routinely achieve higher rates of adequate lymph node evaluation than we found in our study.

The number of lymph nodes required for adequate lymph node evaluation in patients with colorectal cancer has been debated ever since Fielding's 1991 recommendation that a minimum of 12 lymph nodes be evaluated *(25)*. Currently, consensus holds that adequate staging requires the evaluation of as many lymph nodes as possible *(12)*. The 1999 consensus statement by the College of American Pathologists *(26)* recommended evaluating 12–15 lymph nodes in lymph node–negative colorectal cancer patients. If that number cannot be achieved with standard methods, then techniques such as defatting should be used. Of note, many studies *(8,9,11,14,15,18)* actually recommended evaluating more than 12 nodes for adequate staging. As a reflection of the developing consensus regarding adequate staging and the influence of adequate staging on outcome, some authors have recommended that lymph node–negative patients with fewer than 12 lymph nodes examined be routinely excluded from surgical or adjuvant therapy trials *(7)*.

Relatively little is known about factors that influence the adequacy of lymph node evaluation. The number of lymph nodes examined reflects an interaction between patient factors, tumor factors, and the quality of surgical and pathologic care. Individuals vary in terms of the number of lymph nodes present *(27–29)*. Therefore, the maximum number of lymph nodes that can be evaluated will vary

for individual patients. In addition, other patient characteristics, such as obesity, have been found to affect lymph node retrieval *(30)*. Such patient characteristics, however, do not explain the variations in the number of lymph nodes examined in our study associated with patient demographic (i.e., age and geographic location) and tumor (i.e., anatomic site, grade, and stage) characteristics.

Our study indicates that tumor factors are important determinants of lymph node retrieval. We observed that more lymph nodes are evaluated in patients with stage II and III disease than in patients with stage I disease. Retrieving a higher number of lymph nodes increases the probability that, if present, positive lymph nodes will be detected. Thus, it is not surprising that a larger number of lymph nodes was evaluated, on average, in patients with stage III disease than in patients with stage I or II disease. As others have previously shown *(9,31)*, involved lymph nodes are slightly larger, on average, than uninvolved lymph nodes [although even involved lymph nodes are small, with many being <5 mm in greatest diameter *(9,31,32)*]. The discrepancy in lymph node size may explain some of the difference in the number of lymph nodes retrieved between patients with lymph node–negative and those with lymph node–positive disease. Indeed, the average number of lymph nodes retrieved from patients with lymph node–positive disease is more frequently higher than that from patients with lymph node–negative disease *(9,24,33)*.

It is interesting to note that the number of lymph nodes examined also differed between patients with stage II and stage I disease. Moreover, the odds of adequate lymph node evaluation were twice as high in patients with stage II disease than in patients with stage I disease. In fact, the difference in the number of lymph nodes retrieved between patients with stage I (median = 6) and stage II (median = 10) disease was larger than the difference in the number of lymph nodes retrieved between patients with stage II (median = 10) and stage III (median = 11) disease—indicating that the depth of wall penetration (T1 or T2 versus T3 or T4) influenced lymph node retrieval. In addition, we demonstrated that in patients with stage III disease, advanced T stage was predictive of adequate of lymph node evaluation.

Only one other study has evaluated the effect of the depth of wall penetration on lymph node retrieval *(29)*. In that single-center study of 568 patients, the median number of lymph nodes retrieved increased from 12 in patients with T1 tumors to 23 in those with T4 tumors. However, the authors did not control for lymph node positivity (which was strongly associated with T stage in their study), and the median number of nodes they evaluated was high overall, relative to the number seen in population-based studies. Other studies have included few patients with T1 or T2 N0 disease *(8)* or compared only lymph node–positive and lymph node–negative patients without segregating patients with stage I disease from those with stage II disease *(9,24,33)*. The reasons for the interaction between the depth of wall penetration and node retrieval are unclear. The full-thickness penetration of the bowel wall found in patients with T3 or T4 tumors may result in inflammation of the surrounding lymph nodes, thus possibly easing the detection of uninvolved nodes. Alternatively, the presence of a more visibly aggressive tumor may lead to more extensive surgery or more thorough pathologic evaluation.

In our study, the anatomic site of the tumor strongly influenced the adequacy of lymph node examination. Patients with right-sided colon cancer were twice as likely to receive adequate lymph node evaluation as those with left-sided colon cancer or rectal cancers. Moreover, patients with right-sided colon cancer had, on average, more lymph nodes evaluated, as other have noted *(13,33,34)*. Surgical specimens from right-sided colon resections for cancer have been found to be longer than left-sided resections *(23,33),* and the length has been associated with improved lymph node retrieval. Because of the consistently higher number of lymph node retrieved in patients with right-sided colon cancer, it may actually be necessary to examine more lymph nodes in right-sided colon specimens to accurately determine the lymph node status of patients with right-sided disease. This issue should be studied further, as not all studies are in agreement *(35)*.

Tumor factors undoubtedly influence lymph node retrieval. However, our study found wide variation in lymph node retrieval by patient geographic location (the rate of adequate lymph node evaluation ranged from 33% to 53% depending on location), by patient age (patients aged 50 years or younger were twice as likely to receive an adequate lymph node evaluation as patients aged 71 years or older), and over time (the overall rate of adequate lymph node evaluation increased from 32% overall in 1988 to 44% in 2001), indicating that other modifiable factors—particularly the underlying surgical and pathologic practice patterns—may play an important role in adequate lymph node evaluation. Lymph node evaluation, as in our study, represents the community standard, yet single-institution studies have demonstrated that substantially higher numbers of lymph nodes can be routinely identified in most patients by using standard techniques. Institutional excellence likely reflects surgical precision [with routine performance of radical en bloc resection of lymph nodes extending to the origin of the primary feeding vessel, in accordance with the National Cancer Institute's "Guidelines 2000 for Colon and Rectal Surgery" *(7)*] and diligence in pathologic evaluation of the specimen. Surgeon factors, such as procedure volume and specimen length, have been correlated with lymph node retrieval *(23,33)*, as has the academic status of the institution *(23)*. Improvement at an institutional level is clearly possible. Smith et al. *(36)* demonstrated a dramatic increase in the median number of lymph nodes retrieved after an educational intervention (at a single institution), in which the intervention targeted pathologists and surgeons and included the use of a pathology reporting template. The median number of lymph nodes retrieved before the intervention in patients with stage II colorectal cancer was eight. Thirty months after the intervention, however, the median number had increased to 18, indicating a substantial and durable improvement in lymph node retrieval.

Our study has several limitations. One is that we used population-based data, with only limited information on patient and tumor factors. In addition, we had no information regarding surgical and pathologic factors such as procedure volume, specimen adequacy, or the use of specialized techniques (such as xylene or alcohol fat clearance), all of which affect lymph node retrieval. Moreover, SEER does not independently evaluate the quality of surgical treatment or pathologic diagnosis, both of which likely vary in the population. However, given the large numbers of patients included in SEER, and the population-based nature of these data, our study does represent community standards in the United States.

Overall, we demonstrated that most patients with colorectal cancer did not receive adequate lymph node evaluation. In light of the association of lymph node retrieval with postoperative treatment and prognosis, efforts to improve quality of care in this area could produce substantial improvements in outcome. Further

research should evaluate factors associated with increased lymph node retrieval and should assess intervention strategies to ensure proper surgical care and pathologic assessment. Our finding of a low rate of adequate lymph node retrieval in patients with colorectal cancer, a disease in which the importance of accurate staging is well established, may have implications for other types of cancer in which accurate staging is also associated with outcome.

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Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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