Lymph Node Evaluation and Survival After Curative Resection of Colon Cancer: Systematic Review

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Background   Adequate lymph node evaluation for cancer involvement is important for prognosis and treatment of patients with colon cancer. The number of lymph nodes evaluated may be a measure of quality in colon cancer care and appears to be inadequate in most patients treated for colon cancer. We performed a systematic review of the evidence for the association between lymph node evaluation and oncologic outcomes in patients with colon cancer.

Methods   Medline, Scopus, Cochrane, and the National Guidelines Clearinghouse databases were searched from January 1, 1990, through June 30, 2006, for studies in which survival data as a function of number of lymph nodes evaluated were available. These studies were evaluated for methodologic quality, design, and data source. A total of 61 371 patients were included.

Results   Seventeen studies from nine countries were eligible for systematic review, including two secondary analyses of multicenter randomized trials of adjuvant chemotherapy for colon cancer, five population-based observational studies, and 10 single-institution retrospective cohort studies. Despite heterogeneity in methodology and differences in threshold numbers of lymph nodes evaluated (range = 6–40 lymph nodes), 16 of 17 studies reported that increased survival of patients with stage II colon cancer was associated with increased numbers of lymph nodes evaluated. Four of six studies with data from stage III patients also reported a positive association with survival among patients with stage III colon cancer.

Conclusions   The number of lymph nodes evaluated after surgical resection was positively associated with survival of patients with stage II and stage III colon cancer. These results support consideration of the number of lymph nodes evaluated as a measure of the quality of colon cancer care.

J Natl Cancer Inst 2007;99:433–41

New cases of colon cancer are diagnosed in approximately 100 000 individuals in the United States each year, and colon cancer is the second leading cause of cancer death in this country (1). Approximately 75% of these patients will present with potentially curable disease that is treated by surgical resection. Surgical treatment should include resection of the affected segment of bowel and en bloc resection of the associated draining lymph nodes to the level of the origin of the primary blood supply to that segment of the bowel (2). A complete evaluation of the lymph node basin, which collects lymphatic drainage from the affected segment of the bowel, is important for accurately identifying lymph node involvement with colon cancer and for complete resection of disease.

Because of the high risk for recurrence of colon cancer, adjuvant chemotherapy is recommended for patients with lymph node metastases (stage III) and for selected patients without lymph node metastases (stage II) but with adverse prognostic features, such as tumors with poorly differentiated histology or lymphovascular or perineural invasion by tumor cells (3). Thus, adequate lymph node staging of patients with colon cancer is important for determining prognosis and planning further treatment. The 1990 Working Party Report to the World Congresses of Gastroenterology recommended evaluation of at least 12 lymph nodes, a recommendation

that was subsequently reiterated by a National Cancer Institute–sponsored panel of experts to ensure adequate sampling (2,4,5).

Several observational studies (6–8) have found that increased survival is associated with the evaluation of an adequate number of lymph nodes. However, a population-based analysis (9) found that only 37% of patients with colon cancer receive adequate lymph node evaluation. Reasons for this failure may include patient-, tumor-, surgeon-, and/or pathologist-related variables. The two potentially modifiable influences are the completeness of lymph node evaluation by examining pathologists and the adequacy of the surgical resection (10). Because an increased number of lymph

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nodes evaluated has been reported to be associated with increased survival (11), even in patients with known lymph node–positive disease, a therapeutic benefit may be associated with improved lymph node recovery and evaluation. The number of lymph nodes recovered from a patient with colon cancer has been identified as a potentially important measure of the quality of cancer care by many organizations, including the American College of Surgeons, the American Society of Clinical Oncology, the National Comprehensive Cancer Network, the National Quality Forum, health insurance providers, and others. However, there is still controversy over the importance of obtaining increased numbers of lymph nodes during colon cancer surgery (12), and it is not universally accepted that examining more lymph nodes will lead to better outcomes or improved staging accuracy as a means to improved survival (13). The primary objective of this study was to systematically examine the evidence that lymph node recovery and evaluation is associated with oncologic outcomes after surgical treatment of stage II and stage III colon cancer.

Studies and Methods

Search Strategy

The Cochrane Database was searched for systematic reviews on lymphadenectomy and outcomes in colon cancer to ensure that a recent systematic review had not been completed. The National Guidelines Clearinghouse database was then searched by use of the term "colon cancer" for studies that specifically addressed survival outcomes related to lymphadenectomy. The Medline database (http://www.ncbi.nlm.nih.gov/entrez/) was searched from January 1, 1990, through June 30, 2006, for articles by use of the following text words or medical subject heading terms in their titles, abstracts, or their keyword lists: lymph nodes or lymph node, colonic neo-

plasms or colon cancer, mortality or survival. The Scopus database (http://www.scopus.com/scopus/home.url) was searched by use of the text words: lymph node(s); colon cancer; survival with limits to include articles only: [(lymph node or lymph nodes) and survival and colon cancer and pubyear aft 1989 and (limit-to (subjarea, "medi") or limit-to (subjarea, "mult")) and (limit-to (subjarea, "medi") or limit-to (subjarea, "mult") or limit-to (subjarea, "heal")) and (limit-to (doctype, "ar")]. Finally, a manual search of references, citations, and related articles was performed for studies meeting the selection criteria.

Selection Criteria

All clinical trials and observational studies in which overall survival data were reported as a function of the number of lymph nodes evaluated during the curative surgical resection for colon cancer were included. Studies that did not give quantitative information about the number of lymph nodes evaluated, did not evaluate survival outcomes, or included only patients with rectal cancer were excluded. When data for both colon and rectal cancer were included, separate data for colon cancer was sought. Because results of the National Institutes of Health Consensus Conference on adjuvant therapy for colorectal cancer was published in 1990 (14), the analysis was limited to studies published after that time. If duplicate or updated cohort studies were identified, only the more recent study that included the entire cohort of patients was used in the analysis to avoid double counting of patients.

Data Collection and Analysis

Titles identified from the database searches were reviewed. Full-text copies of all potentially relevant studies were obtained, when possible, before assembling the final list of studies. When the final list was identified, the full text of each study was reviewed for data on survival, numbers of lymph nodes evaluated, and disease staging. The results were sorted by study design and data source and, if possible, further categorized by cancer stage at diagnosis. The primary outcome of interest was overall survival; outcomes for patients with stage II or stage III disease were evaluated separately. A total of 61371 patients were included in the studies evaluated in this systematic review.

Grading the Evidence

Each study was critically appraised for the following components: quality of the study design (15), type of data source (single-institution, multi-institution, or population-based data), and summary of the results. Each study was evaluated for number of patients, quality of follow-up and monitoring, handling of missing data, and statistical methodology, including adjustment for confounding variables.

Results

No systematic reviews on the association between lymph node evaluation and survival for colon cancer were found in the Cochrane Collaboration database. None of the 111 articles in the National Guidelines Clearinghouse database addressed survival outcomes related to lymphadenectomy. The Medline database search yielded 379 articles, and the Scopus database search yielded 4245 articles. An initial screen of the titles and further manual search resulted in

the identification of 42 candidate articles that were subjected to full-text review. After excluding seven articles for methodologic problems (e.g., the lack of appropriate comparison groups or patients included as a subset of a separate included report) and 18 articles for incomplete information (e.g., the lack of data regarding numbers of lymph nodes or survival), 17 studies from nine countries remained for final evaluation.

Methodologic Quality

We found no randomized controlled trials that evaluated the association between lymphadenectomy and survival after surgical treatment of colon cancer. Two retrospective nested cohort studies (11,13) of patients who were enrolled in large multi-institutional randomized controlled trials of adjuvant 5-fluorouracil in patients with resected colon cancer were found. Five large population-based retrospective cohort studies from cancer registry data (8,16–19) and 10 single-institutional retrospective cohort studies (6,7,20–27) were found. Two (17–18) of the five cancer registry studies (from Kentucky and the Surveillance, Epidemiology, and End Results [SEER] program) and nine (6,7,20–23,25–27) of the 10 single-institution studies included patients with rectal cancer who could not be analyzed separately from the patients with colon cancer.

The numbers of patients enrolled in the two nested cohort studies (11,13) were based on the primary aims of the associated randomized control trials of adjuvant chemotherapy for colon cancer, and the studies were not powered specifically for analyses of interest to this study. Follow-up and monitoring of the patients were well described; fewer than 5% of total patients had missing data and were excluded from the analyses. Both studies described multiple regression analysis adjusting for potential confounders.

Each of the five population-based studies enrolled more than 1000 patients. Only one of the five population-based studies (i.e., the Ontario Registry) (16) described missing data. Three studies [i.e., the National Cancer Database (NCDB) (8), SEER (18), and Ontario Registry (16)] reported proportional hazards analysis of survival adjusted for covariates, including patient and tumor characteristics.

Although all single-institution studies were consecutive cohort studies, none addressed missing data (e.g., by adjustment or sensitivity analysis) from patients for whom follow-up was unavailable. Only five studies performed covariate-adjusted analyses. Three studies [Goldstein (6), Ratto et al. (25), and Wong et al. (26)] included results obtained over a period of time in which specimen-handling techniques has changed, so that more lymph nodes were recovered later in the study than earlier in it. The potential confounding effect of chemotherapy on overall survival was not addressed in any study. However, the rate of chemotherapy use would not have been expected to be affected by the number of lymph nodes recovered for either stage II or stage III patients during the time periods of the studies.

Nested Cohort Studies

The highest quality studies were two nested cohort studies—the Intergroup 0089 trial from the United States (9) and the National Intergroup Trial for Adjuvant Therapy on Colon Cancer (INTACC) from Italy (11,13). Both trials included patients with either stage II or stage III colon cancer who had undergone surgical treatment with curative intent. Intergroup 0089 analyzed 3411 patients (648 stage II patients and 2763 stage III patients), and INTACC analyzed 3491 patients (1816 stage II patients and 1675 stage III patients). Both studies found an improvement in overall survival among patients with stage II colon cancer as the number of recovered lymph nodes increased.

The Intergroup 0089 study found a 14% higher absolute 5-year overall survival for stage II patients with more than 20 negative lymph nodes examined compared with 10 or fewer negative lymph nodes examined (Table 1). A 12% higher absolute cancer-specific survival also was observed in stage II patients with more than 20 lymph nodes evaluated than in those with 10 or fewer lymph nodes evaluated. A trend toward improved disease-free survival in stage II patients was observed, but it did not reach statistical significance ($P = .11$). The absolute difference in overall survival at 8 years was 20% ($P<.001$) (79% for >20 negative lymph nodes examined versus 59% for <10 negative lymph nodes examined). The Cox proportional hazards regression analysis—using the absolute number of lymph nodes recovered as a continuous variable, as well as age (continuous), T stage (T1 and T2 versus T3 versus T4), tumor type (adenocarcinoma versus colloid versus signet cell versus other), degree of differentiation (well versus moderate versus poor), and adjuvant regimen—showed that the number of recovered lymph nodes was a statistically significant variable for both lymph node–negative (hazard ratio [HR] = 0.968; $P<.001$) and lymph node–postive (HR = 0.971; $P<.001$) cancers.

Among patients with known lymph node metastasis (i.e., stage III disease), increased overall and cause-specific survival was associated with increasing numbers of lymph nodes recovered

Table 1. Five-year overall, cause-specific, and disease-free survival in the Intergroup 0089 trial by number of lymph nodes recovered*

Stage	No. of lymph nodes	Overall survival, %	P†	Cause-specific survival, %	P†	Disease-free survival, %	P†
II	<11	73	<.001	80	.015	72	.11
	11–20	80		85		79	
	>20	87		92		83	
IIIA–IIIB	<11	67	<.001	74	.002	65	<.001
	11–40	74		78		70	
	>40	90		93		93	
IIIC	1–35	51	.002	55	.018	48	.014
	>35	71		71		69	

* Reference (11).

† Log-rank test (11).

Table 2. Five-year overall and relapse-free survival in the National Intergroup Trial for Adjuvant Therapy on Colon Cancer by number of lymph nodes recovered*

Dukes' stage	No. of lymph nodes	Overall survival, %	Uni P†	RR (95% CI)‡	P†	Relapse-free survival, %	Uni P†	RR (95% CI)‡	P†
B + C	0–7	69	.031	1.0 (referent)	.034	56	.002	1.0 (referent)	.003
	8–12	69		0.96 (0.79 to 1.17)		60		0.94 (0.79 to 1.11)	
	13–17	76		0.76 (0.60 to 0.96)		64		0.76 (0.63 to 0.93)	
	>17	76		0.79 (0.63 to 0.98)		67		0.75 (0.62 to 0.90)	
B2–B3	0–7	81	<.001			66	<.001		
	8–12	81				74			
	13–17	87				77			
	>17	89				83			
C	0–7	57	.3			47	.11		
	8–12	69				48			
	13–17	66				53			
	>17	63				54			

* Reference (13).

† Chi-square test for heterogeneity. Uni = univariate.

‡ Cox proportional hazards regression analysis was adjusted for age, sex, tumor grade, and location. RR = risk ratio; CI = confidence interval.

and evaluated. Eight-year absolute overall survival for N1 patients (i.e., patients with no more than three lymph nodes containing metastases) was 34% (P<.001) higher for patients with more than 40 lymph nodes evaluated than for those with 11–40 lymph nodes evaluated. Eight-year absolute overall survival for N2 patients (i.e., patients with more than three lymph nodes containing metastases) was 28% (P = .002) higher for patients with more than 35 lymph nodes examined than for those with 1–35 lymph nodes examined.

The INTACC study (13) categorized patients into one of four groups (quartiles) by the number of lymph nodes recovered: 1) 0–7 lymph nodes, 2) 8–12 lymph nodes, 3) 13–17 lymph nodes, and 4) more than 17 lymph nodes. The median number of lymph nodes recovered was 12 from both stage II and stage III patients. There were 1635 patients with Dukes' B2 or B3 disease and 1613 patients with Dukes' C disease. An increase in the number of lymph nodes recovered was associated with absolute improvements of 8% in overall survival and 17% in relapse-free survival in patients with Dukes' B2 or B3 colon cancer. However, overall survival and relapse-free survival in patients with Dukes' C disease were not affected (Table 2).

Population Registry–Based Cohort Studies

Five retrospective population-based cohort studies included from 1000 to 35 787 patients (8,16–19). In four studies (8,16–18), only stage II disease was evaluated, and in the fifth study (19), stage III disease was also examined. Analyses varied among the five studies, with different cutoff values for lymph node recovery (Table 3). In the three studies that used 12 lymph nodes in stage II disease as a categorical cutoff value [NCDB (8), Kentucky Cancer Registry (17), and Swedish Uppsala/Örebro Regional Oncologic Centre (19)], improved survival was observed with more than 12 lymph nodes evaluated.

The Ontario cancer registry study (16) of a random subset of 1000 patients with colorectal cancer found improved survival in stage II disease when at least 10 lymph nodes were recovered. However, increasing numbers of lymph nodes recovered was not associated with an increase in the odds of having a lymph node–positive status. Thus, the improved survival in stage II patients that was associated with increased numbers of lymph nodes examined could not be attributed entirely to improved staging accuracy.

Two studies [NCDB (8) and SEER (18)] found that survival of patients with stage II cancers increased linearly with the number of lymph nodes evaluated. In the SEER study, no cutoff value for the number of lymph nodes could be identified, and the relative risk for death decreased by 2.1% (95% confidence interval [CI] = 1.6% to 2.6%) for each additional negative lymph node evaluated between 10 and 40 lymph nodes; this relationship remained relatively linear throughout this range.

The Uppsala/Orebro Swedish cancer registry study (19) was the only population-based study to evaluate the association between lymph node recovery and survival among patients with stage III disease. The authors used the ratio of the number of positive lymph nodes to total number of lymph nodes examined (i.e., the index of metastasis) to assess the impact of the number of positive lymph nodes as well as the total number of lymph nodes on colon cancer survival. The median index of metastasis was 0.32, and 12 lymph nodes needed to be examined to correctly classify cases. However, to assure assignment to the lowest quartile for the index of metastasis (i.e., 0.16), 20 lymph nodes needed to be evaluated. Survival was related to index of metastasis, with a 5-year survival of 50%–60% at an index of metastasis of less than 0.33 and of 30%–40% at an index of metastasis of 0.33 or higher. Survival was also related to whether or not 12 lymph nodes were evaluated in N1 disease (P<.005 for both, log-rank test) (19).

Single-Institution Retrospective Cohort Studies

Ten single-institution studies (6,7,20–27) reported on a range from 94 to 2427 patients (Table 4). In six studies (20–24,27), patients were evaluated for survival with only one cutpoint for the number of lymph nodes. Five of these 10 studies (7,20–22,24) found, by use of multivariable regression analysis, that the number of lymph nodes evaluated was still a statistically significant predictor of

Table 3. Five-year overall survival from population-based cohort studies of stage II cancer*

Source, y (reference)	No. of patients	No. of lymph nodes	Overall survival, %	HR or RR (95% CI)	P
NCDB, 2003 (8)	35 787	1–7	49.8	1.0 (referent)†	<.001‡
		8–12	56.2	0.81 (0.77 to 0.84)	
		≥13	63.4	0.68 (0.65 to 0.71)	
Kentucky Cancer Registry, 2004 (17)	2437	1–12	56	–	<.001‡
		>12	63		
Uppala/Orebro Registry, 2005 (19)	3735	1–11	~65	–	<.001‡
		>11	~75		
Ontario Registry, 2006 (16)	1000	1–3	–	1.0 (referent)§	
		4–6		0.9 (0.6 to 1.3)	.59
		7–9		0.9 (0.6 to 1.3)	.53
		10–36		0.6 (0.4 to 1.0)	.03
SEER registry, 2002 (18)	8574	Each additional lymph node	–	0.98 (0.97 to 0.98)‖	<.001

* HR = hazard ratio; RR = risk ratio; CI = confidence interval; NCDB = National Cancer Database; – = no data; SEER = Surveillance, Epidemiology, and End Results.

† Cox proportional hazards regression analysis was adjusted for age, tumor location, grade, and treatment modality.

‡ Log-rank test.

§ Cox proportional hazards regression analysis was adjusted for age, sex, comorbidity, emergent admission status, hospital type and volume, tumor size, specimen length, American Joint Committee on Cancer Tumor–Node–Metastasis T stage, grade, and lymphatic, vascular, or neural invasion.

‖ Cox proportional hazards regression analysis was adjusted for age, sex, year of diagnosis, marital status, SEER region, histology, grade, tumor size, number of primary tumors, location, and use of radiation.

survival after adjusting for covariates, although one study (21) did not provide any details beyond the P value of .002 for improved survival with more than six lymph nodes evaluated. Only the smallest study (23) did not find a difference in overall survival for stage II cancers when nine lymph nodes was used as the cutpoint, but this study did find a statistically significant difference in disease-free survival (82.6% with more than nine lymph nodes versus 58.6% with nine lymph nodes or fewer; difference = 24%; P = .024).

Two studies analyzed the number of lymph nodes evaluated within a series as a multinomial categorical variable (6,7). In the largest single-center study to evaluate the prognostic impact of the number of lymph nodes recovered on survival in colon and rectal cancer (6), a subset of 745 patients with survival data (from a total of 1287 patients with pT3N0 cancers) was evaluated. An increased number of lymph nodes evaluated was associated not only with improved survival but also with an increasing proportion of patients with lymph node metastases (odds ratio = 1.24, 95% CI = 1.22 to 1.26; P<.001, for each additional lymph node). This result lead to more accurate staging. However, a minimum number of lymph nodes necessary for staging accuracy could not be determined. In a multivariable analysis using tertiles of evaluated lymph nodes (7), recovery of fewer than 10 lymph nodes was associated with an increased risk for death, compared with recovery of more than 19 lymph nodes, after adjusting for sex, age, and American Joint Committee on Cancer Tumor–Node–Metastasis (TNM) stage. This relationship was confirmed by evaluating the number of lymph nodes recovered as a continuous variable (HR_{death} = 0.981, 95% CI = 0.968 to 0.995; P<.008, for each additional lymph node).

In a study (26) from a center with a traditionally high rate of lymph node recovery, disease-free survival data of patients with lymph node–negative colon and rectal cancer was compared with those from a national cancer registry (Onco, Inc). Five-year disease-free survival was approximately 90% in the authors' institution compared with 60% in the registry. This higher survival was associated with a higher average number of lymph nodes evaluated (22.6 in that study versus 11.3 in the Onco registry; P<.001). The authors suggested that the improved survival of their stage II patients was associated with improved staging accuracy. When consecutive study periods were compared, the lymph node metastasis rate was increased from 35% (when a mean of 19.5 lymph nodes was evaluated) to 52.3% (when a mean of 26.7 lymph nodes was evaluated).

The impact of changing the protocol for lymph node recovery within a pathology department was studied by Ratto et al. (25). During the 15-year study period from 1981 to 1996, a change in the protocol for lymph node procurement increased the number of lymph nodes recovered from 11.3 ± 5.8 to 29.6 ± 16.7 (mean ± standard deviation) and was associated with an 8% (P = .04) absolute improvement in 5-year survival for patients with lymph node–negative cancers. The rate of detection of lymph node metastasis also improved from 30.2% during the first part of the study period to 37.5% during the second part (P<.05), indicating improved staging accuracy. This study was limited by heterogeneity of the population being evaluated and by the temporal segregation of the two groups, but the use of adjuvant therapy among those patients without lymph node metastasis did not change during this period.

The association between survival of patients with stage III disease and the number of lymph nodes examined was poorly addressed by the single-institution studies. One study found no statistically significant difference in survival when a cutoff of only six lymph nodes was evaluated for Dukes' C disease (21). However, improved survival with improved lymph node evaluation was observed in two studies (23,25), although only one study (23) achieved a statistically significant difference (P = .011).

Table 4. Association between lymph node evaluation and 5-year overall survival in selected single-center studies

First author, year (reference)	No. of patients	Stage	No. of lymph nodes	5-y overall survival, %	HR or RR* (95% CI)	P
Caplin, 1998 (21)	222	Dukes' B	<7	49	–	.001†
			≥7	68		
		Dukes' C	<7	N/A		.7
			≥7	N/A		
Law, 2003 (24)	115	II	<7	62	2.99 (1.28 to 6.97)	.03†
			≥7	86	‡	
Cianchi, 2002 (22)	140	II	<9	54.9	2.67 (1.26 to 5.67)	<.001†
			≥9	79.9	§	
Yoshimatsu, 2005 (27)	94	Dukes' B	<9	67	–	.028†
			≥9	87		
Gumus, 2005 (23)	80	II	<9	72‡	–	.353†
			≥9	85		
	99	III	<9	55.7		.011†
			≥9	78		
Berberoglu, 2004 (20)	301	II	<11	47	2.8 (1.6 to 5.2) ‖	<.001†
			≥11	81		
Goldstein, 2002 (6)	745	II	≤7	62	–	.018†
			8–12	68		
			13–17	71		
			≥18	76		
Sarli, 2005 (7)	480	II	<10	51	1.50 (1.01 to 2.23)	<.045¶
			10–19	69	¶	
			>19	71		
Wong, 2002 (26)	173	II	11.3	–	–	<.001#
			22.6			
Ratto, 1999 (25)	487	I–II	11.4	83		.04**
			29.4	91		
		IIIA		58.9		.06
				84.2		

* For death with fewer lymph nodes evaluated. HR = hazard ratio; RR = risk ratio; CI = confidence interval; – = no data.

† Log-rank test.

‡ Cox proportional hazards regression analysis was adjusted for age of more than 70 years old and Charlson score of more than 3.

§ Cox proportional hazards repression analysis was adjusted for age, sex, and histology.

‖ Cox proportional hazards regression analysis was adjusted for tumor location, histology, and tumor–node–metastasis (TNM) T stage.

¶ Cox proportional hazards regression analysis was adjusted for age, sex, American Joint Committee on Cancer TNM T stage, and for more than 19 lymph nodes versus less than 10 lymph nodes. This analysis used 10-year survival data.

A log-rank test was used to compare single-institution lymph node–negative patients with a mean number of 22.6 lymph nodes with data from the Onco, Inc registry for 7974 lymph node–negative patients with mean 11.3 lymph nodes.

** Log-rank test comparing two different techniques for pathologic lymph node evaluation over overlapping time periods. Mean overall number of lymph nodes evaluated by the two different techniques are listed. Cox proportional hazards regression adjusted for age and TNM N stage and M stage demonstrated a *P* of less than .05. Risk ratio was not given.

Discussion

Although there was variability in the methodology used and a threshold or minimum number of lymph nodes evaluated could not be determined, all but one (23) of the 17 studies (6–8,11,13,16–27) in this systematic review found that an increased number of lymph nodes evaluated was associated with improved survival among patients with stage II colon cancer. When patients with lymph node–positive (stage III) disease were separately evaluated, four (11,19,23,25) of six (11,13,19,21,23,25) studies found that improved survival was associated with increased lymph node evaluation. Thus, the effect of increased lymph node recovery on improving survival may not be fully explained by improved staging accuracy alone.

This study has several limitations. The heterogeneity of the quality of reported series and the type of comparisons performed within each individual study limit comparisons among reported series and do not permit the quantitative evaluation of aggregate data or the determination of a clear cutoff value of the number of lymph nodes evaluated that is associated with improved survival. Because all of the studies were observational (a randomized controlled trial to compare different numbers of lymph nodes evaluated is not possible until all of the determinants of lymph node numbers can be controlled), a causal relationship between the number of lymph nodes evaluated and colon cancer survival cannot be definitively established. Although the association between lymph node recovery and colon cancer outcomes is clear, it can be difficult to assess the strength of this association because it may not be possible to separate the effect of improved staging accuracy from the survival advantage resulting from more lymph nodes being recovered from a tumor's drainage distribution. Furthermore,

many factors that may be important in determining the total number of lymph nodes evaluated may confound the association (e.g., age, tumor location). Finally, it is difficult to determine whether improved lymph node recovery in itself is sufficient to improve outcomes or whether lymph node recovery is also an important marker of better processes of cancer care, including improved quality of surgery, pathologic reporting, or delivery of adjuvant chemotherapy.

Indeed, accurate lymph node staging of patients is a prognostic factor, and it affects the subsequent treatment of patients with colorectal cancer. The need for complete identification of a tumor's draining lymph nodes has been demonstrated by studies (6,10,25,28–31) in which the proportion of patients with at least one positive lymph node has been shown to increase as the total number of lymph nodes recovered increases. However, several reports show diminishing returns for improved staging accuracy beyond examination of 12–17 lymph nodes (8,13,16).

The studies from the NCDB (8), SEER (18) and the secondary analysis of Intergroup 0089 (11) separately evaluated N0 patients with more than 20 lymph nodes evaluated. The analysis in the INTACC trial (13) used 18 or more lymph nodes as the highest category for the number of lymph nodes recovered. In these trials, even at the highest strata of the number of lymph nodes evaluated, increased survival was associated with increased numbers of lymph nodes evaluated. Furthermore, the study from the Ontario Cancer Registry (16) found that, although increasing the number of lymph nodes evaluated did not increase the rate at which lymph node–positive disease was detected, an increased number of lymph nodes examined was still associated with improved survival. Thus, factors other than staging accuracy may account for the improvement in colon cancer survival associated with the increased number of lymph nodes evaluated.

The factors that influence adequate recovery and evaluation of lymph nodes and accurate staging of patients with colon cancer are not fully understood and may depend on many factors, including the quality of the surgical resection, the quality of the pathologic evaluation, tumor factors, and patient factors. The quality of the surgical resection is important because the surgeon must provide an adequate specimen that is composed of the segment of bowel containing the tumor and its associated mesentery to the level of the origin of the draining vessels. Surgeon or hospital volume may be an indicator of surgical quality, because outcomes, including long-term survival and local failure rates after surgical treatment of colorectal cancer and other malignancies, have been associated with surgeon and hospital volume (32–34). High-volume surgeons may also be performing a more complete resection of the primary tumor with its draining lymph nodes: surgeon volume has been found to be associated with lymph node recovery (10), as has the type of practice (i.e., higher recovery in teaching versus nonteaching hospitals) (16,28,31). Hospital volume, which is influenced by both the surgeon and the pathologist, is also associated with the number of lymph nodes recovered; after adjusting for tumor characteristics, patients in low-volume hospitals were more likely to have fewer than seven lymph nodes evaluated and less likely to have positive lymph nodes detected (35).

After the cancer has been resected, the pathologist must identify the lymph nodes that are contained within the mesentery of the resected bowel. The College of American Pathologists has established guidelines (36) for the pathologic evaluation of colorectal cancer resection specimens that include the recommendation that, if fewer than 12 lymph nodes are found, additional techniques for visual enhancement should be considered and that this fact should be communicated in the pathology report. The experience of the pathologist and the technique of pathologic evaluation, including the use of templates, have been shown to be important in lymph node recovery after adjusting for surgeon- and tumor-related factors (10,25). Thus, both surgeon and pathologist factors associated with lymph node recovery may influence the relationship between hospital volume and colon cancer outcome.

Despite the best efforts of the surgeon and pathologist, other factors can still influence lymph node recovery. One is variation in the number of lymph nodes that can be recovered. For example, older age and obesity may be factors that decrease lymph node recovery (9,28,37). However, surgeons may perform less extensive operations on older patients, and this factor may confound the association between age and the number of lymph nodes evaluated (16). The location of the tumor may also be important. Although it is generally agreed that tumors on the right side are associated with higher numbers of lymph nodes examined (7,9,10,13,30), the strength of this association is unclear (22).

The association of increased lymph node recovery with increased survival may represent an effect of higher lymph node yields itself or may reflect higher lymph node yields being a marker for other related factors, including the quality of surgical resection or delivery of more appropriate cancer-directed treatment. The most compelling evidence for a therapeutic benefit of increased lymph node recovery comes from the secondary analysis of the data from the Intergroup 0089 trial (11). After stratification for stage and adjustment for covariates, including the number of positive lymph nodes, both overall and cause-specific survival, were related to the number of lymph nodes recovered. The importance of lymph node recovery in stage III colon cancer has also been found in three other studies (19,23,25). In two separate analyses of the SEER registry for stage III cancers that have been reported in abstract form (38,39) (and not included in this study because the complete data had not yet been published), both the total number of lymph nodes and the number of negative lymph nodes evaluated were associated with improved survival in a dose-dependent manner. These data should be considered in light of conflicting results (13) indicating that among lymph node–positive, stage III patients in the INTACC trial, increased lymph node recovery was not associated with improved survival. However, threshold values of the number of lymph nodes evaluated in this study were lower than those in the Intergroup 0089 trial.

Recent reports (9,16,19,40,41) have found that few patients in the United States, Canada, France, The Netherlands, or Sweden are undergoing an adequate lymph node evaluation. Given the results in our systematic review, efforts to improve lymph node evaluation should result in clinically significant improvements in outcome and also the quality of care for patients with colon cancer.

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