Hospital Lymph Node Counts and Survival After Radical Cystectomy

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BACKGROUND. Several studies suggest that patients in whom more lymph nodes are examined have improved survival after radical cystectomy for bladder cancer. Despite growing calls for using lymph node counts as a hospital quality indicator, it has not been established that hospitals that obtain more lymph node have better outcomes.

METHODS. Using the national Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database (1992–2003), all patients undergoing radical cystectomy for cancer were identified (n = 3603). Hospitals were ranked and sorted into 3 evenly sized groups: low (no patients with ≥10 lymph nodes removed), medium (up to 20% of patients), and high (greater than 20% of patients). Survival rates were assessed for each hospital group, adjusting for potentially confounding patient and hospital characteristics.

RESULTS. On average, low lymph node count hospitals had higher observed mortality rates compared with high lymph node count hospitals (unadjusted hazards ratio [HR], 1.25; 95% confidence interval [95% CI], 1.13–1.39). Low lymph node count hospitals tended to treat patients who were older, had more comorbidity, were of lower socioeconomic status, had higher admission acuity, and had lower procedure volumes. After adjusting for these differences, low lymph node count hospitals tended to have slightly higher mortality (adjusted HR, 1.12; 95% CI, 0.99–1.27), although this finding did not reach statistical significance. Similar findings were evident when other thresholds (lymph node counts ≥5, ≥14, and ≥20) were used.

CONCLUSIONS. Hospitals with high lymph node counts tend to have higher survival rates after radical cystectomy for bladder cancer. However, this effect is modest and is explained, in large part, by confounding patient and hospital factors. ***Cancer*** **2008;112:806–12.** *© 2007 American Cancer Society.*

KEYWORDS: lymphadenectomy, mortality, hospital quality, cancer, lymph node count.

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The number of lymph nodes removed and examined after major cancer surgery appears to be an important prognostic factor for a wide range of cancers.[1–12] Clinical[5] and population-based[6] data suggest that fewer lymph nodes removed during radical cystectomy results in higher long-term mortality rates among patients with bladder cancer. In 1 study, the risk of death among patients with <10 lymph nodes removed was twice that of those in whom ≥10 lymph nodes were removed (adjusted hazards ratio [HR], 2.0; 95% confidence interval [95% CI], 1.4–2.8).[5] In light of such findings, some have recommended using the number of lymph nodes retrieved at the time of radical cystectomy as a measure of the quality of this procedure.[5,13]

However, the relative value of lymph node counts as a performance measure depends largely on the mechanism underlying the

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observed improvements in survival. Lymph node retrieval may have a direct therapeutic effect, either by removing micrometastatic disease or by sorting patients into their true pathologic stage. The former may result in lower recurrence rates, whereas the latter will better identify those in need of potentially curative adjuvant therapy.[14] In either case, lymph node counts would be a valuable measure of quality. Conversely, lymph node counts may serve primarily as a proxy for patient and provider factors that more directly determine outcomes. For example, physicians may reserve more extensive lymph node dissections for younger, healthier patients, thereby selecting those who are more likely to survive longer. Alternatively, higher lymph node counts may reflect a more thorough resection that is more common among more experienced (eg, high volume) and better trained (eg, specialized oncology training) physicians. In these cases, lymph node counts would indirectly reflect the quality of the procedure. Ruling out such confounding factors and distinguishing between these mechanisms (direct vs indirect) would be essential in establishing the value of lymph node counts as a quality indicator. For this reason, we measured the relation between hospital-level lymph node counts and survival after radical cystectomy for bladder cancer. We used a hospital-level analysis to minimize confounding that is inherent in patient-level studies.

MATERIALS AND METHODS

Subjects and Databases

For this study, we used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database for the years 1991–2003. As detailed elsewhere,[15] these files provide a rich source of information concerning Medicare patients included in SEER, a nationally representative collection of population-based registries of all incident cancers from diverse geographic areas in the U.S. By the end of the study period, the SEER registries captured approximately 26% of the U.S. population.[16] For each Medicare patient in SEER, the SEER-Medicare linked files contain 100% of Medicare claims from the inpatient (Medicare Provider and Analysis Review [MEDPAR]), outpatient, and physician (National Claims History) files.

From these files we identified all patients ages 65 to 99 years undergoing a major resection for bladder cancer between 1992 and 2003. All Medicare patients with incident cases were identified by the appropriate bladder cancer code within the Patient Entitlement and Diagnosis Summary file (PEDSF) from SEER. Patients undergoing radical cystectomy were identified in MEDPAR using the appropriate procedure codes (57.7 for *total cystectomy*, 57.71 for *radical cystectomy*, and 57.79 for *other total cystectomy*) from the *International Classification of Diseases* (version 9).

Lymph Node Counts

Next, we identified all U.S. hospitals performing radical cystectomy during the study period. We then characterized each hospital according to the proportion of patients in whom at least 10 lymph nodes were examined, as determined from the appropriate field within the PEDSF file. A 10-lymph node minimum has been recommended by some authors.[4,13,17] However, because of the limited evidence supporting this threshold, we also considered minimum lymph node counts of 5, 14, and 20, as suggested by others,[6] as part of a sensitivity analysis. The hospitals were ranked and sorted into 3 approximately evenly sized patient groups (terciles): low (no patients with $\geq$10 lymph nodes removed), medium (up to 20% of patients with $\geq$10 lymph nodes removed), and high (greater than 20% of patients with $\geq$10 lymph nodes removed). We assessed lymph node counts at the hospital level rather than at the surgeon level because radical cystectomy is an uncommon procedure and estimates of surgeon practice patterns would be considerably less reliable.

Statistical Analysis

Differences between patient characteristics, stratified by the hospital lymph node count group, were assessed using the chi-square test. The correlation between these prognostic factors and our outcome measure, all-cause mortality (determined at 5 years from the date of resection or through December 31, 2003), was measured using a simple Cox proportional hazards model. Overall mortality was chosen in lieu of others (eg, postoperative complications, disease-specific mortality) because of the questionable validity of these alternatives.[18,19] Cox proportional hazards models were used to examine correlations between hospital lymph node counts and mortality, adjusting for patient characteristics, censoring at the end of the follow-up period. The patient was the unit of analysis, with the exposure measured at the hospital level. The models were adjusted for age group (ages 65–69 years, 70–74 years, 75–79 years, 80–84 years, and 85+ years), sex, race (black vs nonblack), year of procedure, the acuity of the index admission (elective, urgent/emergent), and patient comorbidities. The last were identified using information from the index admission, and inpatient and outpatient encounters from the preceding 6 months based on methods described by Elixhauser et al.[20] Finally, we also adjusted for socioeconomic status, assessed at the patient ZIP code level, using a summary measure described by Diez Roux et al.[21]

Rather than adjust for tumor stage and the receipt of chemotherapy in our initial multivariable model, we chose to stratify by these variables in additional analyses to minimize potential bias. Hospital lymph node examination rates and cancer stage are likely correlated given that greater lymph node sampling increases the likelihood of finding positive lymph nodes and patient upstaging. With regard to the latter, because the receipt of chemotherapy may be part of the causal pathway underlying correlations between lymph node counts and survival,[22] it is not a true confounder and adjustment in a multivariable model would be inappropriate.

As described elsewhere,[23] inpatient, outpatient, and physician claims files were used to identify patients receiving chemotherapy, defined as therapy occurring within 6 months before or after surgery. In addition, we adjusted for hospital characteristics that may be associated with improved late survival after cancer surgery, including teaching status and volume.[24] A sensitivity analysis was performed to test the robustness of our effect measure by excluding hospitals that performed fewer than 5 cases during the study. In doing so, this excluded a large number of hospitals (n = 304; 58.0%), but a relatively small number of patients (n = 548; 17.9%) from the secondary analysis.

Because patients admitted to the same hospital may have correlated outcomes,[25] we used marginal survival models that incorporated clustering by hospital to adjust the standard errors.[26] Briefly, within-cluster correlations in mortality were used to derive variance-covariance estimators. These sandwich estimators were then included in the proportional hazards models measuring the relation between lymph node counts and survival. All analyses were performed using computerized statistical software (SAS, version 9.2.1; SAS Inc, Cary, NC) and all testing was 2-sided. The Institutional Review Board of the University of Michigan approved the study protocol.

RESULTS

Between January 1992 and December 2003, we identified 3603 patients with bladder cancer who underwent radical cystectomy at 524 hospitals. At the patient-level, lymph node counts were highly variable, ranging from 0 to 9 at hospitals with the lowest rates to 0 to 76 at hospitals with the highest rates. Table 1 illustrates the variability in lymph node counts among patients according to hospital practice patterns. The majority of patients undergoing cystectomy for bladder cancer had ≤4 lymph nodes removed irrespective of the hospital. However, the distribution of lymph node counts among patients treated at high lymph node count hospitals was considerably more evenly distributed than for those at the other hospitals. The percentages of patients who had ≥10 lymph nodes removed were 0% at low lymph node count hospitals, 12.7% at medium lymph node count hospitals, and 35.3% at high lymph node count hospitals.

TABLE 1
Distribution of Lymph Node Counts Among Patients According to Hospital Lymph Node Count Practice Patterns

	Percentage of patients		
No. of lymph nodes removed	Low lymph node count hospitals	Medium lymph node count hospitals	High lymph node count hospitals
0–4	88.9	72.1	52.8
5–9	11.1	15.2	11.9
10–14	—	7.2	14.2
15–19	—	3.5	9.5
20–24	—	1.0	4.4
25–29	—	0.6	2.5
≥30	—	0.4	4.7

Table 2 illustrates differences in patient demographics, clinical factors, and hospital characteristics according to hospital lymph node counts, and the correlations between these factors and mortality. Because of the contribution of lymph node status to cancer stage (ie, positive lymph nodes alter the pathologic stage), hospitals with higher lymph node counts tended to treat patients with more advanced disease. For example, patients with modified American Joint Committee on Cancer (3rd edition) stage III/IV cancers comprised 46.1% of the population treated by high lymph node count hospitals compared with 41.5% of the population at hospitals with the lowest lymph node retrieval rates ($P = .090$). Relative to low lymph node count hospitals, high lymph node count hospitals treated patients that were younger, healthier, of higher socioeconomic status, and lower admission acuity. Compared with low lymph node count hospitals, high lymph node count hospitals were higher volume and more likely to be teaching institutions.

Crude mortality according to hospital lymph node counts is depicted in Figure 1. Patients treated at hospitals with high lymph node counts fared better than those managed at low lymph node count hospitals, with median survival rates of 29.8 months and 22.5 months, respectively (log-rank $P < .001$). As illustrated in Table 3, low lymph node count hospi-

TABLE 2
Patient Demographics and Clinical Characteristics by Hospital Lymph Node Retrieval Rate and Their Correlation With Mortality From All Causes

	Hospital lymph node counts				HR of mortality associated with variable (95% CI)
	Low	Medium	High	*P*	
No. of patients	1186	1041	1376	—	—
No. of hospitals	326	60	138	—	—
Median no. of lymph nodes recovered (range)	0 (0–9)	0 (0–43)	3 (0–76)	—	—
Age, y (%)				.0033	
65–69	13.1	13.7	16.9		1.0
70–74	31.1	29.8	32.0		1.0 (0.9–1.2)
75–79	29.9	32.5	31.2		1.2 (1.0–1.3)
80–84	19.8	17.8	14.3		1.7 (1.5–2.0)
≥85	6.1	7.2	5.6		2.1 (1.7–2.6)
Sex (% female)	26.9	28.9	27.5	.559	1.2 (1.0–1.3)
Race (% black)	4.3	4.1	2.5	.040	1.3 (1.0–1.7)
Socioeconomic status (%)				<.001	
Low	36.7	29.6	33.3		1.2 (1.1–1.3)
Medium	35.3	34.9	30.4		1.0 (0.9–1.1)
High	28.1	35.5	36.3		1.0
Admission acuity (%)				.048	
Urgent/emergent	17.4	16.5	14.0		1.4 (1.3–1.6)
Comorbidity (%)				.001	
0	24.4	23.3	28.6		1.0
1	31.9	33.0	35.0		1.2 (1.0–1.3)
2	24.3	23.3	19.0		1.4 (1.2–1.6)
3+	19.5	20.5	17.4		1.7 (1.5–2.0)
Tumor stage (modified AJCC)				.090	
Stage 0/I	39.6	36.6	33.4		1.0
Stage II	18.9	19.9	20.5		0.9 (0.8–1.1)
Stage III	20.9	21.9	22.5		1.2 (1.1–1.4)
Stage IV	20.6	21.6	23.6		2.2 (2.0–2.5)
Neoadjuvant and adjuvant chemotherapy (%)	15.0	16.9	16.9	.344	1.2 (1.1–1.4)
Teaching hospital (%)	59.6	77.0	78.6	<.001	0.9 (0.8–1.0)
Hospital procedure volume (%)				<.001	
Low	61.2	14.5	27.8		1.2 (1.1–1.4)
Medium	38.8	35.7	19.0		1.1 (1.0–1.3)
High	0.0	49.8	53.2		1.0

HR indicates hazards ratio; 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer.

tals had higher mortality compared with high lymph node count hospitals (unadjusted HR, 1.25; 95% CI, 1.13–1.39). We observed considerable attenuation of this correlation after adjusting for differences in patients and hospitals. Although not reaching statistical significance, patients treated at low lymph node count hospitals were, on average, at 12% greater risk of death after cystectomy compared with their counterparts treated at high lymph node count hospitals (adjusted HR, 1.12; 95% CI, 0.99–1.27). Clinically significant effects that favored hospitals with higher lymph node counts were evident across all stages of disease and regardless of the use of systemic chemotherapy; however, these differences did not reach statistical significance.

To test the robustness of these trends, we varied the lymph node count thresholds used to segregate hospitals. We observed similar correlations between hospital lymph node counts and survival: the proportion of patients with ≥5 lymph nodes removed—low versus high adjusted HR of 1.08 (95% CI, 0.96–1.22); the proportion of patients with ≥14 lymph nodes removed—low versus high adjusted HR of 1.15 (95% CI, 1.02–1.31); and the proportion of patients with ≥20 lymph nodes removed—low versus high adjusted HR of 1.10 (95% CI, 0.97–1.25). Finally, we noted similar findings when restricting the analysis to hospitals performing at least 5 procedures (adjusted HR, 1.17; 95% CI, 1.02–1.35).

DISCUSSION

Patients undergoing radical cystectomy for bladder cancer at hospitals with higher lymph node counts

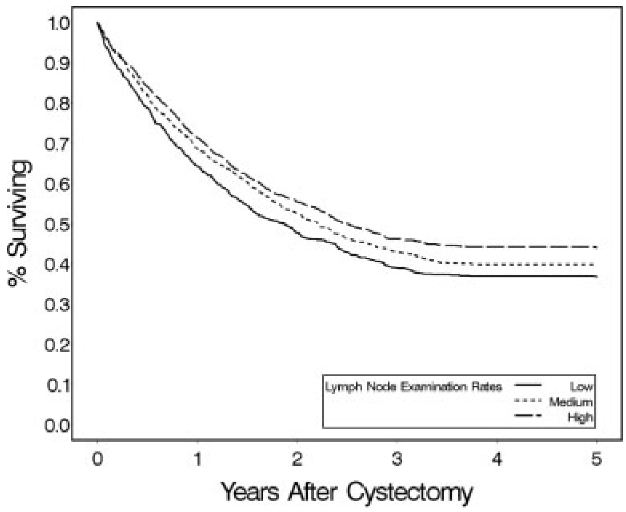

FIGURE 1. Kaplan-Meier plot describing 5-year survival among patients undergoing radical cystectomy for bladder cancer, according to hospital lymph node examination rates (based on data from the Surveillance, Epidemiology, and End Results [SEER]-Medicare linked database, 1992–2003).

TABLE 3
Association Between Hospital Lymph Node Counts and Mortality After Radical Cystectomy, With and Without Adjustment for Patient and Provider Characteristics

	HR of mortality according to hospital lymph node counts, low versus high, (95% CI)		
	Unadjusted	Adjusted for patient characteristics	Adjusted for patient and provider characteristics
All patients	1.25 (1.13–1.39)	1.17 (1.05–1.31)	1.12 (0.99–1.27)
Stage			
0/I	1.22 (1.00–1.48)	1.14 (0.93–1.40)	1.09 (0.85–1.38)
II	1.29 (0.99–1.69)	1.16 (0.88–1.53)	1.32 (0.95–1.82)
III	1.33 (1.07–1.66)	1.27 (1.01–1.60)	1.24 (0.95–1.82)
IV	1.36 (1.12–1.65)	1.35 (1.10–1.65)	1.22 (0.97–1.53)
Chemotherapy			
No	1.24 (1.11–1.40)	1.14 (1.01–1.29)	1.10 (0.96–1.27)
Yes	1.31 (1.02–1.69)	1.27 (0.98–1.66)	1.19 (0.88–1.61)

HR indicates hazards ratio; 95% CI, 95% confidence interval.

tended to have improved long-term survival compared with those treated at hospitals with lower counts. In contrast to patient-level data that have suggested a substantial survival benefit to those achieving higher counts (52–100% reduction in risk),[5,6] we observed a considerably more modest effect (12% reduction in risk), with the majority of the benefit explained by confounding factors. Although not reaching statistical significance, we noted consistent trends in improved long-term survival that were evident across all stages of cancer and seemingly independent of whether chemotherapy was administered. All of these findings were robust to our sensitivity analyses. Indeed, when limiting our analysis to hospitals performing at least 5 procedures, thereby perhaps eliminating those with serendipitous outcomes, we observed a stronger and statistically significant effect.

Clinical data that have suggested that the more lymph nodes removed translates into improved survival,[4–6] even perhaps among those patients with negative lymph nodes.[4] In 1 study, patients who had $\geq$10 lymph nodes removed at the time of radical cystectomy were >60% less likely to die of bladder cancer than those who had no lymph node dissection.[6] This, coupled with supportive patient-level data,[4–6] has prompted many experts to argue that lymph node counts at the time of radical cystectomy reflect the quality of the surgery.[6,13,17]

Despite the evidence supporting the use of lymphadenectomy at the time of radical cystectomy, we were surprised to find that approximately half of patients treated at high lymph node count hospitals had $\geq$5 lymph nodes removed. Unlike some cancer surgeries, the extent of the lymph node dissection at the time of cystectomy is a source of debate,[17] and sometimes not performed at all.[6] Among our population-based cohort, the overwhelming majority of patients had <5 lymph nodes removed. This limited use of pelvic lymphadenectomy may indicate a lack of surgeon buy-in as to its importance or an underestimation of the procedure difficulty by its proponents. Regardless, our data indicate that there is considerable room for improvement to obtain more lymph nodes in the vast majority of bladder cancer patients.

However, for hospital lymph node counts to be a true reflection of quality the performance measure must have a direct therapeutic effect. Although the mechanisms underlying such a relation are unclear, 2 have been posited. First, patients undergoing more extensive lymph node dissections may be more appropriately staged.[5,6] In this context, those with more advanced stage are better identified by a more thorough lymph node dissection. Although conclusive evidence supporting the use of adjuvant chemotherapy for the purpose of improving survival is arguable, reducing the misclassification according to stage may improve the quality of care delivered by better identifying those who may best benefit from additional systemic therapy. Alternatively, some have postulated that more extensive lymph node dissections result in the removal of undetectable, micrometastatic disease.[14] Through lymph node clearance, a more thorough dissection may result in lower local recurrence rates that ultimately translate into improved survival.

In contrast to these direct mechanisms, hospital lymph node counts may exert their effects indirectly by serving as a proxy for patient and provider factors. The extent of the lymph node dissection, which ultimately influences lymph node counts after cystectomy, varies with patient characteristics, including age, sex, and prior therapy.[13] For example, it is plausible that surgeons choose to do a less thorough lymph node dissection on patients perceived to be infirm or those believed to have a short life expectancy. In this context, healthier patients would have higher lymph node counts and ultimately fulfill the prophecy of surviving longer. Conversely, lymph node counts may reflect varying practice patterns according to physician characteristics, including specialized oncology training,[5] that may more directly reflect quality. In either of these cases, lymph node counts would be only a proxy for quality.

The findings of the current study should be interpreted with a few limitations in mind. First, residual selection bias through confounding by unmeasured patient characteristics (ie, patient heterogeneity not available within SEER-Medicare data) can potentially overestimate the benefits of achieving higher lymph node counts.[27] For example, making inferences regarding the correlation between a patient's lymph node count and survival is subject to selection bias. For this reason, we measured lymph node counts at the level of the hospital instead of at that of the patient. The strength of this approach rests on the assumption that the variation in risk factors across patients within hospitals is far greater than the variation in the average of patient risk factors between hospitals. Arguably, this method of exposure classification is less susceptible to selection bias[27,28] than patient-level analyses. Alternative statistical methods, including propensity score methods[29] and instrumental variables analysis,[30] have been proposed to minimize bias when making inference from observational data. Although a formal instrumental variables analysis[30] may further alleviate any residual selection bias, sample size limitations preclude its use and propensity score methods generally perform no better than traditional multivariable modeling when unmeasured factors are a significant source of confounding.[27]

Second, our hospital-level exposure variable ignores wide variation in the number of lymph nodes examined among patients within hospitals. We believe that the variation in the lymph counts reflect the surgeon's decision of whether to perform a lymphadenectomy and alterations in its extent rather than ascertainment variability by pathologists, a hypothesis supported by clinical data.[31,32] Because there is no solid evidence for any particular threshold, we chose multiple levels based on the literature and the findings were consistent throughout. Third, some may argue that lymph node counts and surgical quality should be assessed at the surgeon level. However, radical cystectomy is an uncommon procedure, with an estimated 8000 cases performed annually in the U.S.[33] As a consequence, reliable and valid estimates of surgeon practice patterns with regard to lymph node dissection are impractical, as most perform only a few such procedures annually.[34] Thus, endeavors to measure quality for radical cystectomy are likely to occur at the hospital level, at which most efforts are currently directed. Finally, our study population was limited to patients age $\geq$65 years; therefore, the generalizability of these data to younger patients is unknown. However, the use of SEER-Medicare data, as opposed to SEER data alone, allowed us to account for patient comorbidities, admission acuity, use of chemotherapy, and hospital attributes, all important confounders of correlations between lymph node counts and survival after cancer surgery. Because nearly three-quarters of incident bladder cancer cases arise in the Medicare population,[16] our findings are relevant to the population at greatest risk.

Patients undergoing radical cystectomy for bladder cancer at hospitals with higher lymph node counts tended to have better long-term survival. Although the correlation between hospital lymph node counts and survival is modest when considering all-comers, it appears stronger among those with higher stages of bladder cancer, a population that has arguably the most to gain by a thorough lymph node dissection. Unlike prior patient-level analyses, most, but not all, of the effect appears to be attenuated by differences in patients and hospitals. Although we minimized the potential for selection bias by using hospital-level lymph node counts in lieu of those measured at the patient level, our approach may dilute the true magnitude of the effect of lymph node counts on survival. These findings do not refute a direct link between lymph node counts and survival, or their use as a quality indicator for radical cystectomy; rather, they suggest that the benefits of 'bringing up the rear' might be smaller than hoped.

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